



Northern Lincolnshire
Area Prescribing Committee

GUIDANCE ON THE TREATMENT AND MANAGEMENT OF INFECTION IN PRIMARY CARE (Antimicrobial Prescribing)

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Contents

Contents	2
Summary table – Infections in primary care	4
Summary table – Suspected dental infections in primary care (outside dental setting)	9
References and rationale – Infections in primary care	12
References and rationale – Suspected dental infections in primary care (outside dental setting)	132
Acknowledgements	142
Abbreviations	146

Introduction

This guidance document has been produced in line with the Health Protection Agency and British Infection Association ‘Management of Infection Guidance for Primary Care’ which was first produced in 1999 and last updated in September 2017.

It is intended for use by those clinicians prescribing antimicrobials for the management of infections in Primary Care in North and North East Lincolnshire. Prescribing data will be used to monitor compliance.

Principles of treatment:

1. This guidance is based on the best available evidence, but use professional judgement and involve patients in management decisions.
2. This guidance should not be used in isolation; it should be supported with patient information about safety netting, delayed/back-up antibiotics, self-care, infection severity and usual duration, clinical staff education, and audits. Materials are available on the RCGP **TARGET** website.
3. Prescribe an antibiotic only when there is likely to be clear clinical benefit, giving alternative, non-antibiotic self-care advice, where appropriate.
4. Consider a ‘no’ or ‘delayed/back-up’ antibiotic strategy for acute self-limiting upper respiratory tract infections and mild UTI symptoms.
5. In severe infection, or immunocompromised, it is important to initiate antibiotics as soon as possible, particularly if **sepsis** is suspected. If patient is not at moderate to high risk for sepsis, give information about symptom monitoring, and how to access medical care if they are concerned.
6. Where an empirical therapy has failed or special circumstances exist, microbiological advice can be obtained via Hospital switchboard 01472874111 or 01724282282.
7. Limit prescribing over the telephone to exceptional cases.
8. Use simple, generic antibiotics if possible. Avoid broad spectrum antibiotics (eg co-amoxiclav, quinolones and cephalosporins) when narrow spectrum antibiotics remain effective, as they increase the risk of *Clostridium difficile*, MRSA and resistant UTIs.
9. Always check for antibiotic allergies. A dose and duration of treatment for adults is usually suggested, but may need modification for age, weight, renal function, or if immunocompromised. In severe or recurrent cases, consider a larger dose or longer course.
10. Child doses are provided when appropriate, and can be accessed through the © symbol.
11. Refer to the **BNF** for further dosing and interaction information (eg the interaction between macrolides and statins), and check for hypersensitivity.
12. Have a lower threshold for antibiotics in immunocompromised, or in those with multiple morbidities; consider culture/specimens, and seek advice.
13. Avoid widespread use of topical antibiotics, especially in those agents also available systemically; in most cases, topical use should be limited.
14. In **pregnancy**, take specimens to inform treatment. Where possible, avoid **tetracyclines**, **aminoglycosides**, **quinolones**, **azithromycin** (except in chlamydial infection), **clarithromycin**, and high dose **metronidazole** (2g stat), unless the benefits outweigh the risks. **Penicillins**, **cephalosporins**, and **erythromycin** are safe in pregnancy. Short-term use of **nitrofurantoin** is not expected to cause foetal problems (theoretical risk of neonatal haemolysis). **Trimethoprim** is also unlikely to cause problems unless poor dietary folate intake, or taking another folate antagonist.
15. This guidance is developed alongside the **NHS England Antibiotic Quality Premium**. The required performance in 2017/19 is: a 10% reduction (or greater) in the number of *E. coli* blood stream infections across the whole health economy; a 10% reduction (or greater) in the trimethoprim:nitrofurantoin prescribing ratio for UTI in primary care, and a 10% reduction (or greater) in the number of trimethoprim items prescribed to patients aged 70 years or greater; sustained reduction of inappropriate prescribing in primary care.

Management and treatment of common infections-Antibiotic guidance for primary care

General information on prescribing recommendations

The information contained within this document is for guidance to assist in the prescribing of antimicrobials. The doses specified are recommended for use in those with normal pharmacokinetic handling of the drug. Dose adjustments may be necessary in children or those of advanced age or with co-morbidities that could affect the pharmacokinetics of the drug (e.g. liver or renal impairment, pregnancy). Certain drug interactions may also have an impact on antimicrobial drug dosing. Please refer to the BNF for children for child doses - Clicking on the symbol will take users to the relevant section within the BNF for children.

Before prescribing, the information contained within these guidelines should be read in conjunction with the most recent British National Formulary (<http://www.bnf.org> or www.bnfc.org) or the electronic medicines compendium (www.emc.medicines.org.uk) for contra-indications, cautions, use in pregnancy / breast feeding and other disease states (e.g. renal or hepatic impairment) and drug interactions.

Main Risk Factors for Clostridium difficile associated diarrhoea (CDAD)

Risk factors for CDAD are given below. The more of these risk factors a patient has, the higher the risk is likely to be.

- Age >65 years (especially >75 years)*
- Previous CDAD*
- Recent exposure to cephalosporins*, quinolones* or clindamycin*. Other broad-spectrum antibiotics such as co-amoxiclav (Augmentin®) have been less strongly associated with CDAD, but may also be risk factors especially if prolonged / multiple courses.
- Recent prolonged* / multiple* or IV antibiotic exposure (especially if antibiotics listed above)
- Nursing / residential home resident
- NG or PEG tube in-situ
- Prolonged hospital stay anticipated
- Recent hospital stay
- Extensive co-morbidity
- Gastrointestinal surgery
- Severe underlying / inter-current illness
- Low albumin / poor nutritional status
- H2 antagonist or proton pump inhibitor therapy*
- Immunosuppression

*These are probably the most important, particularly in combination

Summary table – Infections in primary care

ILLNESS	GOOD PRACTICE POINTS	TREATMENT	ADULT DOSE (click on ☺ for child doses)	DURATION OF TREATMENT
UPPER RESPIRATORY TRACT INFECTIONS				
Influenza PHE Influenza Influenza prophylaxis NICE Influenza	Annual vaccination is essential for all those “at risk” of influenza. ^{1D} Antivirals are not recommended for healthy adults. ^{1D,2A+} Treat “at risk” patients with five days oseltamivir 75mg BD, ^{1D} when influenza is circulating in the community, and ideally within 48 hours of onset (36 hours for zanamivir treatment in children), ^{1D,3D} or in a care home where influenza is likely. ^{1D,2A+} At risk: pregnant (including up to two weeks post-partum); children under six months; adults 65 years or older; chronic respiratory disease (including COPD and asthma); significant cardiovascular disease (not hypertension); severe immunosuppression; diabetes mellitus; chronic neurological, renal or liver disease; morbid obesity (BMI>40). ^{4D} See the PHE Influenza guidance for the treatment of patients under 13 years of age. ^{4D} In severe immunosuppression, or oseltamivir resistance, use zanamivir 10mg BD ^{5A+,6A+} (two inhalations by diskhaler for up to 10 days) and seek advice. ^{4D}			
Acute sore throat NICE RTIs FeverPAIN	Avoid antibiotics ^{1B-,2D} as 82% of cases resolve in 7 days, and pain is only reduced by 16 hours. ^{3A+} Use FeverPAIN Score: ^{4B+,5A-} Fever in last 24 hours; Purulence ; Attend rapidly under three days; severely Inflamed tonsils; No cough or coryza. Score 0-1: 13-18% streptococci - no antibiotic. 2-3: 34-40% streptococci - 3 day delayed antibiotic. 4-5: 62-65% streptococci - if severe, immediate antibiotic or 48-hour delayed antibiotic. ^{4B+,5A-,6D} Advise paracetamol, self-care, and safety net. Complications are rare: antibiotics to prevent quinsy NNT>4000, ^{7B-} otitis media NNT200. ^{7B-} 10 days penicillin has lower relapse than five days in patients under 18 years of age. ^{8D,9A+}	<i>Fever pain 0-1:</i> self-care ^{6D} <i>Fever pain 2-3:</i> delayed prescription ^{4B+,5A-,6D} of phenoxymethylpenicillin ^{9A+} <i>Penicillin allergy:</i> clarithromycin ^{9A+,10B-} <i>Penicillin allergy in pregnancy:</i> erythromycin ^{9A+,10B-,11D,12C}	500mg QDS (if severe) ^{13A+} ☺ OR 1g BD (less severe) ^{13A+} 250mg BD ^{9A+} OR ☺ 500mg BD 250-500mg QDS ^{9A+} ☺	5-10 days ^{8D,9A+,14A-,15B+} 5 days ^{9A+} 5 days ^{9A+} 5 days ^{9A+}
Scarlet fever (GAS) PHE Scarlet fever	Prompt treatment with appropriate antibiotics significantly reduces the risk of complications. ^{1D} Observe immunocompromised individuals (diabetes; women in the puerperal period; chickenpox) as they are at increased risk of developing invasive infection. ^{1D}	<i>First line (mild):</i> analgesia ^{2D} Phenoxymethylpenicillin ^{2D} <i>Penicillin allergy:</i> clarithromycin ^{1D}	500mg QDS ^{1D} ☺ 250-500mg BD ^{1D} ☺	10 days ^{3A+,4A+,5A+} 5 days ^{1D,5A+}
Acute otitis media (child doses) NICE RTIs	Optimise analgesia and target antibiotics. ^{1A-,2A+} AOM resolves in 60% of cases in 24 hours without antibiotics. ^{3A+} Antibiotics reduce pain only at two days (NNT15), and do not prevent deafness. ^{3A+} Consider 2 or 3 day delayed, ^{4D,5A+} or immediate antibiotics for pain relief if: <2 years AND bilateral AOM (NNT4), ^{6A+,7A+} bulging membrane, or symptom score >8 for: fever; tugging ears; crying; irritability; difficulty sleeping; less playful; eating less (0 = no symptoms; 1 = a little; 2 = a lot). ^{8A-} All ages with otorrhoea NNT3. ^{7A+} Antibiotics to prevent mastoiditis NNT>4000. ^{9B-,10C}	Amoxicillin ^{11A+,12A+} <i>Penicillin allergy:</i> erythromycin ^{12A+,13D} OR clarithromycin ^{13D}	Neonate: 30mg/kg TDS ^{14A+} 1-11 months: 125mg TDS ^{14A+} 1-4 years: 250mg TDS ^{14A+} >5 years: 500mg TDS ^{14A+} <2 years: 125mg QDS ^{13D} 2-7 years: 250mg QDS ^{13D} >8 years: 250-500mg QDS ^{13D} 1 month-11 years: 7.5mg/kg-250mg BD (weight dosing) ^{13D} 12-18 years: 250mg BD ^{13D}	5 days ^{15A+} 5 days ^{15A+} 5 days ^{13D,15A+}

Management and treatment of common infections-Antibiotic guidance for primary care

ILLNESS	GOOD PRACTICE POINTS	TREATMENT	ADULT DOSE (☺ = child doses)	DURATION OF TREATMENT
Acute otitis externa CKS Otitis externa	First line: analgesia for pain relief, ^{1D,2D} and apply localised heat (eg a warm flannel). ^{2D} Second line: topical acetic acid or topical antibiotic +/- steroid: similar cure at 7 days. ^{2D,3A+,4B-} If cellulitis or disease extends outside ear canal, or systemic signs of infection, start oral flucloxacillin and refer to exclude malignant otitis externa. ^{1D}	Second line: topical acetic acid 2% ^{2D,4B-} Topical neomycin sulphate with corticosteroid ^{2D,5A-} <i>If cellulitis:</i> flucloxacillin ^{6B+}	1 spray TDS ^{5A-} ☺ 3 drops TDS ^{5A-} ☺ 250mg QDS ^{2D} ☺ <i>If severe:</i> 500mg QDS ^{2D} ☺	7 days ^{5A-} 7 days (min) to 14 days (max) ^{3A+} 7 days ^{2D} 7 days ^{2D}
Sinusitis (acute) This guidance summarises the NICE Sinusitis (acute) guidance published in July 2017, and the NICE RTIs guidance published in July 2008	Symptoms <10 days: ^{1A+} do not offer antibiotics as most resolve in 14 days without, ^{2A+} and antibiotics only offer marginal benefit after 7 days (NNT15). ^{3A+} Symptoms >10 days: ^{1A+} no antibiotic, or back-up antibiotic ^{4D} if several of: purulent nasal discharge; ^{1A+} severe localised unilateral pain; fever; marked deterioration after initial milder phase. ^{1A+} Systemically very unwell, or more serious signs and symptoms: ^{1A+} immediate antibiotic. ^{1A+,5A-} Suspected complications: eg sepsis, intraorbital or intracranial, refer to secondary care. ^{1A+} Self-care: paracetamol/ibuprofen for pain/fever. ^{6D} Consider high-dose nasal steroid if >12 years. ^{1A+} Nasal decongestants or saline may help some. ^{1A+}	<i>No antibiotics:</i> self-care ^{6D} <i>First line for delayed:</i> phenoxymethylpenicillin ^{5A-} <i>Penicillin allergy or intolerance:</i> doxycycline ^{1A+,6D} OR clarithromycin ^{1A+} <i>Very unwell or worsening:</i> co-amoxiclav ^{1A+,6D} Mometasone ^{1A+}	500mg QDS ^{5A-,6D} ☺ 200mg stat then 100mg OD ^{6D} 500mg BD ^{6D} ☺ 500/125mg TDS ^{6D} ☺ 200mcg BD ^{1A+} ☺	5 days ^{1A+} 5 days ^{1A+} 14 days ^{1A+}
LOWER RESPIRATORY TRACT INFECTIONS				
<i>Note: Low doses of penicillins are more likely to select for resistance.^{1D} Do not use quinolones (ciprofloxacin, ofloxacin) first line as there is poor pneumococcal activity.^{2B-} Reserve all quinolones (including levofloxacin) for proven resistant organisms.^{1D}</i>				
Acute cough & bronchitis NICE RTIs	Antibiotics have little benefit if no co-morbidity. ^{1A+,2A-} Second line: 7 day delayed antibiotic, ^{3D} safety net, and advise that symptoms can last 3 weeks. ^{3D} Consider immediate antibiotics if >80 years of age and one of: hospitalisation in past year; taking oral steroids; insulin-dependent diabetic; congestive heart failure; serious neurological disorder/stroke, ^{3D} or >65 years with two of the above. ^{3D} Consider CRP if antibiotic is being considered. ^{4A-} No antibiotics if CRP<20mg/L and symptoms for >24 hours; delayed antibiotics if 20-100mg/L; immediate antibiotics if >100mg/L. ^{5D}	<i>First line:</i> self-care ^{1A+} and safety netting advice ^{3D} <i>Second line:</i> amoxicillin ^{3D,6D} <i>Penicillin allergy:</i> doxycycline ^{3D,6D}	500mg TDS ^{3D,6D} ☺ 200mg stat then 100mg OD ^{3D,6D}	5 days ^{3D,6D} 5 days ^{3D,6D}
Acute exacerbation of COPD NICE COPD GOLD COPD	Treat with antibiotics ^{1A+,2A-} if purulent sputum and increased shortness of breath and/or increased sputum volume. ^{1A+,3D,4D} Risk factors for antibiotic resistance: ^{5A+} severe COPD (MRC>3), ^{6B+} co-morbidity; frequent exacerbations; ^{3D} antibiotics in the last 3 months. ^{4D}	amoxicillin ^{4D} OR doxycycline ^{4D} OR clarithromycin ^{7A+} <i>If at risk of resistance:</i> co-amoxiclav ^{4D}	500mg TDS ^{5A-} ☺ 200mg stat then 100mg OD ^{8A-} ☺ 500mg BD ^{7A+} ☺ 500/125mg TDS ^{4D} ☺	5 days ^{7A+} 5 days ^{7A+}
Community-acquired pneumonia NICE Pneumonia	Use CRB65 score to guide mortality risk, place of care, and antibiotics. ^{1D} Each CRB65 parameter scores one: Confusion (AMT≤8 or new disorientation in person, place or time); Respiratory rate ≥30/min; BP systolic <90, or diastolic ≤60; age ≥65. Score 0: low risk, consider home-based care; 1-2: intermediate risk, consider hospital assessment; 3-4: urgent hospital admission. ^{1D} Give safety-net advice^{1D} and likely duration of different symptoms, eg cough 6 weeks. ^{1D} Mycoplasma infection is rare in over 65s. ^{2A+,3C}	CRB65=0: amoxicillin ^{1D,4D} OR clarithromycin ^{2A+,4D,5A+} OR doxycycline ^{2A+,4D} CRB65=1-2 and at home (clinically assess need for dual therapy for atypicals): amoxicillin ^{1D,4D} AND clarithromycin ^{2A+,4D,5A+} OR doxycycline alone ^{4D}	500mg TDS ^{5A+} ☺ 500mg BD ^{5A+} ☺ 200mg stat then 100mg OD ^{6A-} ☺ 500mg TDS ^{5A+} ☺ 500mg BD ^{5A+} ☺ 200mg stat then 100mg OD ^{6A-} ☺	5 days; review at 3 days; ^{1D} 7-10 if poor response ^{1D} 7-10 days ^{1D}
URINARY TRACT INFECTIONS				
<i>Note: As antibiotic resistance and Escherichia coli bacteraemia in the community is increasing, use nitrofurantoin first line,^{1D} always give safety net and self-care advice, and consider risks for resistance.^{2D} Give TARGET UTI leaflet,^{3D} and refer to the PHE UTI guidance for diagnostic information.^{4D}</i>				
UTI in adults (lower) PHE UTI Diagnosis TARGET UTI RCGP UTI SIGN UTI NHS Scotland UTI	All patients first line antibiotic: nitrofurantoin if GFR >45mls/min. ^{1A+,2A+} If GFR 30-45, only use if no alternative. ^{2A+,3D} Treat women with severe/≥3 symptoms. Women <65 years (mild/≤2 symptoms): ^{4D} pain relief, ^{6A-,7A-,8B-} and consider delayed antibiotic. ^{9B-,10A+} If urine not cloudy, 97% NPV of no UTI. ^{11A-} If urine cloudy, use dipstick to guide treatment: nitrite, leukocytes, blood all negative 76% NPV; ^{11A-} nitrite plus blood or leukocytes 92% PPV of UTI. ^{11A-} Men <65 years: consider prostatitis and send MSU, ^{4D,12D} or if symptoms local or non-specific, use negative dipstick to exclude UTI. ^{12D} >65 years: ^{13A-} treat if fever ≥38°C, or 1.5°C above base twice in 12 hours, and >1 other symptom. ^{14B-} If treatment failure: always perform culture. ^{4D}	First line: nitrofurantoin ^{15A-} (if fever, use alternative) ^{15A-} <i>If low risk of resistance:</i> ^{16B+} trimethoprim ^{17D,18A+} If first line unsuitable: ^{2A+} pivmecillinam ^{19B+,20D,21A+} <i>If organism susceptible:</i> amoxicillin ^{22A+,23A+} <i>If high resistance risk:</i> fosfomycin ^{16B+,24A+,25B-,26B-}	100mg m/r BD, OR 50mg i/r QDS ^{27A-} (BD dose increases compliance) ^{28D} 200mg BD ^{23A+} 400mg stat then 200mg TDS ^{29B+,30B+} (400mg if high resistance risk) ^{29B+} 500mg TDS ^{33A+} Women and men: 3g stat ^{26B-} Men: a second 3g stat on day 3 (unlicensed) ^{26B-}	Women: 3 days ^{23A+,31B-,32B-,33B+,34B+,35A-,36A+} Men: 7 days ^{37B+,38A-} 7-10 days ^{1D}
Low risk of resistance: younger women with acute UTI and no risk. Risk factors for increased resistance include: care home resident; ^{13A-,14B-} recurrent UTI; hospitalisation for >7 days in the last 6 months; unresolving urinary symptoms; recent travel to a country with increased resistance; previous UTI resistant to trimethoprim, cephalosporins, or quinolones. ^{39C,40B+,41D} If risk of resistance: send urine for culture and susceptibilities; safety net. ^{26B-}				

Management and treatment of common infections-Antibiotic guidance for primary care

ILLNESS	GOOD PRACTICE POINTS	TREATMENT	ADULT DOSE (☺ = child doses)	DURATION OF TREATMENT	
UTI in patients with catheters: antibiotics will not eradicate asymptomatic bacteriuria; ^{1D,2D,3A-} only treat if systemically unwell or pyelonephritis likely. ^{2D} Do not use prophylactic antibiotics for catheter change unless there is a history of catheter-change-associated UTI or trauma. ^{4D,5A+} Take sample if new onset of delirium, or one or more symptoms of UTI. ^{3A-,6B-,7D}					
UTI in pregnancy SIGN UTI	Send MSU for culture; ^{1D} start antibiotics in all with significant positive culture, even if asymptomatic. ^{1D} First line: nitrofurantoin, unless at term. ^{2A-,3D} Second line: trimethoprim; avoid if low folate status, ^{2A-,4D,5D} or on folate antagonist. ^{4D,5D} Third line: cephalosporins, as risk of <i>C. difficile</i> . ^{6C}	First line: nitrofurantoin (avoid at term) ^{2A-,3D,7A+} Second line: trimethoprim ^{2A-,4D,7A+} (give folate if first trimester) ^{5D} Third line: cefalexin ^{4D,8D}	100mg m/r BD ^{2A-,9C} OR 50mg i/r QDS ^{2A-,9C} 200mg BD (off-label) ^{7A+} 500mg BD ^{9C}	7 days ^{10D}	
Acute prostatitis	Send MSU for culture and start antibiotics. ^{1D} 4 week course may prevent chronic prostatitis. ^{1D,2D} Quinolones achieve high prostate concentrations. ^{2D}	Ciprofloxacin ^{1D,3D} OR ofloxacin ^{1D,3D} Second line: trimethoprim ^{1D}	500mg BD ^{1D} 200mg BD ^{1D} 200mg BD ^{1D}	28 days ^{1D,2D}	
UTI in children NICE UTI in under 16s	Child <3 months: refer urgently for assessment. ^{1D} Child ≥3 months: use positive nitrite to guide antibiotic use; ^{1A-} send pre-treatment MSU. ^{1D} Imaging: refer if child <6 months, or recurrent or atypical UTI. ^{1D}	Lower UTI: nitrofurantoin ^{1A-} OR trimethoprim ^{1A-} Second line: cefalexin ^{1D} If organism susceptible: amoxicillin ^{1A-}	☺ ☺ ☺ ☺	3 days ^{1A+}	
Acute pyelonephritis	If admission not needed, send MSU for culture and susceptibility testing, ^{1D} and start antibiotics. ^{1D} If no response within 24 hours, seek advice. ^{1D,2D} If ESBL risk, ^{3A+} and on advice from a microbiologist, consider IV antibiotic via OPAT. ^{4D}	Ciprofloxacin ^{2D,5A-,6D} OR co-amoxiclav ^{2D,5A-} If organism sensitive: trimethoprim ^{5A-,7A+}	500mg BD ^{2D,5A-,6D} 500/125mg TDS ^{2D} 200mg BD ^{5A-,7A+}	7 days ^{2D,5A-,7A+} 7 days ^{5A-,7A+} 14 days ^{7A+}	
Recurrent UTI in non-pregnant women (2 in 6 months or >3 in a year) TARGET UTI	First line: advise simple measures, ^{1D} including hydration; ^{1D,2D,3D} ibuprofen for symptom relief. ^{4A-,5A-} Cranberry products work for some women. ^{6D,7A+,8A+} Second line: stand-by ^{1D} or post-coital antibiotics. ^{9A+} Third line: antibiotic prophylaxis. ^{1D,9A+,10D} Consider methenamine if no renal/hepatic impairment. ^{11A+}	Antibiotic prophylaxis: First line: nitrofurantoin ^{9A+} Second line: ciprofloxacin ^{9A+} If recent culture sensitive: trimethoprim ^{9A+} Methenamine hippurate ^{11A+}	100mg m/r ^{9A+} 500mg ^{9A+} 100mg ^{9A+} 1g BD ^{11A+}	At night or post-coital stat (off-label) ^{1D,9A+,10D} 3-6 months, ^{1D} then review recurrence rate and need ^{1D,9A+} 6 months ^{1D,11A+}	
MENINGITIS					
Suspected meningococcal disease NICE Meningitis	Transfer all patients to hospital immediately. ^{1D} If time before hospital admission, ^{2D,3A+} and non-blanching rash, ^{2D,4D} give IV benzylpenicillin ^{1D,2D,4D} or IV cefotaxime. ^{2D} Do not give IV antibiotics if there is a definite history of anaphylaxis; ^{1D} rash is not a contraindication. ^{1D}	IV or IM benzylpenicillin ^{1D,2D} OR IV or IM cefotaxime ^{2D}	Child <1 year: 300mg ^{5D} Child 1-9 years: 600mg ^{5D} Adult/child 10+ years: 1.2g ^{5D} Child <12 years: 50mg/kg ^{5D} Adult/child 12+ years: 1g ^{5D}	Stat dose; ^{1D} give IM, if vein cannot be accessed ^{1D}	
Prevention of secondary case of meningitis: Only prescribe following advice from Public Health Doctor: 9 am – 5 pm : ☎ 01904468900 Out of hours: contact on-call doctor: ☎ 01472874111 or 01724282282					
GASTROINTESTINAL TRACT INFECTIONS					
Oral candidiasis CKS Candida	Topical azoles are more effective than topical nystatin. ^{1A+} Oral candidiasis is rare in immunocompetent adults; ^{2D} consider undiagnosed risk factors, including HIV. ^{2D} Use 50mg fluconazole if extensive/severe candidiasis; ^{3D,4D} if HIV or immunocompromised, use 100mg fluconazole. ^{3D,4D}	Miconazole oral gel ^{1A+,4D,5A-} If not tolerated: nystatin suspension ^{2D,6D,7A-} Fluconazole capsules ^{6D,7A-}	2.5ml of 24mg/ml QDS (hold in mouth after food) ^{4D} ☺ 1ml; 100,000 units/mL QDS (half in each side) ^{2D,4D,7A-} ☺ 50mg/100mg OD ^{3D,6D,8A-} ☺	7 days; ^{4D,6D} continue nystatin 2d &azole 7d after resolved ^{4D} 7-14 days ^{6D,7A-,8A-}	
Helicobacter pylori NICE GORD and dyspepsia PHE H. pylori	Treat all positives, if known DU, GU, ^{1A+} or low grade MALToma. ^{2D,3D} NNT in non-ulcer dyspepsia: 14. ^{4A+} Do not offer eradication for GORD. ^{3D} Do not use clarithromycin, metronidazole or quinolone if used in the past year for any infection. ^{5A+,6B+,7A+} Penicillin allergy: use PPI PLUS clarithromycin PLUS metronidazole. ^{2D} If previous clarithromycin, use PPI PLUS bismuth salt PLUS metronidazole PLUS tetracycline hydrochloride. ^{2D,8A-,9D} Relapse and previous metronidazole and clarithromycin: use PPI PLUS amoxicillin PLUS either tetracycline OR levofloxacin. ^{2D,7A+} Retest for H. pylori: post DU/GU, or relapse after second line therapy, ^{1A+} using UBT or SAT, ^{10A+,11A+} consider referral for endoscopy and culture. ^{2D}	Always use PPI ^{2D,3D,5A+,12A+} PPI PLUS amoxicillin PLUS clarithromycin OR metronidazole ^{2D,6B+} Penicillin allergy & previous clarithromycin: PPI WITH bismuth subsalicylate ^{13A+} PLUS metronidazole PLUS tetracycline hydrochloride ^{2D} Relapse: PPI PLUS amoxicillin PLUS tetracycline hydrochloride OR levofloxacin ^{2D,7A+}	1g BD ^{14A+} 500mg BD ^{8A-} 400mg BD ^{2D} 525mg QDS ^{15D} 400mg BD ^{2D} 500mg QDS ^{15D} 1g BD ^{14A+} 500mg QDS ^{15D} 250mg BD ^{7A+}	☺ ☺ ☺ ☺ ☺ ☺ ☺ ☺	7-14 days; ^{14A+} MALToma 14 days ^{7A+,16A+}
Infectious diarrhoea PHE Diarrhoea	Refer previously healthy children with acute painful or bloody diarrhoea, to exclude <i>E. coli</i> 0157 infection. ^{1D} Antibiotic therapy is not usually indicated unless patient is systemically unwell. ^{2D} If systemically unwell and campylobacter suspected (eg undercooked meat and abdominal pain), ^{3D} consider clarithromycin 250-500mg BD for 5-7 days, if treated early (within 3 days). ^{3D,4A+}	First episode: metronidazole ^{1D,2D,4B-} Severe/type O27/recurrent: oral vancomycin ^{1D,2D,5A-} Recurrent or second line: fidaxomicin ^{2D,5A-}	400mg TDS ^{1D,2D} ☺ 125mg QDS ^{1D,2D,5A-} ☺ 200mg BD ^{5A-}	10-14 days ^{1D,4B-} 10-14 days, ^{1D,2D} then taper ^{2D} 10 days ^{5A-}	
Clostridium difficile PHE Clostridium difficile	Stop unnecessary antibiotics, ^{1D,2D} PPIs, ^{3B-} and antiperistaltic agents. ^{2D} Mild cases (<4 episodes of diarrhoea/day) may respond without metronidazole; ^{2D} 70% respond to metronidazole in 5 days; 92% respond to metronidazole in 14 days. ^{4B-} If severe (T>38.5, or WCC>15, rising creatinine, or signs/symptoms of severe colitis): ^{2D} treat with oral vancomycin, ^{1D,2D,5A-} review progress closely, ^{1D,2D} and consider hospital referral. ^{2D}	First episode: metronidazole ^{1D,2D,4B-} Severe/type O27/recurrent: oral vancomycin ^{1D,2D,5A-} Recurrent or second line: fidaxomicin ^{2D,5A-}	400mg TDS ^{1D,2D} ☺ 125mg QDS ^{1D,2D,5A-} ☺ 200mg BD ^{5A-}	10-14 days ^{1D,4B-} 10-14 days, ^{1D,2D} then taper ^{2D} 10 days ^{5A-}	

Management and treatment of common infections-Antibiotic guidance for primary care

ILLNESS	GOOD PRACTICE POINTS	TREATMENT	ADULT DOSE (☺ = child doses)	DURATION OF TREATMENT
Traveller's diarrhoea	Prophylaxis rarely, if ever, indicated. ^{1D} Consider stand-by antimicrobial only for patients at high risk of severe illness, ^{2D} or visiting high risk areas. ^{1D,2D}	<i>Stand-by:</i> azithromycin ^{1D,3A+} <i>Prophylaxis/treatment:</i> bismuth subsalicylate ^{1D,4A-}	500mg OD ^{1D,2D,3A+} 2 tablets QDS ^{1D,2D}	1-3 days ^{1D,2D,3A+} 2 days ^{1D,2D,4A-}
Threadworm CKS Threadworm	Treat all household contacts at the same time. ^{1D} Advise hygiene measures for two weeks ^{1D} (hand hygiene, ^{2D} pants at night; morning shower, including perianal area). ^{1D,2D} Wash sleepwear, bed linen, and dust and vacuum. ^{1D} Child <6 months, add perianal wet wiping or washes three hourly. ^{1D}	<i>Child >6 months:</i> mebendazole ^{1D,3B-} <i>Child <6 months or pregnancy (at least in 1st trimester):</i> only hygiene measure for 6 weeks ^{1D}	100mg stat ^{3B-}	Stat dose, ^{3B-} repeat in 2 weeks if persistent ^{3B-}
GENITAL TRACT INFECTIONS				
STI screening	People with risk factors should be screened for chlamydia, gonorrhoea, HIV, and syphilis. ^{1D} Refer individual and partners to GUM. ^{1D} Risk factors: <25 years; no condom use; recent/frequent change of partner; symptomatic partner; area of high HIV. ^{2B-}			
Chlamydia trachomatis/urethritis SIGN Chlamydia	Opportunistically screen all patients aged 16-24 years. ^{1B-} Treat partners and refer to GUM. ^{2D,3A+} Repeat test for cure in all at three months. ^{1B-,4B-} Pregnancy/breastfeeding: azithromycin is most effective. ^{5A+,6D,7A+,8A+,9D} As lower cure rate in pregnancy, test for cure at least three weeks after end of treatment. ^{1B-,3A+}	<i>First line:</i> azithromycin ^{2D,3A+,5A+,7A+,8A+} OR doxycycline ^{2D,3A+,5A+} <i>Pregnancy/breastfeeding:</i> azithromycin ^{3A+,7A+,8A+,9D} OR erythromycin ^{3A+,6D,7A+,8A+} OR amoxicillin ^{6D,7A+,8A+}	1g ^{2D,3A+,5A+,7A+} 100mg BD ^{2D,3A+,5A+} 1g ^{2D,3A+,5A+,7A+} 500mg BD ^{3A+} OR 500mg QDS ^{3A+} 500mg TDS ^{7A+,8A+}	Stat ^{2D,3A+,5A+,7A+,8A+} 7 days ^{2D,3A+,5A+} Stat ^{2D,3A+,5A+,7A+,8A+} 14 days ^{3A+} 7 days ^{3A+} 7 days ^{7A+,8A+}
Epididymitis	Usually due to Gram-negative enteric bacteria in men over 35 years with low risk of STI. ^{1A+,2D} If under 35 years or STI risk, refer to GUM. ^{1A+,2D}	Doxycycline ^{1A+,2D,3A+} OR ofloxacin ^{1A+,2D} OR ciprofloxacin ^{1A+,2D,3A+}	100mg BD ^{1A+,2D,3A+} 200mg BD ^{1A+,2D} 500mg BD ^{1A+,2D,3A+}	10-14 days ^{1A+,2D} 14 days ^{1A+,2D} 10 days ^{1A+,2D,3A+}
Vaginal candidiasis BASHH Vulvovaginal candidiasis	All topical and oral azoles give over 70% cure. ^{1A+,2A+} Pregnancy: avoid oral azoles, ^{1A+,3D} and use intravaginal treatment for 7 days. ^{4A+} Recurrent (>4 episodes per year): ^{5D} 150mg oral fluconazole every 72 hours for three doses induction, ^{1A+} followed by one dose once a week for six months maintenance. ^{1A+,5D}	Clotrimazole ^{1A+,5D} OR miconazole ^{1A+} OR oral fluconazole ^{1A+,3D} <i>Recurrent:</i> fluconazole (induction/maintenance) ^{1A+}	500mg pessary ^{1A+} OR 5g 10% cream ^{1A+} 100mg pessary ^{1A+} 150mg ^{1A+,3D} 150mg every 72 hours THEN 150mg once a week ^{1A+,3D,5D}	Stat ^{1A+} 14 nights ^{1A+} Stat ^{1A+,3D} 3 doses ^{1A+} 6 months ^{1A+,5D}
Bacterial vaginosis BASHH Bacterial vaginosis	Oral metronidazole is as effective as topical treatment, ^{1A+} and is cheaper. ^{2D} Seven days results in fewer relapses than 2g stat at four weeks. ^{1A+,2D} Pregnant/breastfeeding: avoid 2g dose. ^{3A+,4D} Treating partners does not reduce relapse. ^{5A+}	Oral metronidazole ^{1A+,3A+} OR metronidazole 0.75% vaginal gel ^{1A+,2D,3A+} OR clindamycin 2% cream ^{1A+,2D}	400mg BD ^{1A+,3A+} 2g ^{1A+,2D} 5g applicator at night ^{1A+,2D,3A+} 5g applicator at night ^{1A+,2D}	7 days ^{1A+} Stat ^{2D} 5 nights ^{1A+,2D,3A+} 7 nights ^{1A+,2D,3A+}
Genital herpes BASHH Anogenital herpes	Advise: saline bathing, ^{1A+} analgesia, ^{1A+} or topical lidocaine for pain, ^{1A+} and discuss transmission. ^{1A+} First episode: treat within five days if new lesions or systemic symptoms, ^{1A+,2D} and refer to GUM. ^{2D} Recurrent: self-care if mild, ^{2D} or immediate short course antiviral treatment, ^{1A+,2D} or suppressive therapy if more than six episodes per year. ^{1A+,2D}	<i>First line:</i> oral aciclovir ^{1A+,2D,3A+,4A+} OR valaciclovir ^{1A+,3A+,4A+} OR famciclovir ^{1A+,4A+}	400mg TDS ^{1A+,3A+} 800mg TDS (if recurrent) ^{1A+} 500mg BD ^{1A+} 250mg TDS ^{1A+} 1g BD (if recurrent) ^{1A+}	5 days ^{1A+} 2 days ^{1A+} 5 days ^{1A+} 5 days ^{1A+} 1 day ^{1A+}
Gonorrhoea	Antibiotic resistance is now very high. ^{1D,2D} Use IM ceftriaxone ^{2D} and oral azithromycin, ^{1D,3D} refer to GUM. ^{4B} Test of cure is essential. ^{3D}	Ceftriaxone ^{1D,2D,3D,4B-} PLUS oral azithromycin ^{1D,3D,4B-}	500mg IM ^{1D,2D} 1g ^{1D}	Stat ^{3B-} Stat ^{3B-}
Trichomoniasis BASHH Trichomoniasis	Oral treatment needed as extragenital infection common. ^{1D} Treat partners, ^{1D} and refer to GUM for other STIs. ^{1D} Pregnancy/breastfeeding: avoid 2g single dose metronidazole; ^{2A+,3D} clotrimazole for symptom relief (not cure) if metronidazole declined. ^{2A+,4A-,5D}	Metronidazole ^{1A+,2A+,3D,6A+} <i>Pregnancy for symptoms:</i> clotrimazole ^{2A+,4A-,5D}	400mg BD ^{1A+,6A+} 2g (more adverse effects) ^{6A+} 100mg pessary at night ^{5D}	5-7 days ^{1A+} Stat ^{1A+,6A+} 6 nights ^{5D}
Pelvic inflammatory disease BASHH PID	Refer women and sexual contacts to GUM. ^{1A+} Always culture for gonorrhoea and chlamydia. ^{1A+} If gonorrhoea likely (partner has it; sex abroad; severe symptoms), ^{2A-} use regimen with ceftriaxone, as resistance to quinolones is high. ^{1A+,2A-,3C,4C}	Metronidazole ^{1A+,5A+} PLUS ofloxacin ^{1A+,2A-,5A+} GC: metronidazole PLUS doxycycline ^{1A+,5A+} PLUS ceftriaxone ^{3C,4C}	400mg BD ^{1A+} 400mg BD ^{1A+,2A-} 400mg BD ^{1A+} 100mg BD ^{1A+} 500mg IM ^{1A+,3C}	14 days ^{1A+} Stat ^{1A+,3C}
SKIN AND SOFT TISSUE INFECTIONS				
<i>Note: Refer to RCGP Skin Infections online training.^{1D} For MRSA, discuss therapy with microbiologist.^{1D}</i>				
Impetigo PHE Impetigo	Reserve topical antibiotics for very localised lesions to reduce risk of bacteria becoming resistant. ^{1D,2B+} Only use mupirocin if caused by MRSA. ^{1D,3A+} Extensive, severe, or bullous: oral antibiotics ^{4D} .	Topical fusidic acid ^{2D,3A+} MRSA: topical mupirocin ^{3A+} Oral flucloxacillin ^{1D,3A+} Oral clarithromycin ^{1D,4D}	Thinly TDS ^{4D} 2% ointment TDS ^{3A+} 250-500mg QDS ^{3A+} 250-500mg BD ^{4D}	☺ 5 days ^{1D,2D} ☺ 5 days ^{1D,2D,3A+} ☺ 7 days ^{3A+} ☺ 7 days ^{4D}
Cold sores CKS Cold sores	Most resolve after 5 days without treatment. ^{1A-,2A-} Topical antivirals applied prodromally can reduce duration by 12-18 hours. ^{1A-,2A-,3A-} If frequent, severe, and predictable triggers: consider oral prophylaxis: ^{4D,5A+} aciclovir 400mg, twice daily, for 5-7 days. ^{5A+,6A+}			
PVL-SA PHE PVL-SA	Panton-Valentine leukocidin (PVL) is a toxin produced by 20.8-46% of <i>S. aureus</i> from boils/abscesses. ^{1B+,2B+,3B-} PVL strains are rare in healthy people, but severe. ^{2B+} Suppression therapy should only be started after primary infection has resolved, as ineffective if lesions are still leaking. ^{4D} Risk factors for PVL: recurrent skin infections, ^{2B+} invasive infections, ^{2B+} MSM, ^{3B-} if there is more than one case in a home or close community ^{2B+,3B-} (school children; ^{3B-} military personnel, ^{3B-} nursing home residents, ^{3B-} household contacts). ^{3B-}			
Eczema NICE Eczema	No visible signs of infection: antibiotic use (alone or with steroids) ^{1A+} encourages resistance and does not improve healing. ^{1A+} With visible signs of infection: use oral flucloxacillin ^{2D} or clarithromycin, ^{2D} or topical treatment (as in impetigo). ^{2D}			

Management and treatment of common infections-Antibiotic guidance for primary care

ILLNESS	GOOD PRACTICE POINTS	TREATMENT	ADULT DOSE (☺ = child doses)	DURATION OF TREATMENT
Acne CKS Acne vulgaris	Mild (open and closed comedones)^{1D} or moderate (inflammatory lesions)^{1D}: First line: self-care ^{1D} (wash with mild soap; do not scrub; avoid make-up). ^{1D} Second line: topical retinoid or benzoyl peroxide. ^{2D} Third-line: add topical antibiotic, ^{1D,3A+} or consider addition of oral antibiotic. ^{1D} Severe (nodules and cysts):^{1D} add oral antibiotic (for 3 months max) ^{1D,3A+} and refer. ^{1D,2D}	First line: self-care ^{1D} Second line: topical retinoid ^{1D,2D,3A+} OR benzoyl peroxide ^{1A-,2D,3A+,4A-} Third-line: topical clindamycin ^{3A+} If treatment failure/severe: oral tetracycline ^{1A-,3A+} OR oral doxycycline ^{3A+,4A-}	Thinly OD ^{3A+} ☺ 5% cream OD-BD ^{3A+} ☺ 1% cream, thinly BD ^{3A+} ☺ 500mg BD ^{3A+} ☺ 100mg OD ^{3A+} ☺	6-8 weeks ^{1D} 6-8 weeks ^{1D} 12 weeks ^{1A-,2D} 6-12 weeks ^{3A+} 6-12 weeks ^{3A+}
Cellulitis and erysipelas CREST Cellulitis BLS Cellulitis	Class I: patient afebrile and healthy other than cellulitis, use oral flucloxacillin alone. ^{1D,2D,3A+} If river or sea water exposure: seek advice. ^{1D} Class II: patient febrile and ill, or comorbidity, admit for intravenous treatment, ^{1D} or use OPAT. ^{1D} Class III: if toxic appearance, admit. ^{1D} Erysipelas: often facial and unilateral. ^{4B+} Use flucloxacillin for non-facial erysipelas. ^{1D,2D,3A+}	Flucloxacillin ^{1D,2D,3A+} Penicillin allergy: clarithromycin ^{1D,2D,3A+,5A+} Penicillin allergy and taking statins: doxycycline ^{2D} Unresolving: clindamycin ^{3A+} Facial (non-dental): co-amoxiclav ^{6B-}	500mg QDS ^{1D,2D} ☺ 500mg BD ^{1D,2D} ☺ 200mg stat then 100mg OD ^{2D} 300mg QDS ^{1D,2D} ☺ 500/125mg TDS ^{1D} ☺	7 days, ^{1D} if slow response, continue for a further 7 days ^{1D}
Leg ulcer PHE Venous leg ulcers	Ulcers are always colonised. ^{1C,2A+} Antibiotics do not improve healing unless active infection ^{2A+} (purulent exudate/odour; increased pain; cellulitis; pyrexia). ^{3D}	Flucloxacillin ^{5D} OR clarithromycin ^{5D}	500mg QDS ^{5D} ☺ 500mg BD ^{5D} ☺	As for cellulitis ^{5D}
Bites: CKS Bites	Human: thorough irrigation is important. Antibiotic prophylaxis is advised. ^{1A+,2D,3D} Assess risk of tetanus, rabies, ^{1A+} HIV, and hepatitis B and C. ^{3D} Cat: always give prophylaxis. ^{1A+,3D} Dog: give prophylaxis if: puncture wound; bite to hand, foot, face, joint, tendon, or ligament, ^{1A+} immunocompromised, cirrhotic, asplenic, or presence of prosthetic valve/joint. ^{2D,4A+} Penicillin allergy: Review all at 24 and 48 hours, ^{2D,3D} as not all pathogens are covered.	Prophylaxis/treatment all: co-amoxiclav ^{2D,3D} Human penicillin allergy: metronidazole ^{3D,4A+} AND clarithromycin ^{3D,4A+} Animal penicillin allergy: metronidazole ^{3D,4A+} AND doxycycline ^{3D}	375-625mg TDS ^{3D} ☺ 400mg TDS ^{2D} ☺ 250-500mg BD ^{2D} ☺ 400mg TDS ^{2D} ☺ 100mg BD ^{2D} ☺	7 days ^{3D,5D}
Scabies NHS Scabies	Treat whole body from ear/chin downwards, ^{1D,2D} and under nails. ^{1D,2D} Under 2 years/elderly: also treat face/scalp. ^{1D,2D} Home/sexual contacts: treat within 24 hours. ^{1D}	Permethrin ^{1D,2D,3A+} Permethrin allergy: malathion ^{1D}	5% cream ^{1D,2D} ☺ 0.5% aqueous liquid ^{1D} ☺	2 applications, 1 week apart ^{1D}
Mastitis CKS Mastitis and breast abscess	<i>S. aureus</i> is the most common infecting pathogen. Suspect if woman has: a painful breast; ^{2D} fever and/or general malaise; ^{2D} a tender, red breast. ^{2D} Breastfeeding: oral antibiotics are appropriate, where indicated. ^{2D,3A+} Women should continue feeding, ^{1D,2D} including from the affected breast. ^{2D}	Flucloxacillin ^{2D} Penicillin allergy: erythromycin ^{2D} OR clarithromycin ^{2D}	500mg QDS ^{2D} 250-500mg QDS ^{2D} 500mg BD ^{2D}	10-14 days ^{2D}
Dermatophyte infection: skin PHE Fungal skin and nail infections	Most cases: terbinafine is fungicidal; ^{1D} treatment time shorter than with fungistatic imidazoles. ^{1D,2A+,3A+} If candida possible, use imidazole. ^{4D} If intractable, or scalp: send skin scrapings. ^{1D} If infection confirmed: use oral terbinafine ^{1D,3A+,4D} or itraconazole. ^{2A+,3A+,5D} Scalp: oral therapy, ^{6D} and discuss with specialist. ^{1D}	Topical terbinafine ^{3A+,4D} OR topical imidazole ^{2A+,3A+} For athlete's foot: topical undecenoates ^{2A+} (eg Mycota [®]) ^{2A+}	1% OD-BD ^{2A+} ☺ 1% OD-BD ^{2A+} ☺ OD-BD ^{2A+} ☺	1-4 weeks ^{3A+} 4-6 weeks ^{2A+,3A+}
Dermatophyte infection: nail CKS Fungal nail infection	Take nail clippings; ^{1D} start therapy only if infection is confirmed. ^{1D} Oral terbinafine is more effective than oral azole. ^{1D,2A+,3A+,4D} Liver reactions 0.1 to 1% with oral antifungals. ^{3A+} If candida or non-dermatophyte infection is confirmed, use oral itraconazole. ^{1D,3A+,4D} Topical nail lacquer is not as effective. To prevent recurrence: apply weekly 1% topical antifungal cream to entire toe area. ^{6D} Children: seek specialist advice. ^{4D}	First line: terbinafine ^{1D,2A+,3A+,4D,6D} Second line: itraconazole ^{1D,3A+,4D,6D}	250mg OD ^{1D,2A+,6D} ☺ 200mg BD ^{1D,4D} ☺	Fingers: 6 weeks ^{1D,6D} Toes: 12 weeks ^{1D,6D} 1 week a month: ^{1D} Fingers: 2 courses ^{1D} Toes: 3 courses ^{1D}
Varicella zoster/ chickenpox PHE Varicella Herpes zoster/ shingles PCDS Herpes zoster	Pregnant/immunocompromised/neonate: seek urgent specialist advice. ^{1D} Chickenpox: consider aciclovir ^{2A+,3A+,4D} if: onset of rash <24 hours, ^{3A+} and one of the following: >14 years of age; ^{4D} severe pain; ^{4D} dense/oral rash; ^{4D,5B+} taking steroids; ^{4D} smoker. ^{4D,5B+} Shingles: treat if >50 years ^{5A+,7D} (PHN rare if <50 years) ^{6B+} and within 72 hours of rash, ^{9A+} or if one of the following: active ophthalmic; ^{10D} Ramsey Hunt; ^{4D} eczema; ^{4D} non-truncal involvement; ^{7D} moderate or severe pain; ^{7D} moderate or severe rash. Shingles treatment if not within 72 hours: consider starting antiviral drug up to one week after rash onset, ^{11B+} if high risk of severe shingles ^{11B+} or complications ^{11B+} (continued vesicle formation; ^{4D} older age; ^{6A+,7D,11B+} immunocompromised; ^{4D} severe pain). ^{7D,11B+}	Aciclovir ^{3A+,6A+,9A+,12B+,13A-,14A+} Second line for shingles if poor compliance: not for children: famciclovir ^{7D,13A-,15A-} OR valaciclovir ^{7D,9A+,13A-}	800mg five times daily ^{15A-} ☺ 250-500mg TDS ^{14A+} OR 750mg BD ^{14A+} 1g TDS ^{13A-} ☺	7 days ^{13A-,15A-}

Management and treatment of common infections-Antibiotic guidance for primary care

ILLNESS	GOOD PRACTICE POINTS	TREATMENT	ADULT DOSE (☺ = child doses)	DURATION OF TREATMENT
EYE INFECTIONS				
Conjunctivitis AAO Conjunctivitis	First line: bath/clean eyelids with cotton wool dipped in sterile saline or boiled (cooled) water, to remove crusting. ^{1D} Treat only if severe, ^{2A+} as most cases are viral ^{3D} or self-limiting. ^{2A+} Bacterial conjunctivitis: usually unilateral and also self-limiting. ^{2A+,3D} It is characterised by red eye with mucopurulent, not watery discharge. ^{3D} 65% and 74% resolve on placebo by days 5 and 7. ^{4A-,5A+} Second line: fusidic acid as it has less gram-negative activity. ^{6A-,7D}	First line: self-care ^{1D} Second line: chloramphenicol ^{1D,2A+,4A-,5A+} 0.5% eye drop ^{1D,2A+} OR 1% ointment ^{1D,5A+} Third line: fusidic acid 1% gel ^{2A+,5A+,6A-}	2 hourly for 2 days, ^{1D,2A+} then reduce frequency ^{1D} ☺ 3-4 times daily, ^{1D} or just at night if using eye drops ^{1D} BD ^{1D,7D} ☺	48 hours after resolution ^{2A+,7D}
Blepharitis CKS Blepharitis	First line: lid hygiene ^{1D,2A+} for symptom control, ^{1D} including: warm compresses, ^{1D,2A+} lid massage and scrubs; ^{1D} gentle washing; ^{1D} avoiding cosmetics. ^{1D} Second line: topical antibiotics if hygiene measures are ineffective after 2 weeks. ^{1D,3A+} Signs of Meibomian gland dysfunction,^{3D} or acne rosacea:^{3D} consider oral antibiotics. ^{1D}	First line: self-care ^{1D} Second line: Chloramphenicol ^{1D,2A+,3A-} Third line: oral oxytetracycline ^{1D,3D} OR oral doxycycline ^{1D,2A+,3D}	1% ointment BD ^{2A+,3D} ☺ 500mg BD ^{3D} ☺ 250mg BD ^{3D} ☺ 100mg OD ^{3D} ☺ 50mg OD ^{3D} ☺	6 week trial ^{3D} 4 weeks (initial) ^{3D} 8 weeks (maint) ^{3D} 4 weeks (initial) ^{3D} 8 weeks (maint) ^{3D}

Summary table – Suspected dental infections in primary care (outside dental setting)

Derived from the Scottish Dental Clinical Effectiveness Programme (SDCEP) 2013 Guidelines					
This guidance is not designed to be a definitive guide to oral conditions, as GPs should not be involved in dental treatment. Patients presenting to non-dental primary care services with dental problems should be directed to their regular dentist, or if this is not possible, to the NHS 111 service (in England), who will be able to provide details of how to access emergency dental care.					
ILLNESS	GOOD PRACTICE POINTS	TREATMENT	ADULT DOSE (☺ = child doses)	DURATION OF TREATMENT	
<i>Note: Antibiotics do not cure toothache.^{1D} First line treatment is with paracetamol^{1D} and/or ibuprofen;^{1D} codeine is not effective for toothache.^{1D}</i>					
Mucosal ulceration and inflammation (simple gingivitis) SDCEP Dental problems	Temporary pain and swelling relief can be attained with saline mouthwash. ^{1D} Use antiseptic mouthwash if more severe, ^{1D} and if pain limits oral hygiene to treat or prevent secondary infection. ^{1D,2A-} The primary cause for mucosal ulceration or inflammation (aphthous ulcers, ^{1D} oral lichen planus; ^{1D} herpes simplex infection; ^{1D} oral cancer) ^{1D} needs to be evaluated and treated. ^{1D}	Saline mouthwash ^{1D} Chlorhexidine 0.12-0.2% ^{1D,2A-,3A+,4A+} (do not use within 30mins of toothpaste) ^{1D} Hydrogen peroxide 6% ^{5A-} (spit out after use) ^{1D}	½ tsp salt in warm water ^{1D} ☺ 1 min BD with 10mL ^{1D} ☺ 2-3 mins BD-TDS with 15ml in ½ glass warm water ^{1D} ☺	Always spit out after use ^{1D} Use until lesions resolve ^{1D} /less pain allows for oral hygiene ^{1D}	
Acute necrotising ulcerative gingivitis	Refer to dentist for scaling and hygiene advice. ^{1D,2D} Antiseptic mouthwash if pain limits oral hygiene. ^{1D} Commence metronidazole in the presence of systemic signs and symptoms. ^{1D,2D,3B-,4B+,5A-}	Chlorhexidine 0.12-0.2% ^{1D} OR hydrogen peroxide 6% ^{1D} Metronidazole ^{1D,3B-,4B+,5A-}	See above dosing for mucosal ulceration ^{6D} 400mg TDS ^{1D,2D} ☺	Until pain allows for oral hygiene ^{6D} 3 days ^{1D,2D}	
Pericoronitis SDCEP Dental problems	Refer to dentist for irrigation and debridement. ^{1D} If persistent swelling or systemic symptoms, ^{1D} use metronidazole ^{1D,2A+,3B+} or amoxicillin. ^{1D,3B+} Use antiseptic mouthwash if pain and trismus limit oral hygiene. ^{1D}	Metronidazole ^{1D,2A+,3B+} OR amoxicillin ^{1D,3B+} Chlorhexidine 0.2% ^{1D} OR hydrogen peroxide 6% ^{1D}	400mg TDS ^{1D} ☺ 500mg TDS ^{1D} ☺ See above dosing for mucosal ulceration ^{1D}	3 days ^{1D,2A+} 3 days ^{1D} Until pain allows for oral hygiene ^{1D}	
Dental abscess SDCEP Dental problems	Regular analgesia should be the first option ^{1A+} until a dentist can be seen for urgent drainage, ^{1A+,2B-,3A+} as repeated courses of antibiotics for abscesses are not appropriate. ^{1A+,4A+} Repeated antibiotics alone, without drainage, are ineffective in preventing the spread of infection. ^{1A+,5C} Antibiotics are only recommended if there are signs of severe infection, ^{3A+} systemic symptoms, ^{1A+,2B-,4A+} or a high risk of complications. ^{1A+} Patients with severe odontogenic infections (cellulitis, ^{1A+,3A+} plus signs of sepsis; ^{3A+,4A+} difficulty in swallowing; ^{6D} impending airway obstruction) ^{6D} should be referred urgently for hospital admission to protect airway, ^{6D} for surgical drainage ^{3A+} and for IV antibiotics. ^{3A+} The empirical use of cephalosporins, ^{6D} co-amoxiclav, ^{6D} clarithromycin, ^{6D} and clindamycin ^{6D} do not offer any advantage for most dental patients, ^{6D} and should only be used if there is no response to first line drugs. ^{6D}	If pus is present, refer for drainage, ^{1A+,2B-} tooth extraction, ^{2B-} or root canal. ^{2B-} Send pus for investigation. ^{1A+} If spreading infection ^{1A+} (lymph node involvement ^{1A+,4A+} or systemic signs, ^{1A+,2B-,4A+} ie fever ^{1A+} or malaise) ^{4A+} ADD metronidazole. ^{6D,7B+} Use clarithromycin in true penicillin allergy ^{6D} and, if severe, refer to hospital. ^{3A+,6D}	Amoxicillin ^{6D,8B+,9C,10B+} OR phenoxymethylpenicillin ^{11B-} Metronidazole ^{6D,8B+,9C} Penicillin allergy: clarithromycin ^{8D}	500mg-1g TDS ^{6D} ☺ 500mg-1g QDS ^{6D} ☺ 400mg TDS ^{6D} ☺ 500mg BD ^{6D} ☺	Up to 5 days; ^{6D,10B+} review at 3 days ^{9C,10B+}

Management and treatment of common infections-Antibiotic guidance for primary care

GRADING OF GUIDANCE RECOMMENDATIONS

The strength of each recommendation is qualified by a letter in parenthesis. This is an altered version of the grading recommendation system used by **SIGN**.

STUDY DESIGN	RECOMMENDATION GRADE
Good recent systematic review and meta-analysis of studies	A+
One or more rigorous studies; randomised controlled trials	A-
One or more prospective studies	B+
One or more retrospective studies	B-
Non-analytic studies, eg case reports or case series	C
Formal combination of expert opinion	D

This guidance was originally produced in 1999 by the South West GP Microbiology Laboratory Use Group, in collaboration with the Cheltenham & Tewkesbury Prescribing Group, the Association of Medical Microbiologists, general practitioners, nurses and specialists in the field, as part of the S&W Devon Joint Formulary Initiative. It has since been modified by the PHLS South West Antibiotic Guidelines Project Team, PHLS Primary Care Co-Ordinators, and members of the Clinical Prescribing Sub-Group of the Standing Medical Advisory Committee on Antibiotic Resistance. This guidance underwent a full systematic review and update in 2017, with input from Professor Clodna McNulty; Dr Teh Li Chin; the Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI); the British Society for Antimicrobial Chemotherapy (BSAC); the British Infection Association (BIA); the Royal College of General Practitioners (RCGP); the Royal College of Nursing (RCN); general practitioners; specialists in the field; and patient representatives. Full consensus of the recommendations made was given by all guidance developers and reviewers prior to the dissemination of this guidance. All comments received have been reviewed and incorporated into the guidance, where appropriate. For detailed information regarding the comments provided and action taken, please email sarah.alton@phe.gov.uk. Public Health England works closely with the authors of the **Clinical Knowledge Summaries**.

This guidance should not be used in isolation; it should be supported with patient information about safety netting, delayed/back-up antibiotics, infection severity and usual duration, clinical staff education, and audits. Materials are available on the RCGP **TARGET** website.

If you would like to receive a copy of this guidance with the most recent changes highlighted, please email sarah.alton@phe.gov.uk.

For detailed information regarding the search strategies implemented and full literature search results, please email sarah.alton@phe.gov.uk.

Management and treatment of common infections-Antibiotic guidance for primary care

GENERAL COMMENTS ON SELECTED ANTIBIOTICS AND DOSES RECOMMENDED

Clarithromycin:

This guidance recommends clarithromycin as it has fewer side-effects than erythromycin, greater compliance with a twice daily regimen rather than a four times daily regimen, and generic tablets are of similar cost. Azithromycin may be associated with greater development of resistance than other macrolides, as it has a greater half-life in comparison to clarithromycin and erythromycin so may provide more opportunity for resistant organisms to develop.

Amoxicillin and metronidazole:

The Scottish Dental Clinical Effectiveness Programme 2011 and other guidance sometimes recommend doses of 250mg amoxicillin or 200mg metronidazole when antimicrobials are considered appropriate. This guidance recommends a higher dose of 500mg amoxicillin and 400mg metronidazole, as it is important to have sufficient concentrations of antimicrobial at the site of infection. For β -lactams, such as amoxicillin, the killing effect of the antibiotic is time-dependent (ie the time period for which concentrations of the antibiotic at the site of infection are above the minimum inhibitory concentration (MIC) is most important for that antibiotic to inhibit a particular bacteria), and amoxicillin 500mg TDS is more likely to attain this.

For metronidazole, the killing effect is dose-dependent (ie it is the maximum concentration attained above the MIC that is most important).^{1B+} Metronidazole has simple first-order kinetics, so doubling the dose doubles the plasma concentrations at the site of infection.^{2D} Oral metronidazole is well tolerated and the side-effects reported at doses of 400mg TDS are either very rare or unknown.^{3D} Metronidazole distributes well throughout the body with non-significant differences in the concentrations attained in saliva and crevice fluid compared to plasma.^{4B+} Metronidazole has a volume of distribution of 0.5-1.0l/kg, so increasing body mass will decrease plasma concentrations.^{5D} AUC/MIC>70 is only attainable against *Bacteroides fragilis* with a 400mg dose, and mouth anaerobes have similar susceptibility to this.^{6B-} Evidence suggests that metronidazole 250mg TDS results in concentrations exceeding the MICs of isolated pathogens in crevice fluid. However, as it is more desirable to achieve crevice fluid concentrations several times that of the measured MICs, and the BMI of patients has increased since these trials were undertaken, this guidance recommends metronidazole 400mg three times daily.^{7B+}

References and rationale – Infections in primary care

Upper Respiratory Tract Infections

General references:

1. National Institute for Health and Care Excellence (NICE). Respiratory tract infections – antibiotic prescribing. 2008 Jul. Available from:

<https://www.nice.org.uk/guidance/cg69/evidence/full-guideline-196853293>.

RATIONALE: A NICE guideline providing a clear overview of which antibiotic prescribing strategies may be appropriate for different upper respiratory tract infections. This guideline states that a no antibiotic prescribing strategy or a delayed antibiotic prescribing strategy should be negotiated with patients who have the following conditions: acute otitis media; acute sore throat/acute pharyngitis/acute tonsillitis; common cold; acute rhinosinusitis; acute cough/acute bronchitis. Depending on patient preference and clinical assessment of severity, patients in the following subgroups can be considered for immediate antibiotics in addition to the reasonable options of a no antibiotic strategy or safety netting advice with a back-up/delayed prescribing strategy: bilateral acute otitis media in children under two years; acute otitis media in children with otorrhoea; acute sore throat/acute tonsillitis, when three or four of the Centor criteria are present. For all antibiotic prescribing strategies, patients should be given advice about the usual natural history of the illness, including the average total length of the illness (before and after seeing the doctor): acute otitis media (four days); acute sore throat/acute pharyngitis/acute tonsillitis (one week); common cold (one and a half weeks); acute rhinosinusitis (two and a half weeks); acute cough/acute bronchitis (three weeks). Advice should also be given about managing symptoms (particularly analgesics and antipyretics), including discomfort caused by fever. When a back-up/delayed antibiotic prescribing strategy is adopted, patients should be offered the following: reassurance that antibiotics are not needed immediately because they are likely to make little difference to symptoms and may have side-effects; advice about using the back-up/delayed prescription if symptoms are not starting to settle in accordance with the expected course of the illness, or if a significant worsening of symptoms occurs; advice about re-consulting if there is a significant worsening of symptoms despite using the delayed prescription; a back-up/delayed prescription with instructions, which can either be given to the patient or left at an agreed location to be collected at a later date.

2. Royal College of General Practitioners (RCGP). *Managing Acute Respiratory Tract Infections*. Available from: <http://www.rcgp.org.uk/courses-and-events/online-learning/ole/managing-acute-respiratory-tract-infections.aspx> [Accessed: 25th July, 2016].

RATIONALE: An RCGP webpage hosting a free two-hour training module on managing acute respiratory tract infections for continued professional development. This series of

Management and treatment of common infections-Antibiotic guidance for primary care

training modules enables clinical staff to improve the care provided to patients presenting with: acute ear pain; acute sore throat; sinusitis; acute cough. The module equals two hours towards CPD, and can be imported into the RCGP Revalidation portfolio.

Influenza:

1. National Institute for Health and Care Excellence (NICE). Amantadine, oseltamivir and zanamivir for the treatment of influenza. 2009 Feb. Available from:

<https://www.nice.org.uk/guidance/TA168>.

RATIONALE: A NICE guideline suggesting that oseltamivir and zanamivir are possible treatments for people with influenza if all of the following apply: the person is in an at risk group; the person has a flu-like illness and can start treatment within 48 hours (36 hours for zanamivir treatment in children) of the first sign of symptoms; the influenza virus is known to be going around; it is likely that a flu-like illness has been caused by the influenza virus. Healthcare professionals should discuss the choice of oseltamivir or zanamivir with the person being offered the treatment. The decision should take into account which antiviral the person would prefer, and any possible unwanted effects. If all else is equal, the cheapest antiviral should be used. If there is an outbreak of flu-like illness in a long-term residential or nursing home, oseltamivir and zanamivir may be offered to treat residents in at-risk groups who have symptoms of influenza. This could happen even if the influenza virus is not present in the wider community outside the home, but the healthcare team should be sure that the illness is influenza. This guideline also suggests that the recommended dose of oseltamivir for adolescents and adults is 75mg twice daily for five days.

2. Tappenden P, Jackson R, Cooper K, Rees A, Simpson E, Read R et al. Amantadine, oseltamivir and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67): a systematic review and economic evaluation. *Health Technol Assess*. 2009 Feb; 13(11):1-246. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/19215705>.

RATIONALE: A systematic review and meta-analysis of 22 randomised controlled trials and one unpublished report. Eight RCTs were included for amantadine, six were included for oseltamivir, and nine were included for zanamivir. The study quality was variable, and gaps in the evidence limited the assessment of the clinical effectiveness of the interventions. For seasonal prophylaxis, there was limited evidence for the efficacy of amantadine in preventing symptomatic laboratory-confirmed influenza in healthy adults (RR 0.40; 60% reduction; 95% CI 0.08 to 2.03). Oseltamivir was effective in preventing SLCI, particularly when used in at risk elderly subjects (RR 0.08; 92% reduction; 95% CI 0.01 to 0.63). The preventative efficacy of zanamivir was most notable in at risk adults and adolescents (RR 0.17; 83% reduction; 95% CI 0.07 to 0.44), and healthy and at risk elderly subjects (RR 0.20; 80% reduction; 95% CI 0.02 to 1.72). The authors conclude that all three interventions show some efficacy for seasonal and post-exposure prophylaxis. However, weaknesses and gaps in the clinical evidence base are directly relevant to the interpretation of the health economic model, and rendered the use of advanced statistical analyses inappropriate.

Management and treatment of common infections-Antibiotic guidance for primary care

3. Wellcome Trust: The Academy of Medical Sciences. Use of neuraminidase inhibitors in influenza. 2015 Oct. Available from: <https://acmedsci.ac.uk/file-download/38069-561595082cd83.pdf>.
RATIONALE: A Wellcome Trust guideline recommending that if NIs are to be used in the treatment of influenza, treatment should commence within 48 hours of the first onset of symptoms. The authors conclude that, while the importance of initiating treatment as early as possible in those who do go on to develop severe disease is clear, the use of treatment in other scenarios must rely on clinical judgement, particularly because identifying these patients within 48 hours is not always possible.
4. Public Health England (PHE). PHE guidance on use of antiviral agents for the treatment and prophylaxis of seasonal influenza. 2016 Oct. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/580509/PHE_guidance_antivirals_influenza_2016_2017.pdf.
RATIONALE: A PHE guideline advising that influenza is a viral infection affecting the lungs and airways. Complications include bacterial pneumonia and can be life threatening, especially in older people or those with certain underlying health conditions. It occurs most often during the winter in the UK, and peaks between January and March. There are two types of influenza: influenza A and influenza B, with influenza B causing a milder illness most often seen in children. PHE advise that risk factors for complicated influenza include: chronic neurological, hepatic, renal, pulmonary and chronic cardiac disease; diabetes mellitus; severe immunosuppression; age over 65 years; pregnancy (including up to two weeks' post-partum); children under six months of age; morbid obesity (BMI>40).
5. Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children (Review). *Cochrane Database Syst Rev*. 2014 Apr; 10(4):1-560. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008965.pub4/epdf>.
RATIONALE: A systematic review of 107 clinical study reports aiming to describe the potential benefits and harms of NIs for influenza in all age groups. The results indicate that treatment trials with oseltamivir or zanamivir do not settle the question of whether the complications of influenza (such as pneumonia) are reduced, because of a lack of diagnostic definitions. The authors conclude that the balance between benefits and harms should be considered when making decisions about the use of both NIs for either the prophylaxis or treatment of influenza.
6. Muthuri SG, Venkatesan S, Myles PR, Leonardi-Bee J, Al Khuwaitir TS, Al Mamun A et al. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. *Lancet Respir Med*. 2014 May; 2(5):395-404. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24815805>.
RATIONALE: A meta-analysis including data from 29,234 patients from 78 studies of patients admitted to hospital between January 2nd, 2009, and March 14th, 2011. Compared with no treatment, neuraminidase inhibitor treatment (irrespective of timing)

Management and treatment of common infections-Antibiotic guidance for primary care

was associated with a reduction in mortality risk (adjusted odds ratio 0.81, 19% reduction; 95% CI 0.70 to 0.93; $p=0.0024$). Compared with later treatment, early treatment (within two days of symptom onset) was associated with a reduction in mortality risk (OR 0.48, 52% reduction; 95% CI 0.41 to 0.56; $p<0.0001$), as was early treatment versus no treatment (OR 0.50, 50% reduction; 95% CI 0.37 to 0.67; $p<0.0001$). These associations with reduced mortality risk were less pronounced and not significant in children. The authors conclude that they advocate the early instigation of neuraminidase inhibitor treatment in adults admitted to hospital with suspected or proven influenza infection.

Acute sore throat:

1. Howie JGR, Foggo BA. Antibiotics, sore throats and rheumatic fever. *J R Coll Gen Pract*. 1985 May; 35(274):223-224. Available from:
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1960005/pdf/jroyalcgprac00161-0008.pdf>.
RATIONALE: A Scottish retrospective study confirming the low incidence of rheumatic fever within the UK (0.6 per 100,000 children per year). The risk of developing rheumatic fever was not reduced in this study by treating acute sore throat with antibiotics. This supports the recommendation that, in the UK, antibiotics should not be used to prevent non-suppurative complications of acute sore throat.
2. Scottish Intercollegiate Guidelines Network (SIGN). Management of sore throat and indications for tonsillectomy: a national clinical guideline. 2010 Apr. Available from:
<http://www.sign.ac.uk/assets/sign117.pdf>.
RATIONALE: A SIGN guideline recommending that the Centor clinical prediction score should be used to assist the decision on whether or not to prescribe an antibiotic. This guideline also states that throat swabs should not be carried out routinely in primary care, and that antibiotics should not be used to secure symptomatic relief in sore throat.
3. Spinks A, Glasziou PP, Del Mar CB. Antibiotics for sore throat (Review). *Cochrane Database Syst Rev*. 2013 Nov; 5(11):1-76. Available from:
<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000023.pub4/epdf>.
RATIONALE: A systematic review and meta-analysis including 27 RCTs and 12,835 cases of sore throat. Without antibiotics, 40% of cases resolved in three days, and 82% resolved in seven days. However, antibiotics do confer relative benefits. Throat soreness and fever were reduced by about half compared to placebo. To resolve one sore throat at day three the NNT is less than six, and at day seven the NNT is 21. Antibiotics shorten the duration of symptoms by about 16 hours overall.
4. Little P, Moore M, Hobbs FDR, Mant D, McNulty CA, Williamson I et al. PRImary care Streptococcal Management (PRISM) study: identifying clinical variables associated with Lancefield group A β -haemolytic streptococci and Lancefield non-Group A streptococcal throat infections from two cohorts of patients presenting with an acute sore throat. *BMJ*. 2013 Oct; 3:1-7. Available from: <http://bmjopen.bmj.com/content/3/10/e003943.full.pdf+html>.
RATIONALE: A diagnostic cohort study of 606 patients in cohort one and 517 patients in

Management and treatment of common infections-Antibiotic guidance for primary care

cohort two conducted in UK general practices. This study focuses on the association between features of acute sore throat and the growth of streptococci from culturing a throat swab in patients aged five years or over presenting with acute sore throat. This study was designed to assess not only the validation characteristics of widely available antigen tests, but also which clinical variables were associated with streptococcal infection, specifically Lancefield groups A β -haemolytic, C and G streptococci. FeverPAIN was found to show no significant differences between the percentages of observed and predicted presence of streptococci, whereas Centor showed significant differences of observed and predicted presence of streptococci at low scores. This study provides evidence to confirm that streptococcal sore throat is common in primary care, and that the best predictors of streptococcal infection may not include some of the features traditionally used. Traditional scoring systems, such as Centor, may have limited clinical utility in identifying individuals who have a low likelihood of streptococcal infection and, therefore, do not need antibiotics.

5. Little P, Hobbs FDR, Moore M, Mant D, Williamson I, McNulty CA et al. Clinical score and rapid antigen detection test to guide antibiotic use for sore throats: randomised controlled trial of PRISM (primary care streptococcal management). *BMJ*. 2013 Oct; 347:1-10. Available from: <http://www.bmj.com/content/bmj/347/bmj.f5806.full.pdf>.

RATIONALE: A multicentre randomised controlled trial in UK general practices designed to determine the effect of clinical scores that predict streptococcal infection or rapid streptococcal antigen detection tests, compared with delayed antibiotic prescribing in patients aged three years or over with acute sore throat. This study compared three strategies for limiting or targeting antibiotics using a validated FeverPAIN score in 631 patients with sore throat. The three strategies were: delayed antibiotic prescribing, the use of a clinical score designed to identify streptococcal infection, and the targeted use of rapid antigen tests according to clinical score. Findings suggest that, across a range of practitioners and practices, use of either the FeverPAIN clinical score or the FeverPAIN score with a rapid antigen test is likely to moderately improve symptom control and reduce antibiotic use. The addition of the rapid antigen test to the FeverPAIN score gave no clear advantages compared with the use of the FeverPAIN score alone. Use of antibiotics in the clinical score group (60/161) was 29% lower (adjusted risk ratio 0.71; 95% CI 0.50 to 0.95; $p=0.02$) and in the rapid antigen test group (58/164) was 27% lower (RR 0.73; 95% CI 0.52 to 0.98; $p=0.03$). There were no significant differences in complications or consultations. The authors therefore suggest the use of the following system. FeverPAIN score of 0-1: only 13-18% have streptococcus; close to background carriage and therefore a no antibiotic strategy is appropriate with discussion. FeverPAIN score of 2-3: 34-40% have streptococcus, therefore a back-up/delayed antibiotic is appropriate with discussion. FeverPAIN score of 4-5: 62-65% have streptococcus, therefore consider immediate antibiotic if symptoms are severe.

6. National Institute for Health and Care Excellence (NICE). Respiratory tract infections – antibiotic prescribing. 2008 Jul. Available from: <https://www.nice.org.uk/guidance/cg69/evidence/full-guideline-196853293>.

Management and treatment of common infections-Antibiotic guidance for primary care

RATIONALE: A NICE guideline including evidence from three trials that used a delayed-antibiotic strategy for treating a number of upper respiratory tract infections, including: acute otitis media; acute sore throat/acute pharyngitis/acute tonsillitis; common cold; acute rhinosinusitis; acute cough/acute bronchitis. Two studies in the USA used a two-day delayed antibiotic strategy and a UK primary care study used a three-day delayed antibiotic strategy. Findings indicate that a delayed antibiotic prescribing strategy of a two or three day duration is appropriate for patients presenting with a number of upper respiratory tract infections.

- Peterson I, Johnson AM, Islam A, Duckworth G, Livermore DM, Hayward AC. Protective effect of antibiotics against serious complications of common respiratory tract infections: retrospective cohort study with the UK General Practice Research Database. *BMJ*. 2007 Nov; 335:992-997. Available from: <http://www.bmj.com/content/bmj/335/7627/982.full.pdf>.

RATIONALE: A UK retrospective cohort study of over three million episodes, looking at the extent to which antibiotics prevent serious suppurative complications in self-limiting upper respiratory tract infections. To prevent an episode of quinsy, the NNT of acute sore throat with antibiotics is >4000. This supports the recommendation that, in the UK, antibiotics should not be used to prevent suppurative complications of acute sore throat. The majority of patients with quinsy develop the condition rapidly and do not present with acute sore throat.

- The European Society for Clinical Microbiology and Infectious Diseases (ESCMID) Sore Throat Guideline Group, Pelucchi C, Grigoryan L, Galeone C, Esposito S, Huovinen P et al. Guideline for the management of acute sore throat. *Clin Microbiol Infect*. 2012 Apr; 18(1):1-28. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22432746>.

RATIONALE: An ESCMID guideline outlining the most effective practice in diagnosing and treating patients with acute sore throat. If antibiotics are indicated, penicillin V, twice or three times daily for ten days, is recommended. At present, the authors conclude that there is not enough evidence to indicate a shorter course of treatment.

- Altamimi S, Khalil A, Khalaiwi KA, Milner RA, Pusic MV, Al Othman MA. Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children (Review). *Cochrane Database Syst Rev*. 2012 Aug; 15(8):1-58. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004872.pub3/epdf>.

RATIONALE: A systematic review and meta-analysis of 20 studies including over 13,000 cases, showing that short-course broad-spectrum antibiotics (including five days clarithromycin) are as efficacious as ten days penicillin for sore throat symptom treatment and GABHS eradication. Ten days phenoxymethylpenicillin remains the treatment of choice for sore throat. Evidence suggests that the use of broader spectrum antibiotics will drive the emergence of bacterial resistance, will increase the risk of developing CDAD, and are associated with more adverse drug reactions. Five days clarithromycin or erythromycin should be reserved for those with true penicillin allergy.

- Anderson JT, Peterson M, Jimenez-Solem E, Broedbaek K, Anderson NL, Torp-Pederson C

Management and treatment of common infections-Antibiotic guidance for primary care

et al. Clarithromycin in early pregnancy and the risk of miscarriage and malformation: a register based nationwide cohort study. *PLoS One*. 2013 Jan; 8(1):1-6. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3534696/>.

RATIONALE: A nationwide cohort study of all women in Denmark with a known conception between 1997 and 2007. 931,504 pregnancies were identified, of which there were 705,837 live births, 77,553 miscarriages, and 148,114 induced abortions. Of the 401 women who redeemed a prescription of clarithromycin in the first trimester, 40 (10%) experienced a miscarriage, and among the live born, nine (3.6%) had offspring with malformations. The hazard ratio of having a miscarriage after exposure to clarithromycin was 1.56 (95% CI 1.14 to 2.13). There was no increased hazard of having a miscarriage when being exposed to penicillin or erythromycin, and there was no increased prevalence (OR 1.03; 95% CI 0.52 to 2) of having offspring with malformations after exposure to clarithromycin. The authors conclude that there is an increased hazard of miscarriage, but no increased prevalence of having offspring with malformations among women redeeming a prescription of clarithromycin in early pregnancy. However, further research is required to explore the possible effect of treatment indication on the associations found.

11. UK Teratology Information Service (UKTIS). Use of clarithromycin in pregnancy. 2012 Sep. Available from: <http://www.medicinesinpregnancy.org/bumps/monographs/USE-OF-CLARITHROMYCIN-IN-PREGNANCY/>.

RATIONALE: There are few published data on the use of clarithromycin in human pregnancy, but one study has reported an increased risk of spontaneous abortion after in utero exposure. To date, exposure to clarithromycin during pregnancy has not been associated with teratogenic effects. Associations with an increased incidence of cardiovascular defects and pyloric stenosis have however been made with macrolides as a class, though causality has not been conclusively established. If treatment is required, penicillins along with cephalosporins may be used if clinically appropriate. If a macrolide antibiotic is required in pregnancy, erythromycin would be considered the preferred agent as there is more data on its use. Use of the newer macrolides, such as clarithromycin, should be reserved for compelling indications.

12. Muanda FT, Sheehy O, Berard A. Use of antibiotics during pregnancy and risk of spontaneous abortion. *CMAJ*. 2017 May; 189(17):625-633. Available from: <http://www.cmaj.ca/content/189/17/E625>.

RATIONALE: A nested case-control study within the Quebec Pregnancy Cohort between 1998 and 2009, aiming to quantify the association between antibiotic exposure during pregnancy and risk of spontaneous abortion. Spontaneous abortion was defined as having a diagnosis or procedure related to spontaneous abortion before the twentieth week of pregnancy. Use of antibiotics was defined by filled prescriptions between the first day of gestation and the index date. Results indicated that azithromycin (OR 1.65; 95% CI 1.34 to 2.02), clarithromycin (OR 2.35; 95% CI 1.90 to 2.91), metronidazole (OR 1.70; 95% CI 1.27 to 2.26), sulphonamides (OR 2.01; 95% CI 1.36 to 2.97), and tetracyclines (OR 2.59; 95% CI 1.97 to 3.41) were associated with an increased risk of spontaneous abortion. The authors conclude that the use of macrolides (excluding erythromycin), quinolones,

Management and treatment of common infections-Antibiotic guidance for primary care

tetracyclines, sulphonamides, and metronidazole should be avoided during early pregnancy due to the increased risk of spontaneous abortion. Erythromycin may be used as an alternative treatment for pregnant women.

13. Lan AJ, Colford JM, Colford JM Jr. The impact of dosing frequency of the efficacy of 10-day penicillin or amoxicillin therapy for streptococcal tonsillopharyngitis: a meta-analysis. *Pediatrics*. 2000 Feb; 105(2):19-26. Available from:

<http://pediatrics.aappublications.org/content/pediatrics/105/2/e19.full.pdf>.

RATIONALE: A meta-analysis providing evidence that BD dosing with phenoxymethylpenicillin is as effective as QDS in treating GABHS. However, expert opinion is that phenoxymethylpenicillin should be dosed QDS for severe infections in order to optimise therapeutic drug concentration. This is because the killing effect of penicillins (eg amoxicillin) is time-dependent, and it is therefore important to keep the drug concentration above the MIC for a long period of time, to improve eradication of streptococci, and to reduce the development of resistance. This is better attained with a QDS dosing regimen, as phenoxymethylpenicillin has a short half-life.

14. Schwartz RH, Wientzen RL, Pedreira F, Feroli EJ, Mella GW, Guandolo VL. Penicillin V for group A streptococcal pharyngotonsillitis. A randomized trial of seven vs ten days' therapy. *JAMA*. 1981 Oct; 246(16):1790-1795. Available from:

<https://www.ncbi.nlm.nih.gov/pubmed/6792379>.

RATIONALE: A randomised controlled trial, including 191 middle-class children aged between one and 18 years, demonstrating that a 10 day course of oral phenoxymethylpenicillin is better than a seven day course, in terms of resolution of symptoms and eradication of GABHS. 96 patients were randomly assigned to seven days penicillin therapy, and 95 were assigned to ten days treatment. Symptomatic recurrence was higher with seven days treatment (23%) than with 10 days treatment (12%).

15. Moore M, Stuart B, Hobbs FR, Butler CC, Hay AD, Campbell J et al. Influence of the duration of penicillin prescriptions on outcomes for acute sore throat in adults: the DESCARTE prospective cohort study in UK general practice. *Br J Gen Pract*. 2017 Sep; 67(662):623-633. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/28808076>.

RATIONALE: A prospective study, providing a valuable insight into the real-world medical management of adult patients presenting to their GP with acute sore throat. Around two-thirds of patients were treated with antibiotics, and three-quarters of these received phenoxymethylpenicillin. The authors evaluated outcomes for patients grouped according to the duration of their antibiotic prescription. The proportion of patients who reconsulted their GP within the following month due to new or worsening symptoms was 15.2% in the five day group (n=1,449), 13.9% in the seven day group (n=4,135) and 12.2% in the ten day group (n=1,620). This suggests that 33 patients would have to be treated with a ten day course rather than a five day course to avoid one reconsultation. When the results were adjusted for the severity of symptoms, and other risk factors at presentation, the differences between course lengths were not statistically significant; the duration of moderately bad or worse symptoms was similar regardless of the course length of

Management and treatment of common infections-Antibiotic guidance for primary care

antibiotic treatment. For patients more likely to have a Streptococcal infection (FeverPAIN score of three or above at presentation) the unadjusted reconsultation rate was 15.9% (56/353) in the five day treatment group, and 13.6% (97/712) in the ten day treatment group. This represents an NNT of 43 to avoid one reconsultation by treating this group of higher risk patients for ten days, rather than five days. The argument for five days, therefore, is compelling, even in this higher risk group. A randomised controlled trial of different course lengths (including antibiotic resistance outcomes) is still required to definitively answer the question of which course length is optimal, but in the meantime, this study provides reassurance to clinicians electing to prescribe a shorter antibiotic course to relieve symptoms of acute sore throat. Other useful information from this study is that complication rates were low (around 1% within four weeks), and antibiotics other than phenoxymethylpenicillin (amoxicillin; erythromycin) were associated with a greater risk of reconsultation.

Scarlet fever:

1. Public Health England (PHE). Interim guidelines for the public health management of scarlet fever outbreaks in schools, nurseries and other childcare settings. 2014 Apr. Available from: <https://www.gov.uk/government/publications/scarlet-fever-managing-outbreaks-in-schools-and-nurseries>.

RATIONALE: A PHE guideline stating that scarlet fever is a common childhood infection caused by *Streptococcus pyogenes* (GAS). Under some circumstances GAS can cause non-invasive infections, such as: pharyngitis; impetigo; scarlet fever. On rare occasions they can cause severe disease, including: streptococcal toxic shock syndrome (TSS); necrotising fasciitis; invasive GAS (iGAS) infection. Scarlet fever was once a dangerous disease in the UK, but antibiotic treatment means it is now much less serious. Around 3,000-4,000 cases are diagnosed each year in England, with 80% occurring in children under ten years of age. It is most common in children between the ages of two and eight years, with four year olds most likely to develop the illness. Routine national surveillance data for invasive and non-invasive GAS infections suggests a cyclical pattern, with higher incidence peaks evident in notifications approximately every four years. The incidence of invasive disease tends to mirror that of superficial manifestations of GAS infection in many, but not all, years. As such, monitoring scarlet fever cases nationally can provide an early warning of increases in invasive disease. Seasonal trends show that increased levels of GAS infection typically occur between December and April, with peak incidence usually in March. The symptoms of scarlet fever are non-specific in early illness and may include sore throat, headache, fever, nausea, and vomiting. After 12 to 48 hours, the characteristic red, generalised pinhead rash develops, typically first appearing on the chest and stomach, rapidly spreading to other parts of the body, giving the skin a sandpaper-like texture. On more darkly-pigmented skin, the scarlet rash may be harder to spot, although the sandpaper-like texture should be present. Patients typically have flushed cheeks and pallor around the mouth, which may be accompanied by a “strawberry tongue”. During convalescence, peeling of the skin occurs at the tips of fingers and toes, and less often over wide areas of the trunk and limbs. Although scarlet fever is usually a

Management and treatment of common infections-Antibiotic guidance for primary care

mild illness, patients can develop complications, such as: ear infection; throat abscess (quinsy); pneumonia; sinusitis; meningitis in the early stages; acute glomerulonephritis in the later stages; acute rheumatic fever in the later stages. Prompt treatment with appropriate antibiotics significantly reduces the risk of complications developing. Schools, nurseries, and other childcare settings have been the focus for clusters of iGAS disease, especially where there are concomitant outbreaks of chickenpox and GAS infection. Evidence suggests that chickenpox is the most common risk factor for iGAS disease in children. Other individuals at risk are immunocompromised people, such as those with diabetes, or women in the puerperal period.

2. Clinical Knowledge Summaries (CKS). Scarlet fever. 2015 Oct. Available from: <http://cks.nice.org.uk/scarlet-fever#!topicsummary>.

RATIONALE: A CKS guideline stating that scarlet fever most commonly affects children of school age, peaking at four years of age, and that it is usually a mild, self-limiting illness, which can be managed with analgesia. This guideline also suggests that phenoxymethylpenicillin, amoxicillin, and azithromycin are appropriate antibiotics.

3. Casey JR, Pichichero ME. Metaanalysis of short course antibiotic treatment for group a streptococcal tonsillopharyngitis. *Pediatr Infect Dis J*. 2005 Oct; 24(10):909-917. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16220091>.

RATIONALE: A meta-analysis of 22 trials, involving 7,470 patients. Trials were grouped by a short-course of cephalosporins (n=14), macrolides (other than azithromycin) (n=6), and penicillin (n=2). Cephalosporin trials were further grouped by the comparator, penicillin, or the same cephalosporin. Short-course cephalosporin treatment was superior for bacterial cure rate, compared with ten days' penicillin (OR 1.47; 95% CI 1.06 to 2.03). For trials with short-course macrolide therapy (OR 0.79; 21% reduction; 95% CI 0.59 to 1.06), neither the macrolides nor the ten day comparators showed superiority for bacterial cure rate. Short-course penicillin therapy was inferior in achieving bacterial cure versus ten days of penicillin (OR 0.29; 71% reduction; 95% CI 0.13 to 0.63). Clinical cure rates mirrored bacteriological cure rates. The authors conclude that superior cure rates can be achieved with shorter courses of cephalosporins, but five days is inferior to ten days with penicillin.

4. Falagas ME, Vouloumanou EK, Matthaïou DK, Kapaskelis AM, Karageorgopoulos DE. Effectiveness and safety of short-course vs long-course antibiotic therapy for group a beta hemolytic streptococcal tonsillopharyngitis: a meta-analysis of randomized trials. *Mayo Clin Proc*. 2008 Aug; 83(8):880-889. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18674472>.

RATIONALE: A meta-analysis of eleven randomised controlled trials, comparing short-course and long-course treatment (five with penicillin V; four with oral cephalosporins; one with intramuscular ceftriaxone; one with clindamycin). In the primary analysis, microbiological eradication rates of GAS were inferior for short-course versus long-course treatment (OR 0.49; 51% reduction; 95% CI 0.32 to 0.74; eight RCTs, n=1,607). This association was noted with penicillin V treatment (OR 0.36; 64% reduction; 95% CI 0.13 to 0.99; three RCTs, n=500), but was nonsignificant with cephalosporin treatment (OR 0.62;

Management and treatment of common infections-Antibiotic guidance for primary care

38% reduction; 95% CI 0.38 to 1.03; four RCTs, n=1,018). Microbiological eradication was less likely with short-course treatment in trials involving primarily children and adolescents (OR 0.63; 37% reduction; 95% CI 0.40 to 0.98; six RCTs, n=1,258). Clinical success was inferior in patients who received short-course treatment (OR 0.49; 51% reduction; 95% CI 0.25 to 0.96; five RCTs, n=1,217). Adverse events did not differ between compared groups. The associations were consistent in the analyses involving all included RCTs. The authors conclude that short-course treatment for GAS tonsillopharyngitis, particularly with penicillin V, is associated with inferior bacteriological eradication rates.

5. Altamimi S, Khalil A, Khalaiwi KA, Milner RA, Pusic MV, Al Othman MA. Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children (Review). *Cochrane Database Syst Rev*. 2012 Aug; 15(8):1-58. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004872.pub3/epdf>.

RATIONALE: A systematic review and meta-analysis of 20 studies including over 13,000 cases, showing that short-course broad-spectrum antibiotics (including five days clarithromycin) are as efficacious as ten days penicillin for sore throat symptom treatment and GABHS eradication. Ten days phenoxymethylpenicillin remains the treatment of choice for sore throat. Evidence suggests that the use of broader spectrum antibiotics will drive the emergence of bacterial resistance, will increase the risk of developing *Clostridium difficile* associated disease, and are associated with more adverse drug reactions. Five days clarithromycin or erythromycin should be reserved for those with true penicillin allergy.

Acute otitis media:

1. Little P, Gould C, Williamson I, Moore M, Warner G, Dunleavey J. Pragmatic randomised controlled trial of two prescribing strategies for childhood acute otitis media. *BMJ*. 2001 Feb; 322(7282):336-342. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC26576/>.
RATIONALE: A randomised controlled trial of 315 children aged between six months and ten years presenting with acute otitis media. Two important observations were noted: parents tend to underestimate the amount of analgesia they have administered, and when recommending a no antibiotic strategy, it is all the more important to optimise analgesia.
2. Sjoukes A, Venekamp RP, van de Pol AC, Hay AD, Little P, Schilder AG et al. Paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs, alone or combined, for pain relief in acute otitis media in children (Review). *Cochrane Database Syst Rev*. 2016 Dec; 15(12):1-74. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011534.pub2/epdf>.
RATIONALE: A systematic review and meta-analysis, aiming to assess the effectiveness of paracetamol or NSAIDs, alone or combined, compared with placebo or no treatment in relieving pain in children with acute otitis media. Three randomised controlled trials, involving 327 children, were included, all of which demonstrated that both paracetamol and ibuprofen as monotherapies were more effective than placebo in relieving pain at 48 hours. However, the authors suggest that current evidence is limited, and that there is insufficient evidence of a difference between ibuprofen and paracetamol in relieving short-

Management and treatment of common infections-Antibiotic guidance for primary care

term ear pain in children. Further research is therefore needed to provide insights into the role of analgesics for children with acute otitis media.

3. Venekamp RP, Sanders S, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children (Review). *Cochrane Database Syst Rev*. 2015 Jun; 23(6):1-85. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000219.pub4/epdf>.

RATIONALE: A systematic review, including 13 trials, and 3,401 children aged between two months and 15 years of age, comparing antibiotics against placebo in high-income countries, with a low risk of bias. Three trials were performed in a general practice setting, six in an outpatient hospital setting, and four in both settings. The review found that antibiotics were not very useful for most children with AOM. Antibiotics did not decrease the number of children with pain at 24 hours (when 60% of children were better anyway), only slightly reduced the number of children with pain in the days following, and did not reduce the number of children with late AOM recurrences and hearing loss (that can last several weeks) at three months. Antibiotics did, however, slightly reduce the number of children with perforations of the eardrum and AOM episodes in the initially unaffected ear. Results from an individual patient data meta-analysis, including data from six high quality trials (1,643 children), showed that antibiotics seem to be most beneficial in children younger than two years of age with infection in both ears, and in children with both AOM and a discharging ear. There was no difference between immediate antibiotics and expectant observational approaches in the number of children with pain at three to seven days, and 11 to 14 days after assessment. Furthermore, no differences in the number of children with hearing loss at four weeks, perforations of the eardrum, and late AOM recurrences were observed between groups. There was not enough information to state whether or not antibiotics reduced rare complications, such as mastoiditis (infection of the bones around the ear). Data is lacking from populations in which the AOM incidence and risk of progression to mastoiditis is higher. The authors conclude that the benefits of antibiotics must be weighed against the possible harms, eg for every 14 children treated with antibiotics, one child experienced an adverse event (vomiting; diarrhoea; rash) that would not have occurred if antibiotics were withheld. Therefore, clinical management should emphasise providing advice about adequate analgesia and the limited role for antibiotics in treating acute otitis media. For most children with mild disease, an expectant observational approach seems justified.

4. National Institute for Health and Care Excellence (NICE). Respiratory tract infections – antibiotic prescribing. 2008 Jul. Available from:

<https://www.nice.org.uk/guidance/cg69/evidence/full-guideline-196853293>.

RATIONALE: A NICE guideline including evidence from three trials that used a delayed-antibiotic strategy for treating a number of upper respiratory tract infections, including: acute otitis media; acute sore throat/acute pharyngitis/acute tonsillitis; common cold; acute rhinosinusitis; acute cough/acute bronchitis. Two studies in the USA used a two day delayed antibiotic strategy and a UK primary care study used a three day delayed antibiotic strategy. Findings indicate that a delayed antibiotic prescribing strategy of a two or three day duration is appropriate for patients presenting with a number of upper

Management and treatment of common infections-Antibiotic guidance for primary care respiratory tract infections.

5. Spurling GK, Del Mar CB, Dooley L, Foxlee R, Farley R. Delayed antibiotics for respiratory infections (Review). *Cochrane Database Syst Rev*. 2013 Apr; 30(4):1-65. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004417.pub4/pdf>.
RATIONALE: A systematic review and meta-analysis, aiming to evaluate the use of delayed antibiotics compared to immediate or no antibiotics as a prescribing strategy for upper respiratory tract infections. Ten studies, with a total of 3,157 participants, were included in the review. Results indicated that, in patients with acute otitis media, immediate antibiotics were more effective than delayed antibiotics for fever, pain, and malaise. However, delayed antibiotics resulted in a significant reduction in antibiotic use compared to immediate antibiotics. Both delayed and immediate antibiotic strategies had similar satisfaction rates, with both strategies achieving over 80% satisfaction (OR 1.44; 95% CI 0.99 to 2.10). The authors conclude that, in patients with upper respiratory tract infections where clinicians feel it is safe to do so, a delayed prescription can be given, or no prescription with the caveat that the patient should return if symptoms do not resolve.
6. Rovers MM, Glasziou P, Appelman CL, Burke P, McCormick DP, Damoiseaux RA et al. Predictors of pain and/or fever at 3 to 7 days for children with acute otitis media not treated initially with antibiotics: a meta-analysis of individual patient data. *Pediatrics*. 2007 Mar; 119(3):579-585. Available from: <http://pediatrics.aappublications.org/content/119/3/579>.
RATIONALE: A meta-analysis demonstrating that the risk of prolonged illness was twice as high for children younger than two years of age with bilateral acute otitis media than for children with unilateral acute otitis media. For this sub-group, parents should be advised that symptoms may persist for up to seven days, and they should optimise analgesia use. The protective immunity against infections with encapsulated bacteria, such as the species that cause acute otitis media, depends on the ability to produce specific antibodies against bacterial capsular polysaccharides, which is inadequate until two years of age. The anatomic features of the Eustachian tubes and the nasopharynx also differ with age. Consequently, children under two years of age seem to be more susceptible to acute otitis media. The authors also state that clinicians should use certain features (ie age of less than two years, and bilateral acute otitis media) to inform parents more explicitly about the expected course of their child's otitis media, and to explain which features should prompt parents to contact their clinician for re-examination of the child.
7. Rovers MM, Glasziou P, Appelman CL, Burke P, McCormick DP, Damoiseaux RA et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. *Lancet*. 2006 Oct; 368(9545):1429-1435. Available from: <http://www.sciencedirect.com/science/article/pii/S0140673606696062>.
RATIONALE: A sub-analysis of data from children less than two years old. In children with bilateral acute otitis media, 30% were on antibiotics and 50% of controls had pain and/or fever at three to seven days (RD -25%; 95% CI -36, -14); the NNT was four. In children with otorrhoea, 24% were on antibiotics and 60% of controls had pain and/or fever at three to seven days (RD -36%; 95% CI -53, -19); the NNT was three.

Management and treatment of common infections-Antibiotic guidance for primary care

8. Hoberman A, Paradise JL, Rockette HE, Shaikh N, Wald ER, Kearney DH et al. Treatment of acute otitis media in children under 2 years of age. *N Engl J Med*. 2011 Jan; 364(2):105-115. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3042231/pdf/nihms264759.pdf>.

RATIONALE: A randomised controlled study of 291 children aged between six and 23 months with otoscopically confirmed otitis media, comparing the use of co-amoxiclav to placebo. To be included in the study, children had to have acute otitis media that was diagnosed on the basis of three criteria from the Acute Otitis Media Severity of Symptoms (AOM-SOS) scale: tugging of ears; crying; irritability; difficulty sleeping; diminished activity; diminished appetite; fever. There was no significant difference in initial resolution of symptoms between co-amoxiclav and placebo ($p=0.14$). Sustained resolution of symptoms was slightly higher for co-amoxiclav (20% by day two, 41% by day four, and 67% by day seven) compared with placebo (14%, 36%, and 53%, respectively; $p=0.04$). At days 10-12, clinical results were less favourable in children with bilateral acute otitis media ($p=0.002$), more bulging tympanic membrane ($p<0.001$), and higher symptom scores at entry ($p=0.004$).

9. Thompson PL, Gilbert RE, Long PF, Saxena S, Sharland M, Wong IC. Effect of antibiotics for otitis media on mastoiditis in children: a retrospective cohort study using the United Kingdom general practice research database. *Pediatrics*. 2009 Feb; 123(2):424-430. Available from: <http://pediatrics.aappublications.org/content/123/2/424>.

RATIONALE: A retrospective cohort study showing that antibiotics halved the risk of mastoiditis, but GPs would have to treat 4,831 episodes of acute otitis media to prevent one episode of mastoiditis. Although mastoiditis is a serious illness, most children make an uncomplicated recovery after mastoidectomy or IV antibiotics. The incidence of mastoiditis is 0.15 per 1000 children per year.

10. Groth A, Enoksson F, Hermansson A, Hulcrantz M, Stalfors J, Stenfeldt K. Acute mastoiditis in children in Sweden 1993-2007: no increase after new guidelines. *Int J Pediatr Otorhinolaryngol*. 2011 Dec; 75(12):1496-1501. Available from: <http://www.sciencedirect.com/science/article/pii/S0165587611004071>.

RATIONALE: This review states that the incidence of acute mastoiditis in children in Sweden did not increase following the introduction of new guidelines in 2000 for the diagnosis and treatment of acute otitis media. This is despite the fact that a significant decrease in antibiotic prescriptions for acute otitis media has been reported during the same time period. The characteristics of acute mastoiditis reflecting severity of illness did not change over time. Acute mastoiditis was most common and increased after 2000 only in children younger than two years of age, in which antibiotics were still recommended in all cases of acute otitis media.

11. Shekelle PG, Takata G, Newberry SJ, Coker T, Limbos MA, Chan LS et al. Management of acute otitis media: update. *Evid Rep Technol Assess (Full Rep)*. 2010 Nov; 1(198):1-426. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/23126594>.

RATIONALE: A systematic review and meta-analysis, examining the use of different antibiotics compared to placebo for the treatment of acute otitis media. For ampicillin or

Management and treatment of common infections-Antibiotic guidance for primary care

amoxicillin versus placebo (seven studies; n=2,058), clinical success rates by day 14 were significantly higher in patients who received treatment, compared to placebo (95% CI 5% to 18%; NNT9). There were no statistically significant differences in success rate at day 14 for ampicillin or amoxicillin versus ceftriaxone (four studies; n=518), amoxicillin-clavulanate versus azithromycin (nine studies; n=1,826), or cefaclor versus azithromycin (three studies; n=427). There was also no statistically significant difference in success rate at day 16 for amoxicillin-clavulanate versus ceftriaxone (five studies; n=1,362). Findings for antibiotics versus delayed prescriptions were mixed. The authors conclude that there is insufficient data to draw conclusions about the comparative effectiveness of different treatment strategies. However, adverse effects were generally more frequent for amoxicillin-clavulanate than for cefdinir, ceftriaxone, or azithromycin, so this should be considered when discussing treatment options.

12. Courter JD, Baker WL, Nowak KS, Smogowicz LA, Desjardins LL, Coleman CI et al. Increased clinical failures when treating acute otitis media with macrolides: a meta-analysis. *Ann Pharmacother*. 2010 Mar; 44(3):471-478. Available from:

<http://www.ncbi.nlm.nih.gov/pubmed/20150506>.

RATIONALE: A meta-analysis of ten trials, evaluating children aged six months to 15 years. The authors found that the use of macrolide antibiotics was associated with an increased risk of clinical failure (RR 1.31, 95% CI 1.07 to 1.60; p=0.008), corresponding to a number needed to harm of 32. The authors conclude that patients treated with macrolides for AOM may be more likely to have clinical failures. They, therefore, recommend that macrolides be reserved for patients who cannot receive amoxicillin.

13. Clinical Knowledge Summaries (CKS). Otitis media – acute. 2015 Jul. Available from:

<https://cks.nice.org.uk/otitis-media-acute#!topicsummary>.

RATIONALE: A CKS guideline stating that the treatment duration for acute otitis media is five days. Dosing regimens are provided for amoxicillin, erythromycin and clarithromycin, and co-amoxiclav in neonates, children between one month and one year, children between one and five years, children between five and 18 years, and adults. It also provides information on when dosages should be reduced, and any contraindications that primary care clinicians should be aware of.

14. Thanaviratnanich S, Laopaiboon M, Vatanasapt P. Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media (Review). *Cochrane Database Syst Rev*. 2013 Dec; 13(12):1-61. Available from:

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004975.pub3/epdf>.

RATIONALE: A systematic review and meta-analysis, aiming to compare the effectiveness of one or two daily doses, with three or four daily doses of amoxicillin, with or without clavulanate, for the treatment of AOM in children. Five studies, involving 1,601 children, were included in the review. Pooled analysis demonstrated that the following outcomes were comparable between the two groups: clinical cure at the end of therapy (RR 1.03; 95% CI 0.99 to 1.07); during therapy (RR 1.06; 95% CI 0.85 to 1.33) and at follow-up (RR 1.02; 95% CI 0.95 to 1.09); recurrent AOM (RR 1.21; 95% CI 0.52 to 2.81);

Management and treatment of common infections-Antibiotic guidance for primary care

compliance rate (RR 1.04; 95% CI 0.98 to 1.10); overall adverse events (RR 0.92; 8% difference; 95% CI 0.52 to 1.63). When subgroup analyses were performed separately for trials with amoxicillin only and amoxicillin clavulanate only, results indicated that all important outcomes were comparable between once or twice daily groups, and the three times daily group. The authors conclude that the results of using once or twice daily doses of amoxicillin, with or without clavulanate, were comparable with three doses for the treatment of uncomplicated AOM. Three times daily dosing is preferable if patient circumstances allow, as the killing effect of penicillins, including amoxicillin and co-amoxiclav, is time-dependent, and it is therefore important to keep the drug concentration above the MIC for a long period of time, to improve eradication of bacteria, and to reduce the development of resistance.

15. Kozyrskyj A, Klassen TP, Moffatt M, Harvey K. Short-course antibiotics for acute otitis media (Review). *Cochrane Database Syst Rev*. 2010 Sep; 8(9):1-151. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001095.pub2/epdf>.

RATIONALE: A systematic review including 49 trials and 12,045 participants, comparing short- and long-course antibiotic treatment for acute otitis media. The antibiotics reviewed were: amoxicillin or amoxicillin/clavulanate; azithromycin; cefaclor; cefdinir; cefixime; cefpodoxime; cefprozil; cefuroxime; ceftriaxone; clarithromycin; penicillin; trimethoprim-sulfamethoxazole. Results indicated that comparisons between most of the short-acting antibiotics showed no alteration in treatment outcomes. Comparability was demonstrated between ceftriaxone and a longer course of antibiotics, although the sample size of the consolidated trials was smaller. The equivalence observed between a three or five day course of azithromycin and a 10 day course of other antibiotics was unchanged in sensitivity analysis. The authors also note that the increased prescription of amoxicillin-clavulanate did alter resistance to penicillin. The authors conclude that the treatment failure rate following less than seven days antibiotic treatment was similar to the failure rate following seven days or more treatment. Therefore, five days' treatment is the most appropriate treatment duration for treating acute otitis media.

Acute otitis externa:

1. Rosenfeld RM, Schwartz SR, Cannon CR, Roland PS, Simon GR, Ashok Kumar K et al. Clinical practice guideline: acute otitis externa. *Otolaryngol Head Neck Surg*. 2014 Feb; 150(1):1-24. Available from: http://oto.sagepub.com/content/150/1_suppl/S1.full.pdf+html.
RATIONALE: An update of the earlier 2006 clinical practice guideline, providing evidence-based recommendations to manage acute otitis externa. Key recommendations include assessing patients with acute otitis externa for pain, and recommending analgesic treatment based on severity; not prescribing systemic antimicrobials as the initial therapy for diffuse, uncomplicated acute otitis externa, unless there is extension outside the ear canal, or specific host factors are present, indicating a need for systemic therapy; reassessing patients who fail to respond to initial therapeutic options within 48 to 72 hours.
2. Clinical Knowledge Summaries (CKS). Otitis externa. 2015 Jul. Available from:

Management and treatment of common infections-Antibiotic guidance for primary care

<http://cks.nice.org.uk/otitis-externa#!topicsummary>.

RATIONALE: A CKS guideline stating that analgesia and localised heat (eg a warm flannel) should be used as first line measures for patients with acute otitis externa. These measures are sufficient for most cases of localised otitis externa, as folliculitis is usually mild and self-limiting. For topical treatment, acetic acid alone has not been compared with placebo for treating otitis externa in randomised controlled trials. One double-blind RCT found no statistically significant difference in efficacy between topical acetic acid and a topical antibiotic-corticosteroid combination at day seven. However, an antibiotic-corticosteroid combination was more effective after 14 and 21 days of treatment. A single-blind RCT found that a topical acetic acid-antibiotic-corticosteroid combination was more effective than topical acetic acid alone after 14 days. The evidence comparing topical acetic acid-antibiotic-corticosteroid combinations with topical antibiotic-corticosteroid combinations is not of sufficient quality to determine which is more effective. Aluminium acetate has also not been compared with placebo for the treatment of otitis externa. Two RCTs found no clinically important difference between topical aluminium acetate and topical antibiotics with or without corticosteroid. However, these results should be interpreted with caution because of the very low methodological quality of the studies. For oral antibiotics, flucloxacillin should only be prescribed if disease extends outside the ear canal, at a dose of 250-500mg, four times daily, for seven days.

3. Kaushik V, Malik T, Saeed SR. Interventions for acute otitis externa (Review). *Cochrane Database Syst Rev*. 2010 Jan; 20(1):1-121. Available from:

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004740.pub2/epdf>.

RATIONALE: A systematic review and meta-analysis of 19 low quality randomised controlled trials, only two of which are from primary care and, therefore, probably included more severe or chronic cases. It is important to note that over half of the trials involved ear cleaning, which the authors stress is likely not to be wholly generalisable to primary care. This meta-analysis demonstrates that topical treatments alone are adequate for treating most cases of acute otitis externa. Acetic acid was as effective, and comparable to antibiotics/steroids for the first seven days, but inferior after this point. The authors conclude that it is important to instruct patients to use drops for at least one week, and to continue for up to 14 days if symptoms persist.

4. Thorp MA, Kruger J, Oliver S, Nilssen EL, Prescott CA. The antibacterial activity of acetic acid and Burow's solution as topical otological preparations. *J Laryngol Otol*. 1998 Oct; 112(10):925-928. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10211213>.

RATIONALE: A prospective study demonstrating little evidence to support the use of one agent over another in the treatment of acute otitis externa. Both acetic acid and Burow's solution have shown a similar efficacy compared to other topical treatments, such as antibiotics and corticosteroids, although caution should be taken due to the lack of quality in these studies. Based on the fact that acetic acid is recommended as first line treatment for mild otitis externa, whilst aluminium is for more resistant cases or extensive swelling and requires specialist referral for ear wick insertion, acetic acid's availability compared to aluminium acetate would suggest that this is the better first line option. Although there are

Management and treatment of common infections-Antibiotic guidance for primary care

no trials of acetic acid versus placebo, there are trials comparing its use to a topical antibiotic-corticosteroid combination, which show equivalence. Only one study was found from a literature search which compared the efficacy between acetic acid and Burow's solution. This was a small (n=20) in vitro study, which compared the activity of one, two and three percent acetic acid with Burow's solution (aluminium acetate 13%) on an agar plate with the following organisms: *Pseudomonas aeruginosa*; *Staphylococcus aureus*; *Proteus mirabilis*; *Streptococcus pyogenes*. The activity of each agent was ascertained by the size of the zone of inhibition of bacterial growth. Burow's solution showed significantly larger average zones of inhibition than acetic acid (p<0.001). Both the two and three percent acetic acid, as well as the Burow's solution, were active against all the organisms.

5. Abelardo E, Pope L, Rajkumar K, Greenwood R, Nunez DA. A double-blind randomised clinical trial of the treatment of otitis externa using topical steroid alone versus topical steroid-antibiotic therapy. *Eur Arch Otorhinolaryngol*. 2009 Jan; 266(1):41-45. Available from: <http://link.springer.com/article/10.1007%2Fs00405-008-0712-y>.

RATIONALE: A hospital outpatient randomised controlled trial demonstrating superiority of topical steroid-antibiotic therapy, as all patients in the betamethasone-neomycin group showed symptom improvement, but five patients worsened in the group receiving betamethasone alone. Neomycin sulphate with corticosteroid is suggested as a combination therapy, as it contains an antibiotic that is not used orally. Neomycin is active against *Pseudomonas* and *Staphylococci*, which are the most common bacterial causes.

6. Ninkovic G, Dullo V, Saunders NC. Microbiology of otitis externa in the secondary care in United Kingdom and antimicrobial sensitivity. *Auris Nasus Larynx*. 2008 Dec; 35(4):480-484. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/18314283>.

RATIONALE: A prospective study, in which swabs were taken from the external auditory canals of patients who presented to otolaryngology emergency clinics with symptoms of otitis externa. Swabs were analysed using microscopy, culture, and sensitivity testing. The most commonly identified pathogen was *Pseudomonas aeruginosa* (45.1%), followed by *Staphylococcus aureus* (9%), anaerobes (6.3%), beta-haemolytic *Streptococcus* group G (2.8%), beta-haemolytic *Streptococcus* group A (1.4%), *Streptococcus pneumoniae* (0.7%), MRSA (0.7%), *Candida* species (9.7%), *Aspergillus* species (4.2%), and *Absidia corymbifera* (0.7%). 100% resistance of *Pseudomonas* isolates was recorded with neomycin, chloramphenicol, trimethoprim, and amoxicillin, whilst most were sensitive to ciprofloxacin (100%), polymixin B (100%) and gentamicin (98.5%). *Staphylococcus aureus* isolates were sensitive to gentamicin and flucloxacillin (100%). The authors suggest that topical preparations should be used as first line treatment of otitis externa, but oral treatments including polymixin B, gentamycin, ciprofloxacin, or flucloxacillin can be used if the infection does not settle.

Sinusitis (acute):

1. National Institute for Health and Care Excellence (NICE). Sinusitis (acute): antimicrobial prescribing. 2017 Jun. Available from: <https://www.nice.org.uk/guidance/gid->

Management and treatment of common infections-Antibiotic guidance for primary care

[apg10002/documents/consultation-document](https://www.nice.org.uk/primarycare/antibiotic-guidance-for-primary-care/apg10002/documents/consultation-document).

RATIONALE: A NICE guideline, providing the base for rhinosinusitis guidance, providing evidence-based advice for the management of acute sinusitis. This guidance advises that acute sinusitis is a self-limiting infection, usually triggered by a viral infection, indicating that most people will not benefit from antibiotic treatment. The guidance presents evidence from three systematic reviews and meta-analyses of randomised controlled trials, that indicate that antibiotics do not significantly increase the proportion of adults with cure or improvement at three to five days follow-up, compared with placebo. At longer durations of follow-up (approximately seven to 15 days), there is a statistically significant difference in effectiveness for antibiotics compared with placebo, although the clinical difference in cure, improvement, or clinical failure is small. This benefit was not maintained in the longer term (approximately 16 to 60 days follow-up). Where statistically significant benefits were seen for antibiotics compared to placebo, the NNT ranged between seven and 20. Only 0.5% to 2.2% of cases become complicated with bacterial infection, there NICE advise that clinicians do not offer antibiotics to patients presenting with symptoms for 10 days or less. For patients presenting with acute sinusitis for more than 10 days, NICE advise no antibiotic, but a delayed antibiotic, or a high-dose nasal corticosteroid, may be preferred when multiple factors suggest a bacterial cause. The presence of increasing numbers of factors may increase the likelihood of a bacterial cause: symptoms for more than 10 days; discoloured or purulent nasal discharge; severe localised unilateral pain (particularly over teeth and jaw); fever; marked deterioration after an initial milder phase ('double-sickening'). The evidence for delayed antibiotics comes from one RCT in adults that found that a delayed antibiotic prescription (either patient-led or prescription collection), or no antibiotic prescription, was as effective as an immediate antibiotic prescription for managing upper respiratory tract infections. There was no significant difference in adverse events between delayed antibiotic prescription and no antibiotic prescription strategies, compared with immediate antibiotic prescriptions. The evidence for nasal corticosteroids comes from one systematic review of RCTs, and one additional RCT, which found that nasal corticosteroids, with or without an antibiotic, for 14 to 21 days, produces a statistically significant improvement in symptoms in adults and children aged 12 years and over, compared with placebo. However, it is not clear whether these statistically significant reductions in symptom scores are clinically important. The NNT was 15 for one additional person with acute sinusitis to have improved or resolved symptoms with nasal corticosteroids, compared with placebo. Higher (twice daily) doses appear to be most effective. When an antibiotic is prescribed, penicillin V is considered to be the drug of choice first line. This is considered appropriate as penicillin covers *Streptococcus pneumoniae*, the most common cause of acute sinusitis. Penicillin V does not cover *Haemophilus influenzae*, *Neisseria catarrhalis*, or *Staphylococcus aureus*, which are other less common causes of acute sinusitis. These organisms are not usually covered by amoxicillin either, which is currently the most common antibiotic prescribed for this condition. Moreover, in the systematic reviews cited, penicillin had similar efficacy as amoxicillin, and is also the first line recommendation for sinusitis in Swedish guidance.

2. Lemiengre MB, van Driel ML, Merenstein D, Young J, De Sutter AI. Antibiotics for clinically

Management and treatment of common infections-Antibiotic guidance for primary care

diagnosed acute rhinosinusitis in adults (Review). *Cochrane Database Syst Rev*. 2012 Oct; 17(10):1-86. Available from:

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006089.pub4/epdf>.

RATIONALE: A systematic review and meta-analysis reporting on ten trials involving over 2,400 patients. Antibiotics can shorten the time to cure, but only five more participants per 100 will cure faster at any time point between seven and 14 days if they receive an antibiotic instead of placebo (NNTB=18, 95% CI 10 to 115, I^2 0%, eight trials). Purulent secretion resolves faster with antibiotics (OR 1.58, 95% CI 1.13 to 2.22; NNTB=11, 95% CI 6 to 51, I^2 0%, three trials). 27% of the participants who received antibiotics, and 15% of those who received placebo experienced adverse events (OR 2.10, 95% CI 1.60 to 2.77; NNTH=8, 95% CI 6 to 13, I^2 13%, seven trials). More participants in the placebo group needed to start antibiotic therapy because of an abnormal course of rhinosinusitis (OR 0.49, 51% of participants; 95% CI 0.36 to 0.66; NNTH=20, 95% CI 14 to 35, I^2 0%, eight trials). The authors conclude that the potential benefit of antibiotics in the treatment of clinically diagnosed acute rhinosinusitis needs to be seen in the context of a high prevalence of adverse events. Taking into account antibiotic resistance and the very low incidence of serious complications, there is no place for antibiotics for the patient with clinically diagnosed, uncomplicated acute rhinosinusitis.

3. Young J, De Sutter A, Merenstein D, van Essen GA, Kaiser L, Varonen H et al. Antibiotics for adults with clinically diagnosed acute rhinosinusitis: a meta-analysis of individual patient data. *Lancet*. 2008 Mar; 371(9616):908-914. Available from:

<http://www.sciencedirect.com/science/article/pii/S014067360860416X>.

RATIONALE: A meta-analysis including 2,547 patients from nine placebo-controlled trials, showing that 15 people would need to be given antibiotics before an additional patient was cured. The odds ratio (OR) of treatment effect for antibiotics relative to placebo was 1.37 (95% CI 1.13 to 1.66). A further sub-group analysis showed that those patients with purulent discharge were more likely to benefit from antibiotics, with an NNT of eight. There was no additional benefit of antibiotics for older patients, more severe symptoms, or longer duration of symptoms.

4. National Institute for Health and Care Excellence (NICE). Respiratory tract infections – antibiotic prescribing. 2008 Jul. Available from:

<https://www.nice.org.uk/guidance/cg69/evidence/full-guideline-196853293>.

RATIONALE: A NICE guideline suggesting that, although there are no specific studies looking at delayed antibiotics for acute rhinosinusitis, the same approach as for other self-limiting respiratory tract infections should be taken. The seven day delayed antibiotic strategy is recommended, as a systematic review shows that there is no benefit of antibiotics in acute rhinosinusitis within the first seven days.

5. Hansen JG, Schmidt H, Grinsted P. Randomised, double blind, placebo controlled trial of penicillin V in the treatment of acute maxillary sinusitis in adults in general practice. *Scand J Prim Health Care*. 2000 Mar; 18(1):44-47. Available from:

<http://www.ncbi.nlm.nih.gov/pubmed/10811043>.

Management and treatment of common infections-Antibiotic guidance for primary care

RATIONALE: A primary care randomised, double blind, placebo controlled trial of 133 adult patients, demonstrating that penicillin V is more effective than placebo in the treatment of acute maxillary sinusitis, but only in cases with pronounced pain. The results showed that the cure rate was 71% in the penicillin group and 37% in the placebo group, and that significantly more patients achieved normal CRP values when treated with penicillin (88%) as opposed to placebo (75%).

6. Rosenfeld RM, Piccirillo JE, Chandrasekhar SS, Brook I, Ashok Kumar K, Kramper M et al. Clinical practice guideline (update): adult sinusitis. *Otolaryngol Head Neck Surg.* 2015 Apr; 152(2):1-39. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25832968>.

RATIONALE: A clinical practice guideline stating that if a decision is made to treat acute bacterial sinusitis (ABRS) with an antibiotic agent, the clinician should prescribe amoxicillin with or without clavulanate as first line therapy, for five to ten days, for most adults. Additionally, the authors recommend that the use of high-dose amoxicillin with clavulanate (2g orally twice daily, or 90mg/kg/d orally twice daily) is recommended for adults with ABRS who are at a high risk of being infected with an amoxicillin-resistant organism. High-dose amoxicillin is preferred over standard-dose amoxicillin, primarily to cover penicillin nonsusceptible *Streptococcus pneumoniae*. This risk exists in: those from geographic regions with high endemic rates of invasive PNS *S. pneumoniae* (>10%); those with severe infection (eg evidence of systemic toxicity with a temperature of 39°C or higher, and a threat of suppurative complications); aged >65 years; recent hospitalisation; antibiotic use within the past month; those who are immunocompromised. This guideline also recommends that analgesics or antipyretic drugs may be given for pain or fever.

Lower Respiratory Tract Infections

General references:

1. Woodhead M, Blasi F, Ewig S, Garau J, Huchon G, Ieven M et al. Guidelines for the management of adult lower respiratory tract infections – full version. *Clin Microbiol Infect.* 2011 Nov; 17(6):1-59. Available from: <http://www.sciencedirect.com/science/article/pii/S1198743X1461404X>.

RATIONALE: A guideline providing definitions of subtypes of lower respiratory tract infections, the microbiological aetiologies of these infections, and the pharmacodynamics/pharmacokinetic properties of the antibiotics used to treat them. *Streptococcus pneumoniae* remains the most commonly isolated pathogen in both community-acquired pneumonia and exacerbations of COPD, but not in bronchiectasis. Antibiotic classes are discussed with reference to their mode of action, in terms of time-dependent or concentration-dependent effect, their tissue penetration, and whether or not they exert a post-antibiotic effect.

2. Patel SN, McGeer A, Melano R, Tyrrell GJ, Green K, Pillai DR et al. Susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. *Antimicrob Agents Chemother.*

Management and treatment of common infections-Antibiotic guidance for primary care

2011 Aug; 55(8):3703-3708. Available from:

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3147653/>.

RATIONALE: A study conducted by the Canadian Bacterial Surveillance Network, aiming to examine isolates of pneumococci received between 1998 and 2009. The poor potency of ciprofloxacin against pneumococci is noted, and explained by the fact that the parameter that best predicts the efficacy of fluoroquinolones in eradicating pneumococci is the ratio of the area under the concentration-time curve (AUC), compared to the minimum inhibitory concentration (MIC) for the organism. At doses used for therapy, ciprofloxacin never achieves the target ratio of 30-40. The authors postulate that this poor potency may be part of the reason for the increasing ciprofloxacin resistance seen in their study, as well as the fact that fewer mutations are required for the development of resistance when using ciprofloxacin compared to other fluoroquinolones.

Acute cough & bronchitis:

1. Smith SM, Fahey T, Smucny J, Becker LA. Antibiotics for acute bronchitis (Review). *Cochrane Database Syst Rev*. 2014 Mar; 1(3):1-60. Available from:

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000245.pub3/epdf>.

RATIONALE: A systematic review and meta-analysis of 17 trials and 3,936 participants, demonstrating limited evidence to support the use of antibiotics in acute bronchitis. Findings indicated that there was no difference in participants described as being clinically improved between antibiotic and placebo groups (RR 1.07; 95% CI 0.99 to 1.15; NNTB22). The results did suggest that duration of symptoms was reduced by half a day in participants given antibiotics, compared to placebo (MD -0.46 days; 95% CI -0.87 to -0.04), but the differences in presence of a productive cough at follow-up did not reach statistical significance. Thus, the benefit in healthy adults is minimal. Antibiotics may have a modest beneficial effect in some patients, such as frail, elderly people with multiple morbidities, but these patients have not been included in trials to date. The magnitude of this benefit needs to be considered in the broader context of potential side-effects, medicalisation for a self-limiting condition, increased resistance, and cost of treatment.

2. Francis NA, Butler CC, Hood K, Simpson S, Wood F, Nuttall J. Effect of using an interactive booklet about childhood respiratory tract infections in primary care consultations on reconsulting and antibiotic prescribing: a cluster randomised controlled trial. *BMJ*. 2009 Jul; 339:1-8. Available from: <http://www.bmj.com/content/bmj/339/bmj.b2885.full.pdf>.

RATIONALE: A pragmatic cluster randomised controlled trial, aiming to establish whether an interactive booklet on respiratory tract infections in children reduces reconsultation for the same illness episode, reduces antibiotic use, and affects future consulting intentions, while maintaining parental satisfaction with care. 528 children were included, all of whom had presented to primary care with an acute respiratory tract infection, excluding those with suspected pneumonia, asthma, or a serious concomitant illness, or those needing immediate hospital admission. Results indicated that utilising an information booklet during primary care consultations for children with RTIs significantly decreases antibiotic use (ARR 21.3%; 95% CI 13.7 to 28.9; $p < 0.001$). Reconsultation occurred in 12.9% of

Management and treatment of common infections-Antibiotic guidance for primary care

children in the intervention group, and in 16.2% in the control group (ARR 3.3%; no statistical significance). There was no detriment noted in patient satisfaction in the intervention group.

3. National Institute for Health and Care Excellence (NICE). Respiratory tract infections – antibiotic prescribing. 2008 Jul. Available from:

<https://www.nice.org.uk/guidance/cg69/evidence/full-guideline-196853293>.

RATIONALE: A NICE guideline describing strategies for limiting antibiotic prescribing in self-limiting respiratory tract infections, and advises in which circumstances antibiotics should be considered. A no antibiotic or delayed antibiotic prescribing strategy should be agreed for patients with acute cough/chronic bronchitis. In the two randomised controlled trials included in the review, the delay was seven to 14 days between symptom onset and commencement of antibiotic therapy. Patients should be advised that resolution of symptoms can take up to three weeks, and that antibiotic therapy will make little difference to their symptoms and may result in side-effects. Patients should also be advised to seek advice from a professional if their condition worsens or becomes prolonged. There has been no systematic review of the evidence of length of antibiotic treatment for acute cough or bronchitis, when antibiotics are prescribed. However, evidence for the efficacy of five days antibiotic treatment for pneumonia has been recorded, therefore it is reasonable to consider that five days would also be effective in bronchitis. This guideline provides information on identifying those patients with RTIs who are likely to be at risk of developing complications. It is stated that if the patient is older than 65 years with acute cough and two or more of the following criteria, or older than 80 years with acute cough and one or more of the following criteria, a no or delayed antibiotic prescribing strategy should not be considered: hospitalisation in the previous year; type 1 or type 2 diabetes; history of congestive heart failure; current use of oral glucocorticoids.

4. Cals JW, Ament AJ, Hood K, Butler CC, Hopstaken RM, Wassink GF et al. C-reactive protein point of care testing and physician communication skills training for lower respiratory tract infections in general practice: economic evaluation of a cluster randomized trial. *J Eval Clin Pract.* 2011 Dec; 17(6):1059-1069. Available from:

<http://www.ncbi.nlm.nih.gov/pubmed/20666881>.

RATIONALE: A cluster randomised trial indicating that the use of point of care CRP tests in general practice can assist diagnosis, improve patient satisfaction, and reduce overall antibiotic use. Various implementation scenarios according to GP preference were modelled with corresponding net monetary benefit, based on a given willingness-to-pay for a 1% lower antibiotic prescribing rate. The total mean antibiotic prescribing rate was 68%: patients managed by GPs using CRP tests (39%); patients managed by GPs trained in enhanced communication skills (33%); patients managed by GPs using both interventions (23%). The authors conclude that the use of CRP tests in addition to communication skills training are cost-effective interventions to reduce antibiotic prescribing for lower respiratory tract infections.

5. NICE clinical guideline 191. Pneumonia in adults: diagnosis and management. Issued December 2014. <https://www.nice.org.uk/guidance/cg191> Accessed 17.11.17

Management and treatment of common infections-Antibiotic guidance for primary care

RATIONALE: For people presenting with symptoms of lower respiratory tract infection in primary care, consider a point of care C-reactive protein test if after clinical assessment a diagnosis of pneumonia has not been made and it is not clear whether antibiotics should be prescribed. Use the results of the C-reactive protein test to guide antibiotic prescribing in people without a clinical diagnosis of pneumonia as follows: Do not routinely offer antibiotic therapy if the C-reactive protein concentration is less than 20 mg/litre. Consider a delayed antibiotic prescription (a prescription for use at a later date if symptoms worsen) if the C-reactive protein concentration is between 20 mg/litre and 100 mg/litre. Offer antibiotic therapy if the C-reactive protein concentration is greater than 100 mg/litre. If antibiotics are indicated, amoxicillin 500mg TDS for five days.

6. Clinical Knowledge Summaries (CKS). Chest infections – adult. 2015 Nov. Available from:

<https://cks.nice.org.uk/chest-infections-adult#!topicsummary>.

RATIONALE: For people presenting with symptoms of lower respiratory tract infection in primary care, consider a point of care C-reactive protein test if after clinical assessment a diagnosis of pneumonia has not been made and it is not clear whether antibiotics should be prescribed. Use the results of the C-reactive protein test to guide antibiotic prescribing in people without a clinical diagnosis of pneumonia as follows: Do not routinely offer antibiotic therapy if the C-reactive protein concentration is less than 20 mg/litre. Consider a delayed antibiotic prescription (a prescription for use at a later date if symptoms worsen) if the C-reactive protein concentration is between 20 mg/litre and 100 mg/litre. Offer antibiotic therapy if the C-reactive protein concentration is greater than 100 mg/litre. If antibiotics are indicated, amoxicillin 500mg TDS for five days. If true penicillin allergy, doxycycline 200mg on the first day and then 100mg once daily for 5 days.

Acute exacerbation of COPD:

NB Infective exacerbations of COPD are defined as: worsening breathlessness; cough; increased sputum production; change in sputum colour. A change in these symptoms often warrants a change in regular medication. These exacerbations are usually caused by H. influenzae, S. pneumoniae, or S. aureus.

1. Ram FSF, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC. Antibiotics for exacerbations of chronic obstructive pulmonary disease (Review). *Cochrane Database Syst Rev*. 2009 Apr; 1:1-52. Available from:

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004403.pub2/epdf>.

RATIONALE: A systematic review and meta-analysis of 11 trials, including 917 participants, indicating that antibiotic therapy (amoxicillin 250mg QDS; clarithromycin; doxycycline 200mg, followed by 100mg OD) regardless of antibiotic choice, significantly reduces mortality (RR 0.23; 77% reduction; 95% CI 0.10 to 0.52; NNT8), treatment failure (RR 0.47; 53% reduction; 95% CI 0.36 to 0.62; NNT3), and sputum purulence (RR 0.56; 44% reduction; 95% CI 0.41 to 0.77; NNT8). The authors conclude that antibiotics should be prescribed for patients with COPD exacerbations with increased cough and sputum purulence, who are moderately or severely ill.

Management and treatment of common infections-Antibiotic guidance for primary care

2. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med.* 1987 Feb; 106(2):196-204. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/3492164>.
RATIONALE: A randomised, double-blind, crossover trial, in which the effects of broad-spectrum antibiotic and placebo therapy in 535 patients with exacerbations of chronic obstructive pulmonary disease were compared. The success rate with placebo was 55%, and with antibiotic was 68%; the rate of failure with deterioration was 19% with placebo, and 10% with antibiotic, suggesting that there is a significant benefit associated with antibiotic treatment for exacerbations of COPD.
3. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2016 Jan. Available from: <http://goldcopd.org/global-strategy-diagnosis-management-prevention-copd-2016/>.
RATIONALE: An international guideline, citing one systematic review and two randomised controlled trials, which recommend that antibiotics should be given to patients with exacerbations of COPD who have three cardinal symptoms (increase in dyspnoea; sputum volume; sputum purulence), or have two of the cardinal symptoms if increased purulence of sputum is one of them, or if the patient requires mechanical ventilation. The recommended length of antibiotic therapy is usually five to ten days, and the choice of antibiotic should be based on the local bacterial resistance pattern.
4. National Institute for Health and Care Excellence (NICE). Chronic obstructive pulmonary disease in over 16s: diagnosis and management. 2010 Jun. Available from: <https://www.nice.org.uk/guidance/cg101>.
RATIONALE: A NICE guideline, advising that the role of antibiotics should be to treat exacerbations of COPD associated with a history of more purulent sputum. Patients with exacerbations without more purulent sputum do not need antibiotic therapy, unless there is consolidation on a chest radiograph, or clinical signs of pneumonia. Initial empirical treatment should be an aminopenicillin (eg amoxicillin), a macrolide, or a tetracycline. When initiating empirical antibiotic treatment, prescribers should always take account of any guidance issued by their local microbiologists. When sputum has been sent for culture, the appropriateness of antibiotic treatment should be checked against laboratory culture and sensitivities, when they become available.
5. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ.* 2010 Mar; 340(2096):1-11. Available from: <http://www.bmj.com/content/bmj/340/bmj.c2096.full.pdf>.
RATIONALE: A systematic review and meta-analysis of 24 studies, 22 involving patients with symptomatic infections, and two involving healthy volunteers, aiming to investigate subsequent antibiotic resistance in individuals prescribed antibiotics in primary care. In seven studies of respiratory tract bacteria (n=2,605), pooled ORs were 2.4 (95% CI 1.4 to 3.9) and 2.4 (95% CI 1.3 to 4.5) for the same time periods. The authors state that risk factors for resistance include: indiscriminate or poor use of antibiotics; quantity of antibiotic prescribed, especially for longer durations and multiple courses; exposure to antibiotics,

Management and treatment of common infections-Antibiotic guidance for primary care

with the strongest association in the first month, with reduced association at subsequent time points, and a small but important residual association within 12 months; receiving one or more courses of antibiotics in 12 months, especially if a further antibiotic treatment is necessary. The authors conclude that primary care antibiotic prescriptions make an important contribution to antimicrobial resistance. Primary care clinicians and patients may wish to consider this evidence when discussing the benefits and risks of prescribing and consuming antibiotics.

6. Bestall J, Paul E, Garrod R, Garnham R, Jones P, Wedzicha J. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax*. 1999 Jul; 54(7):581-586. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1745516/pdf/v054p00581.pdf>.

RATIONALE: A prospective study discussing the MRC dyspnoea scale as a way of classifying chronic obstructive pulmonary disease. The questionnaire consists of five statements regarding perceived breathlessness: Grade One – “I only get breathless with strenuous exercise”; Grade Two – “I get short of breath when hurrying on the level or up a slight hill”; Grade Three – “I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking at my own pace on the level”; Grade Four – “I stop for breath after walking 100 yards, or after a few minutes on the level”; Grade Five – “I am too breathless to leave the house”. The authors conclude that the MRC dyspnoea scale is a simple and valid method of categorising patients with COPD in terms of their disability, and could be used to complement FEV1.

7. El Moussaoui R, Roede BM, Speelman P, Bresser P, Prins JM, Bossuyt PM. Short-course antibiotic treatment in acute exacerbations of chronic bronchitis and COPD: a meta-analysis of double-blind studies. *Thorax*. 2008 May; 63(5):415-422. Available from: <http://thorax.bmj.com/content/63/5/415.full.pdf+html>.

RATIONALE: A meta-analysis of 21 double-blind, randomised studies, in which the authors concluded that a short-course of antibiotic treatment was as effective as the traditional longer treatment in patients with mild to moderate exacerbations of chronic bronchitis and COPD. At early follow-up (<25 days), the summary odds ratio (OR) for clinical cure with short treatment (less than or equal to five days) versus conventional treatment (more than five days) was 0.99 (95% CI 0.90 to 1.08). At late follow-up, the summary OR was 1 (95% CI 0.91 to 1.10). No trials of amoxicillin or doxycycline were included in this meta-analysis, however there is no microbiological reason that a five day course of these agents would be inferior to a five day course of clarithromycin in acute exacerbations of COPD.

8. Hunter MH, King DE. COPD: Management of acute exacerbations and chronic stable disease. *Am Fam Physician*. 2001 Aug; 64(4):603-613. Available from: <http://www.aafp.org/afp/2001/0815/p603.html>.

RATIONALE: An editorial, providing information on the epidemiology, pathophysiology, prognostic indicators, pharmacologic management and treatment of both acute exacerbations and chronic stable COPD. The authors state that findings from numerous clinical studies suggest that antibiotic therapy has a small but important effect on clinical

Management and treatment of common infections-Antibiotic guidance for primary care

recovery, so administration should be considered at the beginning of treatment for exacerbations of COPD. Treatment recommendations include: amoxicillin 500mg TDS; doxycycline 200mg stat, then 100mg once daily; clarithromycin 500mg twice daily.

Community-acquired pneumonia:

1. NICE clinical guideline 191. Pneumonia in adults: diagnosis and management. Issued December 2014. <https://www.nice.org.uk/guidance/cg191> Accessed 17.11.17
RATIONALE: A NICE guideline stating that for people presenting with symptoms of lower respiratory tract infections in primary care, a C-reactive protein (CRP) test should be considered, if after clinical assessment a diagnosis of pneumonia has not been made and it is not clear whether or not antibiotics should be prescribed. The results of the CRP test should be used to guide antibiotic prescribing in people without a clinical diagnosis of pneumonia, as follows: do not routinely offer antibiotic therapy if the CRP concentration is less than 20mg/litre; consider a delayed antibiotic prescription if the CRP concentration is between 20mg/litre and 100mg/litre; offer antibiotic therapy if the CRP concentration is greater than 100mg/litre. This guideline includes information on diagnosis, severity assessment, microbiological profile, and therapeutic management in both community and hospital settings. Assessing severity using CRB65 scores, in addition to clinical judgement, allows patients to be stratified according to increasing risk of mortality (score 0: mortality risk 1%; score 1-2: mortality risk 1-10%; score 3-4: mortality risk >10%). Patients with a CRB65 score ≥ 1 are deemed to have moderately severe CAP and should be assessed with a view to hospital admission, especially if the score is >2. Patients with moderately severe CAP should receive antibiotics, which also cover atypical organisms. For patients treated at home, five days' treatment is appropriate with safety net advice to return for urgent review if they are worsening, or at three days if they are not improving. With moderate to severe pneumonia, seven to ten days' treatment should be considered, based on severity and response. NICE advise that glucocorticosteroids should not be given unless indicated for another condition. Explain to patients with community-acquired pneumonia that, after starting treatment, their symptoms should steadily improve, although the rate of improvement will vary with the severity of the pneumonia. Most people can expect the following: at one week fever should have resolved; at four weeks chest pain and sputum production should have substantially reduced; at six weeks cough and breathlessness should have substantially reduced; at three months most symptoms should have resolved, but fatigue may still be present; at six months most people will feel back to normal.
2. Torres A, Blasi F, Peetermans WE, Viegi G, Welte T. The aetiology and antibiotic management of community-acquired pneumonia in adults in Europe: a literature review. *Eur J Clin Microbiol Infect Dis*. 2014 Feb; 33(7):1065-1079. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4042014/>.
RATIONALE: A literature review providing up-to-date information on the aetiology of community-acquired pneumonia and its antibiotic management in adults across Europe. *Streptococcus pneumoniae* was the most commonly isolated pathogen in patients with CAP, and was identified in 12 to 85% of patients. Other frequently identified pathogens were *Haemophilus influenzae*, gram-negative enteric bacilli, respiratory viruses, and

Management and treatment of common infections-Antibiotic guidance for primary care

Mycoplasma pneumoniae. The authors found several age-related trends: *S. pneumoniae*, *H. influenzae*, and respiratory viruses were more frequent in elderly patients aged >65 years, whereas *M. pneumoniae* was more frequent in those aged <65 years. Limited data on antibiotic resistance was available in the studies, however penicillin resistance of *S. pneumoniae* was reported in 8.4 to 20.7% of isolates, and erythromycin resistance was reported in 14.7 to 17.1% of isolates.

3. Public Health England (PHE). Annual summary of *Mycoplasma pneumoniae* laboratory surveillance data, 2016, England and Wales. 2017 Jan. Available from:

<https://www.gov.uk/guidance/mycoplasma>.

RATIONALE: A PHE report, stating that *Mycoplasma pneumoniae* is a bacterium that causes acute respiratory illness ranging in severity from mild illness to severe pneumonia. The overall reported case numbers seemed to decline over 2013 and 2014, but increased again during 2015 and 2016, with highest numbers being reported in the 15-44 year age group (103). *Mycoplasma* infection is found in patients of all ages, including children under five years, but only rarely in adults aged 65 years and older (6), in comparison to 0 to 4 years (76), 5 to 9 years (22), 10 to 14 years (7), and 45 to 64 years (27). Cases have started to decrease throughout 2017.

4. Public Health England (PHE). English surveillance programme for antimicrobial utilisation and resistance (ESPAUR): Report 2016. 2016 Nov. Available from:

<https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report>.

RATIONALE: An ESPAUR report, stating that antimicrobial resistance is stable in pneumococcal infections, and that the key antibiotics recommended to treat upper and lower respiratory tract infections include amoxicillin, phenoxymethylpenicillin, erythromycin, clarithromycin, azithromycin, and doxycycline. This report provides line charts that demonstrate that, by 2015, *K. pneumoniae* resistance to co-amoxiclav had risen to between 20% and 30%, third generation cephalosporins were recorded at a resistance rate of 10%, with carbapenems at a resistance rate of just over 0%. This report also suggests that there is less resistance to combined treatment, compared to one antimicrobial alone (2.0% versus 18.5%, respectively).

5. Pakhale S, Mulpuru S, Verheij TJ, Kochen MM, Rohde GG, Bjerre LM. Antibiotics for community-acquired pneumonia in adult outpatients (Review). *Cochrane Database Syst Rev*. 2014 Oct; 1(10):1-71. Available from:

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002109.pub4/pdf>.

RATIONALE: A systematic review and meta-analysis of 11 randomised controlled trials, and 3,352 participants over 12 years of age. Results indicate that less adverse effects are experienced with clarithromycin 250-500mg BD when compared to cethromycin, and levofloxacin when compared to nemonoxacin. Higher rates of gastrointestinal side-effects were recorded when comparing amoxicillin 500mg TDS to 1g TDS, suggesting that a lower dose may be more appropriate. The individual study results did not reveal significant differences in efficacy between the various antibiotics and antibiotic groups. Taking this into consideration, the authors conclude that the available evidence from recent RCTs is insufficient to make new evidence-based recommendations for the choice of antibiotic to

Management and treatment of common infections-Antibiotic guidance for primary care

be used for the treatment of CAP in outpatient settings. Based on severity of side-effects, however, clarithromycin would make a good first choice for treatment of CAP, in comparison to erythromycin .

6. Mokabberi R, Haftbaradaran A, Ravakhah K. Doxycycline vs. levofloxacin in the treatment of community-acquired pneumonia. *J Clin Pharm Ther.* 2010 Apr; 35(2):195-200. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/20456738>.

RATIONALE: A prospective double-blind trial, in which 65 adults with community-acquired pneumonia requiring hospitalisation were enrolled, aiming to study whether doxycycline is as efficacious as levofloxacin in the treatment of community-acquired pneumonia in general medical wards. 30 patients were prescribed 500mg levofloxacin for five days, and 35 patients were prescribed 100mg doxycycline twice daily for five days. Results indicated that length of stay was less in the doxycycline group in comparison to the levofloxacin group (4.0 + 1.82 days, and 5.7 + 2.05 days, respectively; $p < 0.0012$). Failure rate was similar in both groups ($p = 0.893$). The authors conclude that 100mg doxycycline can be used as an effective and economical alternative therapy to levofloxacin in the empirical treatment of community-acquired pneumonia.

Urinary Tract Infections

General references:

1. Public Health England (PHE). English surveillance programme for antimicrobial utilisation and resistance (ESPAUR): Report 2016. 2016 Nov. Available from:

<https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report>.

RATIONALE: An ESPAUR report analysing data up to 2015. The report states that antibiotic resistance and *E. coli* blood stream infections have continued to rise. This report states that there is a variation in resistance rates across England. Trimethoprim resistance in Gram-negative UTIs ranges from 16.3% to 66.7% which could be related to variations in samples being sent for testing. However, 86% of CCGs have resistance rates greater than 25% highlighting that trimethoprim should no longer be advised as a first-line empiric antibiotic treatment for UTIs in England. Nitrofurantoin resistance to Gram-negative infections ranged from 0.3% to 12.8% and its use for treatment of UTIs has increased yearly across the 2010-2015 period.

2. Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI). 5th Annual Report, April 2013 – March 2014. 2015 Feb. Available from: <https://www.gov.uk/government/publications/advisory-committee-on-antimicrobial-resistance-and-healthcare-associated-infections-annual-reports>.

RATIONALE: An ARHAI report, noting that mandatory surveillance over the past ten years has demonstrated a sustained increase in *E. coli* bacteraemia, that is unexplained by improved diagnosis. The analysis demonstrates that only a small proportion of infections are related to urinary catheterisation. Other risk factors, such as repeated urinary tract infections treated by sub-optimal antibiotic prescribing, and dehydration, have a significant impact. The report recommends that: all organisations providing care to patients with

Management and treatment of common infections-Antibiotic guidance for primary care

indwelling urinary catheters should ensure that the recommendations of EPIC 3 (short-term catheters) and NICE (long-term catheters) are being implemented, and provide evidence of compliance; hydration status must be a priority for those at risk of dehydration, particularly those in hospitals, and long-term care facilities; treatment of UTI should be based on local antibiotic resistance patterns, and patients diagnosed with a UTI (especially those with a history of repeated infections), should be subject to a safety netting procedure to ensure that treatment has been effective.

3. Royal College of General Practitioners (RCGP). *Treating Your Infection – Urinary Tract Infection Leaflet*. Available from:

http://www.rcgp.org.uk/~/link.aspx?_id=9FCF9DA4B4A045519593320478DFD9E7&_z=z

[Accessed: 16th June, 2017].

RATIONALE: An RCGP webpage hosting a range of patient information leaflets on treating common infections. The leaflets are designed to be used during the consultation, and aim to improve the patient's confidence to self-care, and the prescriber's communication with patients and carers. The UTI leaflet contains information on: possible urinary symptoms; the outcome, and recommended care (self-care; pain relief; delayed antibiotic strategy; immediate antibiotic strategy); types of urinary tract infection (urethritis; cystitis; pyelonephritis); self-care to help yourself get better more quickly; when you should get help, including the presence of fever, or signs or symptoms of sepsis; options to help prevent a UTI; antibiotic resistance.

4. Public Health England (PHE). Diagnosis of urinary tract infections. Quick reference guide for primary care: For consultation and local adaptation. 2016 Dec. Available from:

<https://www.gov.uk/government/publications/urinary-tract-infection-diagnosis>.

RATIONALE: A PHE quick reference guide covering the diagnosis and management of urinary tract infections. The guide targets primary care prescribers in general practice and out of hours settings and those giving first point of contact care for urinary tract infections. The aim is provide a simple effective economical and empirical approach to the diagnosis and treatment of UTIs and to minimise the emergence of antibiotic resistance in the community.

UTI in adults (*lower*):

1. Bains A, Buna D, Hoag NA. A retrospective review assessing the efficacy and safety of nitrofurantoin in renal impairment. *CPJRPC*. 2009 Oct; 142(5):248-252. Available from:

<http://cph.sagepub.com/content/142/5/248.full.pdf+html>.

RATIONALE: A retrospective review of the literature, conducted to determine the efficacy and safety of nitrofurantoin in patients with a UTI and an estimated GFR <50mL/min (impaired renal function group) compared to >50mL/min (control group). Results indicated that the majority of patients showed cure of their UTI, with comparable cure rates for the impaired renal function group (71%; 95% CI 63 to 79), and control group (78%; 95% CI 73 to 84). The cure rates did not vary significantly when using the Elderly-Adjusted MCG formula (impaired renal function: 75%; 95% CI 69 to 83, versus control: 76%; 95% CI 69 to 83), or the MDRD formula (impaired renal function: 72%; 95% CI 62 to 83, versus control: 76%; 95% CI 71 to 81). The authors suggest that nitrofurantoin could be used

Management and treatment of common infections-Antibiotic guidance for primary care

down to a creatinine clearance of 40mL/min. The occurrence of adverse effects was comparable between the two groups.

2. Oplinger M, Andrews CO. Nitrofurantoin contraindication in patients with a creatinine clearance below 60 mL/min: looking for the evidence. *Ann Pharmacother*. 2013 Jan; 47(1):106-111. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23341159>.

RATIONALE: A review of all the available literature, in which the authors conclude that the data supporting the contraindication of nitrofurantoin for patients with a CrCl less than 60mL/min is non-existent, as one study demonstrated that patients with a CrCl of 30 to 40ml/min and those with a CrCl of 60 to 110ml/min had similar amounts of nitrofurantoin in their urine. The amount of drug recovered in patients with a CrCl of 20ml/min or less was low (less than 50mg/24 hours). Well-designed clinical trials with urinary concentration information and clinical end points on patients with various degrees of renal impairment are much needed to provide further evidence. Until such a study becomes available, the authors suggest that, based on the limited data available, nitrofurantoin should only be considered in patients known to have a creatinine clearance of 40mL/min or higher.

3. Medicines and Healthcare products Regulatory Agency (MHRA). Nitrofurantoin now contraindicated in most patients with an estimated glomerular filtration rate (eGFR) of less than 45 ml/min/1.73m². 2014 Sep. Available from: [https://www.gov.uk/drug-safety-update/nitrofurantoin-now-contraindicated-in-most-patients-with-an-estimated-glomerular-filtration-rate-egfr-of-less-than-45-ml-min-1-73m²](https://www.gov.uk/drug-safety-update/nitrofurantoin-now-contraindicated-in-most-patients-with-an-estimated-glomerular-filtration-rate-egfr-of-less-than-45-ml-min-1-73m2).

RATIONALE: A PHE document, stating that the antibacterial efficacy of nitrofurantoin in UTIs depends on the renal secretion of nitrofurantoin in the urinary tract. The use of nitrofurantoin was previously contraindicated in patients with creatinine clearance of less than 60ml/min, but this was revised to suggest a contraindication against use in patients with an eGFR of less than 45ml/min/1.73m². This document also suggests that a short course (three to seven days) nitrofurantoin may be used with caution in certain patients with an eGFR of 30 to 44ml/min/1.73m². Nitrofurantoin should only be prescribed in these patients if they have suspected or proven multidrug resistant pathogens, and only if the benefits are considered to outweigh the risks of side-effects.

4. Scottish Intercollegiate Guidelines Network (SIGN). Management of suspected bacterial urinary tract infection in adults: a national clinical guideline. 2012 Jul. Available from: <http://www.sign.ac.uk/assets/sign88.pdf>.

RATIONALE: A SIGN guideline stating that it is reasonable to start empirical antibiotics in women younger than 65 years of age with three symptoms of UTI, without urine dipstick or urine culture. Symptoms of UTI are listed as: dysuria; frequency of urination; suprapubic tenderness; urgency; polyuria; haematuria. A three-day course of treatment is normally sufficient for women. In men, a urine sample is recommended for UTI because they are generally regarded as complicated (the result of an anatomic or functional abnormality), and there are no studies on the predictive value of dipstick testing.

5. Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five

Management and treatment of common infections-Antibiotic guidance for primary care

countries: results of the EPIC study. *Eur Urol.* 2006 Dec; 50(6):1306-1315. Available from: <http://www.sciencedirect.com/science/article/pii/S030228380601116X>.

RATIONALE: A population-based survey across the UK, Canada, Germany, Italy, and Sweden, including 19,165 men and women with urinary symptoms. Results indicated that lower urinary tract symptoms are highly prevalent, the prevalence of which increases with age. Presence of single symptoms alone do not necessarily indicate UTI, but the presence of three of these symptoms should warrant consideration of infection. In this study, women reported urinary storage symptoms (nocturia; urgency; frequency) more frequently than men (59.2% versus 51.3%, respectively), whereas men reported more voiding symptoms (intermittency; slow stream; straining; terminal dribble; 19.5% versus 25.7%, respectively), and postmicturition symptoms (incomplete emptying; postmicturition dribble; 14.2% versus 16.9%, respectively).

6. Bleidorn J, Gagyor I, Kochen MM, Wegscheider K, Hummers-Pradier E. Symptomatic treatment (ibuprofen) or antibiotics (ciprofloxacin) for uncomplicated urinary tract infection? – Results of a randomized controlled pilot trial. *BMC Med.* 2010 May; 8(30):1-8. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2890534/pdf/1741-7015-8-30.pdf>.

RATIONALE: A double-blind randomised controlled pilot trial across 29 German general practices. 80 otherwise healthy women aged between 18 and 85 years presenting with at least one common symptom of UTI (dysuria; frequency) were randomly assigned to one of two treatment arms: ibuprofen 3 x 400mg orally for three days; ciprofloxacin 2 x 250mg (plus one placebo) orally for three days. 79 participants were analysed (ibuprofen n=40; ciprofloxacin n=39). On day four, 21 of 36 (58.3%) of patients in the ibuprofen group were symptom free, versus 17 of 33 (51.5%) of patients in the ciprofloxacin group. Patients receiving ibuprofen also reported fewer symptoms of UTI than patients receiving ciprofloxacin (PP analysis -0.33; 95% CI -1.13 to 0.47). Between days zero and nine, 12 out of 36 (33%) patients in the ibuprofen treatment arm received secondary antibiotic treatment due to ongoing or worsening symptoms, compared to six out of 33 (18%) patients in the ciprofloxacin treatment arm, but these results were not significant. The authors conclude that their results support the assumption of non-inferiority of ibuprofen compared to ciprofloxacin for treatment of symptomatic uncomplicated UTI in women.

7. Gagyor I, Bleidorn J, Kochen MM, Schmiemann G, Wegscheider K, Hummers-Pradier E. Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: randomised controlled trial. *BMJ.* 2015 Dec; 23(351):1-11. Available from: <http://www.bmj.com/content/bmj/351/bmj.h6544.full.pdf>.

RATIONALE: A randomised controlled trial across 42 German general practices, aiming to determine if treatment of symptoms of uncomplicated UTI with ibuprofen can reduce the rate of antibiotic prescriptions without a significant increase in symptoms, recurrences, or complications. 494 women aged between 18 and 65 with typical symptoms of uncomplicated UTI were included and randomly assigned to one of two treatment arms: a single dose of fosfomycin 3g for three days (n=246), or ibuprofen 3 x 400mg for three days (n=248). In both groups, additional antibiotic treatment was subsequently prescribed as necessary for persistent, worsening, or recurrent symptoms. Results indicated that, out of the 248 women in the ibuprofen group, two thirds treated symptomatically recovered

Management and treatment of common infections-Antibiotic guidance for primary care

without any antibiotics. Recurrent urinary tract infections were more common in the fosfomycin group, suggesting that antimicrobial treatment may result in recurrent UTIs. The authors conclude that, although they cannot generally recommend ibuprofen as first line treatment for uncomplicated UTI in women, the treatment option can be discussed with women with mild to moderate symptoms in a shared decision making approach, or within a strategy of delayed or back-up prescribing. As there are more side-effects with ibuprofen than with naproxen, the latter could be considered an alternative NSAID to use.

8. Arfe A, Scotti L, Varas-Lorenzo C, Nicotra F, Zambon A, Kollhorst B et al. Non-steroidal anti-inflammatory drugs and risk of heart failure in four European countries: nested case-control study. *BMJ*. 2016 Sep; 354(4857):1-11. Available from:

<http://www.bmj.com/content/354/bmj.i4857>.

RATIONALE: A nested case-control study aiming to investigate the cardiovascular safety of non-steroidal anti-inflammatory drugs, and estimate the risk of hospital admission for heart failure with use of individual NSAIDs. 92,163 hospital admissions for heart failure and NSAID treatment were identified and matched with 8,246,403 controls. Results indicated that current use of NSAIDs were found to be associated with a 19% increase of risk of hospital admission for heart failure, compared with past use of any NSAID (AOR) 1.19; 95% CI 1.17 to 1.22). Risk of admission for heart failure increased for seven traditional NSAIDs (diclofenac; ibuprofen; indomethacin; ketorolac; naproxen; nimesulide; piroxicam), and two COX2 inhibitors (etoricoxib; rofecoxib). The authors conclude that the risk of hospital admission for heart failure associated with current use of NSAIDs appears to vary between individual NSAIDs, and this effect is dose dependent. The side-effects of various NSAIDs should be considered before taking for pain relief.

9. Knotterus BJ, Geerlings SE, Moll van Charante EP, ter Riet G. Women with symptoms of uncomplicated urinary tract infection are often willing to delay antibiotic treatment: a prospective cohort study. *BMC Fam Pract*. 2013 May; 14(71):1-6. Available from:

<http://bmcfampract.biomedcentral.com/articles/10.1186/1471-2296-14-71>.

RATIONALE: A prospective cohort study, aiming to investigate how many women presenting with UTI symptoms were willing to delay antibiotic treatment when asked by their general practitioner. 137 of 176 women were asked by their GP to delay antibiotic treatment, and 37% (51/137) were willing to delay. After one week, 55% (28/51) of delaying women had not used antibiotics, with 71% (20/28) reporting clinical improvement or cure, and none of the participating women developed pyelonephritis. The authors conclude that women with UTI symptoms may be more receptive to delayed antibiotic prescriptions than is assumed by many clinicians. As a safe alternative to antibiotics (without the risk of bacterial resistance), symptomatic treatment may be offered.

10. Little P, Moore MV, Turner S, Rumsby K, Warner G, Lowes JA et al. Effectiveness of five different approaches in management of urinary tract infection: randomised controlled trial. *BMJ*. 2010 Feb; 340(199):1-6. Available from: <http://www.bmj.com/content/340/bmj.c199>.

RATIONALE: A randomised controlled trial of 309 non-pregnant women with a suspected uncomplicated UTI, aiming to assess five UTI management strategies: empirical antibiotics; empirical delayed antibiotics (by 48 hours); targeted antibiotics, based on a symptom score (two or more of urine cloudiness, urine smell, nocturia, or dysuria), dipstick

Management and treatment of common infections-Antibiotic guidance for primary care

result (nitrite, or both leukocytes and blood), or positive midstream urine analysis. All participants were also given written information on symptom management specific to their management approach. Patients were excluded if immediate antibiotic treatment was necessary (pregnant; pyelonephritis; nausea; vomiting; severe systemic symptoms), if they were aged over 75, or if they had psychosis or dementia, or needed terminal care. Patients had 3.5 days of moderately bad symptoms if they took antibiotics immediately, and there were no significant differences in duration or severity of symptoms between the five groups. Patients who waited at least 48 hours to start taking antibiotics reconsulted less (HR 0.57; 43% reduction; 95% CI 0.36 to 0.89; $p=0.014$), but on average, had symptoms for 37% longer than those taking immediate antibiotics. The authors conclude that antibiotics targeted with dipstick tests and a delayed prescription as back-up, or empirical delayed prescription, help to reduce antibiotic use.

11. Little P, Turner S, Rumsby K, Warner G, Moore M, Lowes JA et al. Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort and qualitative study. *Health Technol Assess*. 2009 Mar; 13(19):1-73. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19364448>.

RATIONALE: Six studies were carried out, aiming to estimate clinical and dipstick predictors of infection and develop and test clinical scores, and to compare management using clinical and dipstick scores with commonly used alternative strategies. The results showed that, in women with uncomplicated UTI, the negative predictive value when nitrite, leukocytes, and blood are all negative was 76%. The positive predictive value for having nitrite and either blood or leukocytes was 92%. The authors conclude that, to achieve good symptom control and reduce antibiotic use, clinicians should either offer a 48-hour delayed antibiotic prescription to be used at the patient's discretion, or target antibiotic treatment by dipsticks (positive nitrite or positive leukocytes and blood) with the offer of a delayed prescription if dipstick results are negative.

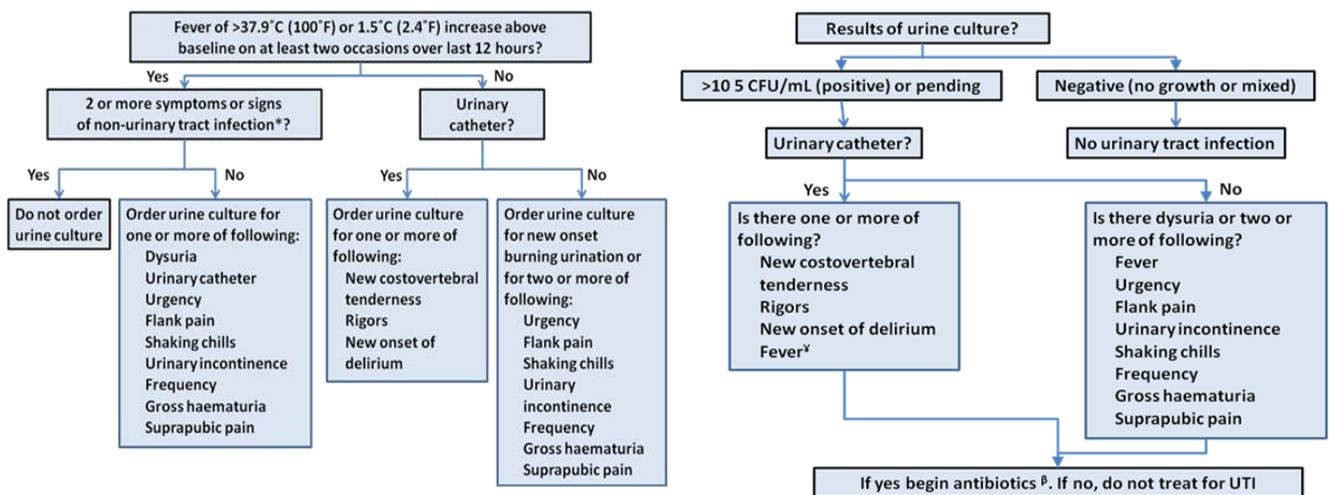
12. European Association of Urology. Guidelines on urological infections. 2015 Mar. Available from: http://uroweb.org/wp-content/uploads/19-Urological-infections_LR2.pdf.

RATIONALE: An expert guideline, aiming to provide both urologists and physicians from other medical specialities with evidence-based guidance regarding the treatment and prophylaxis of urinary tract infections. This guideline states that, in men, a urine sample is recommended for UTIs because they are generally regarded as complicated (the result of an anatomic or functional abnormality), and there are no studies on the predictive value of dipstick testing. There is no evidence to guide duration of treatment in men, but expert consensus is that seven days of antibiotics should be used, as there is likely to be a complicating factor. Although the use of dipstick testing has not been well studied in men, it seems reasonable to extrapolate results from studies of dipstick testing in women with suspected UTI to men with mild symptoms of UTI, as contamination is likely to be lower.

13. Loeb M, Brazil K, Lohfeld L, McGeer A, Simor A, Stevenson K et al. Effect of a multifaceted intervention on number of antimicrobial prescriptions for suspected urinary tract infections in residents of nursing homes: cluster randomised controlled trial. *BMJ*. 2005 Sep; 331(7518):669. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1226247/>.

Management and treatment of common infections-Antibiotic guidance for primary care

RATIONALE: A cluster randomised controlled trial in 24 nursing homes in Ontario, Canada, and Idaho, United States, with 12 allocated to a multifaceted intervention, and 12 allocated to usual care. A diagnostic and treatment algorithm was implemented in the multifaceted intervention, suggesting that urine cultures should only be ordered if there is a fever of $>37.9^{\circ}\text{C}$, or a 1.5°C increase above baseline on at least two occasions over the previous 12 hours, and one or more of the following: dysuria; urinary catheter; urgency; flank pain; shaking chills; urinary incontinence; frequency; gross haematuria; suprapubic pain. Antibiotics should only be prescribed on a positive or pending culture ($>10^5$ CFU/mL). Fewer courses of antimicrobials were prescribed in the intervention nursing homes than in the usual care homes (weighted mean difference -0.49 ; 95% CI -0.93 to -0.06). Antimicrobials for suspected urinary tract infection represented 28.4% of all courses of drugs prescribed in the intervention nursing homes, compared with 38.6% prescribed in the usual care homes. The difference in total antimicrobial use between intervention and usual care groups was not significantly different (weighted mean difference -0.37 ; 95% CI -1.17 to 0.44). A multifaceted intervention using algorithms can reduce the number of antimicrobial prescriptions for UTIs in residents of nursing homes.



14. Kandel R, Doron S, Salen-Schatz S, McElroy N, Griswold P, DeMaria A. Antimicrobial stewardship in long-term care facilities: an urgent need. 2016 Mar (*unpublished*). Available from: <http://www.macoalition.org/evaluation-and-treatment-uti-in-elderly.shtml>.

RATIONALE: A collaborative study, showing that a complex intervention in care homes, using the Loeb diagnostic criteria, improves diagnosis of UTIs, antibiotic use, and rates of *C. difficile*. Four clinician materials were used: a checklist-based worksheet in practice to guide decisions and communication about testing urine and treating UTIs in long-term care, adapted from the Loeb criteria; a clinician education sheet; a mnemonic poster for assessing change in mental status; talking with families about UTIs, bacteriuria and antibiotics. Several brochures were also developed for residents and families to educate them about the problem of antibiotic overuse and resistance, and appropriate diagnosis of UTIs. 36 facilities participated with 17 submitting data (47%) in the first collaborative, and 32 facilities participated with 25 submitting data (78%) in the second collaborative. Statistically significant decreases in urine culture and UTI diagnosis rates were seen over

Management and treatment of common infections-Antibiotic guidance for primary care

the course of both the first and second collaboratives. There was a downward trend over all time periods for rates of UTIs diagnosed that did not meet criteria for symptomatic UTIs as set forth by the collaboratives. There was also a trend toward decreased *Clostridium difficile* rates over the course of the study, but this was not statistically significant. The authors conclude that this current study adds to the literature demonstrating behaviour change with a multifaceted educational program directed at long-term care facilities, including multiple venues for teaching and support, literature for distribution to staff and families, and a practical algorithm adapted from the Loeb criteria.

15. Christiaens TCM, De Meyere M, Verschraegen G, Peersman W, Heytens S, De Maeseneer JM. Randomised controlled trial of nitrofurantoin versus placebo in the treatment of uncomplicated urinary tract infection in adult women. *Br J Gen Pract.* 2002 Sep; 52(482):729-734. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1314413/>.

RATIONALE: A small double-blind randomised controlled trial, including 166 women consulting with symptoms suggestive of UTI. 78 women had pyuria and agreed to participate in the study; of these, 40 received nitrofurantoin and 38 received placebo. Results indicated that nitrofurantoin 100mg QDS for three days was more effective than placebo at attaining symptomatic cure (80% and 88% at three and seven days; placebo 54% and 51%, respectively). Nitrofurantoin 100mg QDS for three days was also more effective than placebo at attaining bacteriological cure ($<10^5$ CFU/ml) at both three days and seven days (81% and 74%, respectively).

16. Chin TL, MacGowan AP, Bowker KE, Elder F, Beck CR, McNulty C. Prevalence of antibiotic resistance in *Escherichia coli* isolated from urine samples routinely referred by general practitioners in a large urban centre in south-west England. *J Antimicrob Chemother.* 2015 Mar; 70(7):2167-2169. Available from: <https://academic.oup.com/jac/article-lookup/doi/10.1093/jac/dkv050>.

RATIONALE: A prospective study, in which the authors analysed the activity of 15 antimicrobials against 193 consecutive *E. coli* urinary isolates. The authors found that the agents widely used or recommended for the treatment of UTI, ie amoxicillin; co-amoxiclav; trimethoprim, had levels of susceptibility of less than 65%. Only nitrofurantoin and cefradine had susceptibility rates of over 90%. For *E. coli*, 32% were resistant to amoxicillin and trimethoprim; 12% were resistant to amoxicillin, trimethoprim, and ciprofloxacin; 6% were resistant to amoxicillin, co-amoxiclav, trimethoprim, and ciprofloxacin. Of the other possible oral agents to treat UTI, co-trimoxazole offered little advantage over trimethoprim alone (susceptibility 64% versus 58%, respectively), while only cefixime and fosfomycin had clinically useful in vitro activity against over 90% of strains. As only 58% of isolates were susceptible to trimethoprim, the authors suggest that trimethoprim should not be used empirically in this population, contrary to NICE and SIGN recommendations. Also, given that susceptibility to nitrofurantoin, mecillinam and fosfomycin is high, there is potential for increased use of these agents in the community.

17. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A

Management and treatment of common infections-Antibiotic guidance for primary care

2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*. 2011 Mar; 52(5):103-120. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/21292654>.

RATIONALE: An international guideline and consensus statement based on a meta-analysis of evidence from 1998. In this guideline, the authors assert that nitrofurantoin monohydrate/macrocrystals (100mg, twice daily, for five days) is an appropriate choice for therapy due to minimal resistance and propensity for collateral damage, and the efficacy is comparable to three days of trimethoprim/sulfamethoxazole.

Trimethoprim/sulfamethoxazole (160/800mg, twice daily, for three days) is an appropriate choice for therapy, given its efficacy as assessed in numerous clinical trials, if local resistance rates of uropathogens causing acute uncomplicated cystitis do not exceed 20%, or if the infecting strain is known to be susceptible.

18. Zalmanovici Trestioreanu A, Green H, Paul M, Yaphe J, Leibovici L. Antimicrobial agents for treating uncomplicated urinary tract infection in women (Review). *Cochrane Database Syst Rev*. 2010 Oct; 6(10):1-100. Available from:

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007182.pub2/epdf>.

RATIONALE: A systematic review and meta-analysis of 21 studies, involving 6,016 participants. The authors found that trimethoprim/sulfamethoxazole (TMP-SMX) was as effective as fluoroquinolones in achieving short-term (RR 1.0; no difference; 95% CI 0.97 to 1.03) and long-term (RR 0.99; 1% difference; 95% CI 0.94 to 1.05) symptomatic cure. Beta-lactam drugs were as effective as TMP-SMX for short-term (RR 0.95; 5% difference; 95% CI 0.81 to 1.12) and long-term (RR 1.06; 95% CI 0.93 to 1.21) symptomatic cure. Short-term cure for nitrofurantoin was similar to that of TMP-SMX (RR 0.99; 1% difference; 95% CI 0.95 to 1.04), as was long-term symptomatic cure (RR 1.01; 95% CI 0.94 to 1.09). Fluoroquinolones were more effective than beta-lactams for short-term bacteriological cure (RR 1.22; 95% CI 1.13 to 1.31). The authors conclude that no differences were observed between the classes of antimicrobials included in this review for the symptomatic cure of uncomplicated UTI. Fluoroquinolones should be reserved for the treatment of pyelonephritis. Individualised treatment should take into consideration the predictable susceptibility of urinary pathogens in local areas, possible adverse events, resistance development, and patient preference.

19. Baines SD, O'Connor R, Huscroft G, Saxton K, Freeman J, Wilcox MH. Mecillinam: a low-risk antimicrobial agent for induction of *Clostridium difficile* infection in an in vitro human gut model. *J Antimicrob Chemother*. 2009 Apr; 63(4):838-839. Available from:

<https://academic.oup.com/jac/article-lookup/doi/10.1093/jac/dkp017>.

RATIONALE: A prospective study stating that pivmecillinam is the oral preparation of mecillinam. Pivmecillinam is a prodrug that is very well absorbed intestinally, and as such, has minimal effect on the normal intestinal microflora. The authors conclude that there is a lower rate of *Clostridium difficile* with pivmecillinam than with other antimicrobials. However, future use of quantitative molecular technologies may help to elucidate the behaviour of *C. difficile* exposed to antimicrobial stresses, and so help to identify bacterial groups potentially important in colonisation resistance.

Management and treatment of common infections-Antibiotic guidance for primary care

20. Dewar S, Reed LC, Koerner RJ. Emerging clinical role of pivmecillinam in the treatment of urinary tract infection in the context of multidrug-resistant bacteria. *J Antimicrob Chemother.* 2014 Feb; 69(2):303-308. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/24068280>.
RATIONALE: A review article, stating that UTI, usually due to Gram-negative bacteria, are among the most common infections seen in the community. Bacterial strains producing extended-spectrum β -lactamases (ESBLs) that are resistant not only to cephalosporins and penicillins, but also to fluoroquinolones and trimethoprim, are becoming more prevalent in the community. The author's state that there is emerging in vitro and in vivo evidence of pivmecillinam's activity against ESBL-producing organisms, and suggest that pivmecillinam has a minimal effect on the intestinal and vaginal flora, thus, there is a lower rate of selection of resistant bacteria. When considering *C. difficile* specifically the author's note that mecillinam did not elicit *C. difficile* germination, proliferation or toxin production. They then conclude that pivmecillinam appears to be a 'low-risk agent' for the induction of *C. difficile* infection.
21. Milo G, Katchman EA, Paul M, Christiaens T, Baerheim A, Leibovici L. Duration of antibacterial treatment for uncomplicated urinary tract infection in women (Review). *Cochrane Database Syst Rev.* 2005 Apr; 18(2):1-83. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004682.pub2/epdf>.
RATIONALE: A systematic review demonstrating no difference in outcome between a three day, five day, or a ten day antibiotic treatment course for uncomplicated UTI in women (RR 1.06; 95% CI 0.88 to 1.28; 32 trials; n=9,605). In this systematic review, there were several trials of pivmecillinam used at 200mg three times daily for three days, which showed similar efficacy to pivmecillinam 200mg for ten days, cephalexin 250mg for seven days, or cotrimoxazole for seven days. One trial showed that pivmecillinam 400mg TDS for three days had similar efficacy to 200mg TDS for seven days, or ten days. Another study showed that pivmecillinam 400mg BD for three days had similar efficacy to pivmecillinam 400mg BD for seven days.
22. Falagas ME, Kotsantis IK, Vouloumanou EK, Rafailidis PI. Antibiotics versus placebo in the treatment of women with uncomplicated cystitis: a meta-analysis of randomized controlled trials. *J Infect.* 2009 Feb; 58(2):91-102. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19195714>.
RATIONALE: A systematic review and meta-analysis of five double-blind randomised controlled trials, assessing the benefits of antibiotics versus placebo in 1,407 patients. Antibiotics included were pivmecillinam, nitrofurantoin, cefixime, co-trimoxazole, and amoxicillin. The results of the meta-analysis provided evidence that clinical success was significantly more likely in women treated with antibiotics versus those treated with placebo (OR 4.81; 95% CI 2.51 to 9.21; four RCTs, n=1,062). Antibiotics were also superior to placebo, regarding cure (OR 4.67; 95% CI 2.34 to 9.35; four RCTs; n=1,062); microbiological eradication at the end of treatment (OR 10.67; 95% CI 2.96 to 38.43; three RCTs, n=967); microbiological eradication after the end of treatment (OR 5.38; 95% CI 1.63 to 17.77; three RCTs, n=738); microbiological reinfection or relapse (OR 0.27; 73% reduction; 95% CI 0.13 to 0.55; five RCTs, n=843). Adverse events were more likely to

Management and treatment of common infections-Antibiotic guidance for primary care

occur in antibiotic-treated patients versus placebo-treated patients (OR 1.64; 95% CI 1.10 to 2.44; four RCTs, n=1,068). No difference was found between the compared treatment arms regarding study withdrawal from adverse events, the development of pyelonephritis, or the emergence of resistance.

23. Huttner A, Verhaegh EM, Harbarth S, Muller AE, Theuretzbacher U, Mouton JW. Nitrofurantoin revisited: a systematic review and meta-analysis of controlled trials. *J Antimicrob Chemother.* 2015 Sep; 70(9):2456-2464. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26066581>.

RATIONALE: A systematic review and meta-analysis of 27 controlled clinical trials and 4,807 patients, to assess nitrofurantoin's efficacy and toxicity in the treatment of lower UTI. This review sites one open-label randomised trial, which compares three day regimens of high-dose nitrofurantoin (100mg four times daily), trimethoprim/sulfamethoxazole (200mg twice daily), cefadroxil (500mg twice daily), and amoxicillin (500mg three times daily). Results indicated that, at six weeks post-therapy, nitrofurantoin's clinical efficacy is only 61%. Results confirmed that nitrofurantoin appears to have good clinical and microbiological efficacy for UTI caused by common uropathogens, with clinical cure rates varying between 79% and 92%. The most methodologically robust studies indicated an overall equivalence between nitrofurantoin, when given for five or seven days, and trimethoprim/sulfamethoxazole, ciprofloxacin and amoxicillin. Meta-analyses of randomised controlled trials confirmed equivalence in clinical cure, but indicated a slight advantage to comparator drugs in microbiological efficacy (RR 0.93, 7% advantage; 95% CI 0.89 to 0.97). If given for only three days, nitrofurantoin's clinical efficacy was diminished (61% to 70%); toxicity was infrequent (5% to 16%), mild, reversible, and predominantly gastrointestinal. The authors conclude that nitrofurantoin appears to have clinical efficacy equivalent to that of trimethoprim/sulfamethoxazole, ciprofloxacin and amoxicillin, although meta-analyses for microbiological cure indicate a slightly more favourable effect for comparators. Nitrofurantoin appears to achieve therapeutic concentrations only in the lower urinary tract, restricting its indication to the treatment of lower UTI. Acquisition of resistance to nitrofurantoin is still relatively rare, although it is likely to rise given recent increases in consumption. It is important to note that treatment durations of at least five days do appear to optimise efficacy. However, this review does not include any studies that directly compare three to five days' nitrofurantoin.

24. Falagas ME, Kastoris AC, Kapaskelis AM, Karageorgopoulos DE. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum beta-lactamase producing, Enterobacteriaceae infections: a systematic review. *Lancet Infect Dis.* 2010 Jan; 10(1):43-50. Available from: <http://www.sciencedirect.com/science/article/pii/S1473309909703251>.

RATIONALE: A systematic review of the literature, stating that 97% of ESBL-producing *Escherichia coli* isolates and 81% of *Klebsiella pneumoniae* ESBL-producing isolates are susceptible to fosfomycin. Fosfomycin is available commercially as an intravenous and oral licensed product in the UK. Food intake can slow down the absorption of fosfomycin, with a result of lower concentrations of the antimicrobial in the urine. The authors therefore conclude that fosfomycin should be administered whilst fasting, or two or three hours

Management and treatment of common infections-Antibiotic guidance for primary care

before meals.

25. Naber KG, Schito G, Botto H, Palou J, Mazzei T. Surveillance study in Europe and Brazil on clinical aspects and Antimicrobial Resistance Epidemiology in Females with Cystitis (ARESC): implications for empiric therapy. *Eur Urol.* 2008 Nov; 54(5):1164-1175. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18511178>.

RATIONALE: A surveillance study across 68 centres in nine European countries and Brazil, including clinical data from 4,264 patients. In all countries, despite wide cross-country variability of bacterial susceptibility/resistance rates, susceptibility rates to *E. coli* above 90% ($p < 0.0001$) were found for fosfomycin, mecillinam (the active component of pivmecillinam), and nitrofurantoin. The authors conclude that these antimicrobials may therefore represent good options for the empiric therapy of female patients with uncomplicated cystitis. It is, however, noted that fosfomycin is contraindicated in patients with a creatinine clearance of less than 10mL/min, so should be avoided in this population.

26. National Institute for Health and Care Excellence (NICE). Multidrug resistant urinary tract infections: fosfomycin trometamol. 2013 Jul. Available from:

<https://www.nice.org.uk/advice/esuom17/chapter/Key-points-from-the-evidence>.

RATIONALE: A NICE guideline, based on four small observational studies, stating that, following advice from a microbiologist, fosfomycin should be considered for treating adults with uncomplicated urinary tract infections, due to extended-spectrum beta-lactamase-producing *Escherichia coli*. Results from these trials indicated that the use of fosfomycin results in a clinical cure rate of between 92.9% and 95%, and a microbiological cure rate of between 58.5% and 78.8%. This guideline states that a single 3g dose of fosfomycin is recommended in women, and in men, a second 3g dose should be taken on day three.

27. Spencer RC, Moseley DJ, Greensmith MJ. Nitrofurantoin modified release versus trimethoprim or co-trimoxazole in the treatment of uncomplicated urinary tract infection in general practice. *J Antimicrob Chemother.* 1994 May; 33(1):121-129. Available from:

<http://www.ncbi.nlm.nih.gov/pubmed/7928829>.

RATIONALE: A non-blinded randomised controlled trial ($n=538$), which found that nitrofurantoin m/r had equivalent clinical cure rates to co-trimoxazole and trimethoprim. The rate of gastrointestinal adverse effects was similar between the co-trimoxazole and trimethoprim groups (7.3% to 8.8%), but was reportedly less in the nitrofurantoin m/r group (5.6%). A seven day treatment regimen was used with each antibiotic; no shorter durations were trialled.

28. MeReC Bulletin National Prescribing Centre. Modified-release preparations. 2000 Aug.

Available from: [http://www.palliativedrugs.com/download/MeReCBull%20200011\(4\).pdf](http://www.palliativedrugs.com/download/MeReCBull%20200011(4).pdf).

RATIONALE: A bulletin stating that modified-release preparations can be used to reduce dosing frequency of antimicrobials. The authors note that reduced dosing frequency (eg, from four times daily to twice daily) improves patient compliance.

29. Soraas A, Sundsfjord A, Jorgensen SB, Liestol K, Jennum PA. High rate of per oral mecillinam

Management and treatment of common infections-Antibiotic guidance for primary care

treatment failure in community-acquired urinary tract infections caused by ESBL-producing *Escherichia coli*. *PLoS One*. 2014 Jan; 9(1):1-7. Available from:

<http://journals.plos.org/plosone/article/asset?id=10.1371%2Fjournal.pone.0085889.PDF>.

RATIONALE: A Norwegian prospective study, in which treatment failure of UTI with mecillinam was attributed to the 200mg dose used in Norway. The authors present evidence that the 200mg dose will only achieve a serum concentration above the MIC for 40% of the time, even if the MIC is less than 0.25mg/L. Therefore, a 400mg dose of mecillinam should be prescribed for patients with an increased risk of antibiotic resistance.

30. Jansaker F, Frimodt-Moller N, Sjogren I, Dahl Knudsen J. Clinical and bacteriological effects of pivmecillinam for ESBL-producing *Escherichia coli* or *Klebsiella pneumoniae* in urinary tract infections. *J Antimicrob Chemother*. 2014 Mar; 69(3):769-772. Available from:

<http://jac.oxfordjournals.org/content/69/3/769.full.pdf+html>.

RATIONALE: A prospective GP and hospital-based study across Denmark, Holland and Sweden, following 39 patients diagnosed with UTI caused by ESBL-producing enterobacteriaceae, susceptible to and treated with pivmecillinam. The bacteriological cure for 400mg and 200mg three times daily was 80% (24/30) and 78% (7/9), respectively. Of the eight patients with bacteriological failure, five were reported to have an indwelling urinary catheter, pathological urinary tract, and/or recurrent UTI. Two patients who received 200mg and one who received 400mg three times daily, with bacteriological cure, still had a positive urine sample ($\geq 10^3$ CFU/mL), but with a significant reduction (pre-treatment urine of $\geq 10^5$ CFU/mL). The authors conclude that pivmecillinam is bacteriologically and clinically effective for the treatment of lower UTI caused by ESBLs.

31. Malcolm W, Kavanagh K, Wiuff C, Reid N, Deshpande A, Marwick C et al. Risk factors associated with antibiotic resistance in urinary isolates in the community: an exemplar of NHS Scotland's Infection Intelligence Platform. 2016 Oct (*unpublished*). Available from: <http://fishis2016-abstracts.elsevierdigitaledge.com/#16/z>.

RATIONALE: A surveillance study in Glasgow and Clyde CCG, aiming to use individual level linked data to characterise factors associated with antibiotic resistance in urine samples in 17,046 patients. All positive community urine samples from January 2012 to June 2015 were included and analysed. All cases were linked to national hospital activity data and patient-level community prescribing data. Risk factors associated with antibiotic susceptibility were assessed using multivariable multinomial logistic regression. Results indicated that age, care home residence, and increasing comorbidity were significantly associated with both categories of resistance after adjustment for other factors. Interestingly, there were no significant differences in repeat prescriptions within 42 days depending on whether patients were prescribed three (17.1%), five (16.8%), or seven days (17.3%) nitrofurantoin.

32. Goettsch G, Janknegt R, Herings RM. Increased treatment failure after 3 days' courses of nitrofurantoin and trimethoprim for urinary tract infections in women: a population-based retrospective cohort study using the PHARMO database. *B J Clin Pharmacol*. 2003 Nov; 58(2):184-189. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1884592/>.

Management and treatment of common infections-Antibiotic guidance for primary care

RATIONALE: A retrospective cohort study of 16,703 Dutch women between 15 and 65 years of age, aiming to assess determinants of treatment failure after antimicrobial therapy for urinary tract infections in women. Participants received a first course (three, five, or seven days) of trimethoprim, nitrofurantoin, or norfloxacin. A multivariate analysis showed that treatment with trimethoprim or nitrofurantoin for five days (RR 0.67; 33% effectiveness; 95% CI 0.57 to 0.82; RR 0.82; 95% CI 0.73 to 0.91, respectively) and seven days (RR 0.64; 36% effectiveness; 95% CI 0.53 to 0.77; RR 0.85; 95% CI 0.71 to 1.02, respectively) appeared to be more effective than three days treatment. The authors note that treatment failure was highest in patients receiving a three day course of nitrofurantoin (18.9%), with longer treatments of five and seven days demonstrating lower failure rates, with 13.1% and 12.5%, respectively. It is noted that recommendation for three days' treatment with nitrofurantoin is based on one small clinical trial, in which cure rate was measured at only 61%. The authors conclude that three day courses of nitrofurantoin are less effective than five and seven day courses in the treatment of uncomplicated urinary tract infections in women. However, expert opinion is that the patients given five or seven day treatment probably had different illness severity to those given three days treatment.

33. Hooton TM, Winter C, Stamm WE. Randomized comparative trial and cost analysis of 3 day antimicrobial regimens for treatment of acute cystitis in women. *JAMA*. 1995 Jan; 273(1):41-45. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/7654268>.

RATIONALE: A prospective randomised trial of 149 female students in four different treatment arms for acute cystitis, showing that three days nitrofurantoin 100mg m/r QDS in 38 patients was not as effective as three days trimethoprim sulfamethoxazole 160mg/800mg BD in 40 patients. At four to six days after enrolment (early follow-up), only one of 40 participants treated with trimethoprim sulfamethoxazole had persistent significant bacteriuria with the initial infecting strain, compared to six out of 38 treated with nitrofurantoin, none of 37 treated with cefadroxil, and six out of 43 treated with amoxicillin. At four to six weeks after treatment (late follow-up), the trimethoprim sulfamethoxazole treatment arm achieved clinical cure in 82% of cases, compared to 61% in the nitrofurantoin treatment arm (p=0.04; 95% CI 1% to 41%), 66% in the cefadroxil treatment arm (p=0.11; 95% CI -4% to 37%), and 67% in the amoxicillin treatment arm (p=0.11; 95% CI -3% to 34%). This indicates that, if bacteriological clearance is important, a longer course of treatment may be appropriate. Symptomatic cure was reported as 32/39 for the trimethoprim-sulfamethoxazole group (82%), 22/36 for the nitrofurantoin group (61%), 21/32 for the cefadroxil group (66%), and 28/42 for the amoxicillin group (67%). The authors conclude that a three day regimen of trimethoprim sulfamethoxazole is effective in treating uncomplicated urinary tract infections, and should be considered as more effective than treatment with nitrofurantoin m/r, cefadroxil, or amoxicillin.

34. Marsh BT, Menday AP. Comparative efficacy of 3 day and 7 day chemotherapy with pivmecillinam in urinary tract infections in general practice. *J Int Med Res*. 1980 Jul; 8(2):105-111. Available from: <http://journals.sagepub.com/doi/pdf/10.1177/030006058000800201>.

RATIONALE: A prospective study of 125 non-pregnant women, aiming to evaluate 3 day versus 7 day courses of treatment with pivmecillinam in uncomplicated urinary tract

Management and treatment of common infections-Antibiotic guidance for primary care

infections. 67 women received a 7 day course of pivmecillinam 200mg three times daily, and 58 were given a 3 day course of pivmecillinam 200mg three times daily. Findings indicated that all patients given seven days treatment had insignificant bacteriuria post-treatment, and 91% in the 3 day group were cured of their infection. Both treatments seemed equally effective in infections due to sensitive and resistant organisms. Only two women who had received three days pivmecillinam were still infected with the original pathogen at follow-up. There was no significant difference between the two treatment regimens in symptomatic recurrences. The authors conclude that, although the investigation comprised a limited number of patients, in women with uncomplicated acute cystitis, three days' treatment with pivmecillinam seems to be as effective as a seven day course of the same drug at the same dosage. Although seven days treatment gave a higher bacteriological cure rate (100%) when compared to that obtained with three days therapy (91%), this difference is not significant.

35. Sutcliffe PA. A comparison between a 3 day and a 5 day course of pivmecillinam as a treatment for acute lower urinary tract infections in general practice. *Current Medical Research and Opinion*. 1982 Jul; 7(9):563-568. Available from:

<http://www.tandfonline.com/doi/abs/10.1185/03007998209110100>.

RATIONALE: A multi-centre study of 88 general practice patients (82 females and six males) with symptoms of acute urinary tract infection. Patients were randomly assigned to a ten tablet (2g) course of pivmecillinam, either as a twice or three times daily dosage. Positive bacteriological cultures were obtained from 44 (50%) patients before treatment, and recorded bacteriological cure rates were 95% in the three day treatment group, and 96% in the five day treatment group. A good clinical response was seen in the majority of patients, and 55 (63%) patients became symptom-free by the follow-up visit. Pivmecillinam was well tolerated, with side-effects reported in three (7%) patients in the three day treatment group, and nine (17%) patients in the five day treatment group. The authors conclude that a three day course of pivmecillinam is as effective as a five day course of treatment.

36. Lutters M, Vogt-Ferrier NB. Antibiotic duration for treating uncomplicated, symptomatic lower urinary tract infections in elderly women (Review). *Cochrane Database Syst Rev*. 2008 Jul; 16(3):1-70. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/18646074>.

RATIONALE: A systematic review and meta-analysis of four studies comparing three days treatment to seven days treatment with ciprofloxacin or norfloxacin, and one study comparing three days treatment to five days treatment with trimethoprim, in uncomplicated UTI in elderly women (age 60 or over). No significant differences were recorded in persistent UTI, clinical failure, or re-infection rates, but side-effects were higher in those given seven days treatment.

37. Gupta K, Hooton TM, Roberts PL, Stamm WE. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. *Arch Intern Med*. 2007 Nov; 167(20):2207-2212. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/17998493>.

RATIONALE: A randomised, open-label trial, involving 338 women aged between 18 and

Management and treatment of common infections-Antibiotic guidance for primary care

45 with acute uncomplicated cystitis. Two treatment arms were included, one with women being treated with trimethoprim sulfamethoxazole one double-strength tablet twice daily for three days, and one with women being treated with nitrofurantoin 100mg twice daily for five days. Clinical cure 30 days after therapy was measured. Results indicated that 79% of the women being treated with trimethoprim sulfamethoxazole achieved clinical cure, compared with 84% of the group treated with nitrofurantoin (95% CI -13% to 4%). Similar proportions of women reported adverse effects to medication (31% with trimethoprim; 28% with nitrofurantoin), with most effects being of a gastrointestinal nature. However, fewer women in the nitrofurantoin group required treatment for adverse effects (6%, compared to 11% in the trimethoprim group). The authors conclude that a five day course of nitrofurantoin is equivalent clinically and microbiologically to a three day course of trimethoprim sulfamethoxazole, and should be considered as an effective treatment. It is however noted that at three days, 98% of women had achieved microbiological cure.

38. Nicolle LE. Pivmecillinam in the treatment of urinary tract infections. *J Antimicrob Chemother.* 2000 Sep; 46(1):35-39. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/11051622>.

RATIONALE: A review of the literature, suggesting that bacteriological cure rates with pivmecillinam are consistently more than 85%, therefore suggesting that a three day course is appropriate for the treatment of uncomplicated urinary tract infections. Findings from a range of studies have indicated that: at early post-therapy follow-up, bacteriological cure rate for pivmecillinam is 75%; after four days, there is a satisfactory clinical response in 95% of subjects; after 11 days, 82% of subjects receiving pivmecillinam had achieved clinical cure (95% CI 0.9% to 10.3%). Another clinical trial compared pivmecillinam 200mg TDS for seven days, 200mg BD for seven days, and 400mg BD for three days, compared with placebo. Of the 69% bacteriologically evaluable patients, eight to ten days after therapy, cure rates were 85%, 90%, 79%, and 28%, respectively. This suggests that both seven day regimens were better than the three day regimen ($p=0.002$), but the seven day TDS regimen showed only a trend to improved outcome ($p=0.068$). The authors conclude that a seven day treatment regimen gives better outcomes than a three day course, but clinical response may be better than bacteriological response. The authors also state that the shorter three day course of pivmecillinam would be effective empirical therapy for the majority of women with uncomplicated UTI, particularly premenopausal women.

39. Ben-Ami R, Rodriguez-Bano J, Arslan H, Pitout JD, Quentin C, Calbo ES et al. A multinational survey of risk factors for infection with extended-spectrum beta-lactamase-producing enterobacteriaceae in nonhospitalized patients. *Clin Infect Dis.* 2009 Sep; 49(5):682-690. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/19622043>.

RATIONALE: A survey paper, in which the authors identified significant risk factors through multivariate analysis. These risk factors included: recent antibiotic use; residence in a long-term care facility; recent hospitalisation; aged 65 years or older; male sex. The authors do note, however, that 34% of ESBL-producing isolates (115 of 336) were obtained from patients with no recent healthcare contact.

40. Rossignol L, Maugat S, Blake A, Vauz S, Heym B, Le Strat Y et al. Risk factors for resistance

Management and treatment of common infections-Antibiotic guidance for primary care

in urinary tract infections in women in general practice: a cross-sectional survey. *J Infect.* 2015 Sep; 71(3):302-311. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/26054878>.

RATIONALE: A cross-sectional survey conducted in 2012-2013 in women visiting a general practitioner for a urinary tract infection, aiming to identify the factors associated with UTIs due to a multi-drug-resistant Enterobacteriaceae. Urine analyses were performed for all adult women presenting with signs of UTI. Findings indicated that significant factors associated with MDREB included: the use of penicillin by the patient in the last three months (OR = 3.1; 1.2 to 8.0); travel in the previous 12 months to a country at high risk for drug resistance (OR = 4.0; 1.2 to 15.1); the consumption of raw meat within the previous three months (OR = 0.3; 0.1 to 0.9). The authors conclude that, in the community, antibiotic use and exposure to a person from an area with a high risk of drug resistance are associated with UTIs due to MDREB.

41. Drug and Therapeutics Bulletin (DTB). Risks of extended-spectrum beta-lactamases. *BMJ.* 2008 Mar; 46(3):21-24. Available from: <http://dtb.bmj.com/content/46/3/21.abstract>.

RATIONALE: A bulletin stating that some bacteria produce extended-spectrum beta-lactamases. These are able to hydrolyse antibiotics that were designed to resist the action of older beta-lactamases. These organisms may be resistant to most antibiotics commonly used to treat UTI, such as trimethoprim, ciprofloxacin, co-amoxiclav, and cephalosporins.

UTI in patients with catheters:

1. National Institute for Health and Care Excellence (NICE). Urinary tract infections in adults. 2015 Jun. Available from: <https://www.nice.org.uk/guidance/qs90>.

RATIONALE: A NICE guideline, providing information on assessment, antibiotic treatment, and referral for specialist assessment in urinary tract infections in adults. This guideline states that antibiotics should not be prescribed to treat asymptomatic bacteriuria in adults with catheters, as they are not effective, and can increase the resistance of the bacteria that cause urinary tract infections.

2. European Association of Urology. Guidelines on urological infections. 2015 Mar. Available from: http://uroweb.org/wp-content/uploads/19-Urological-infections_LR2.pdf.

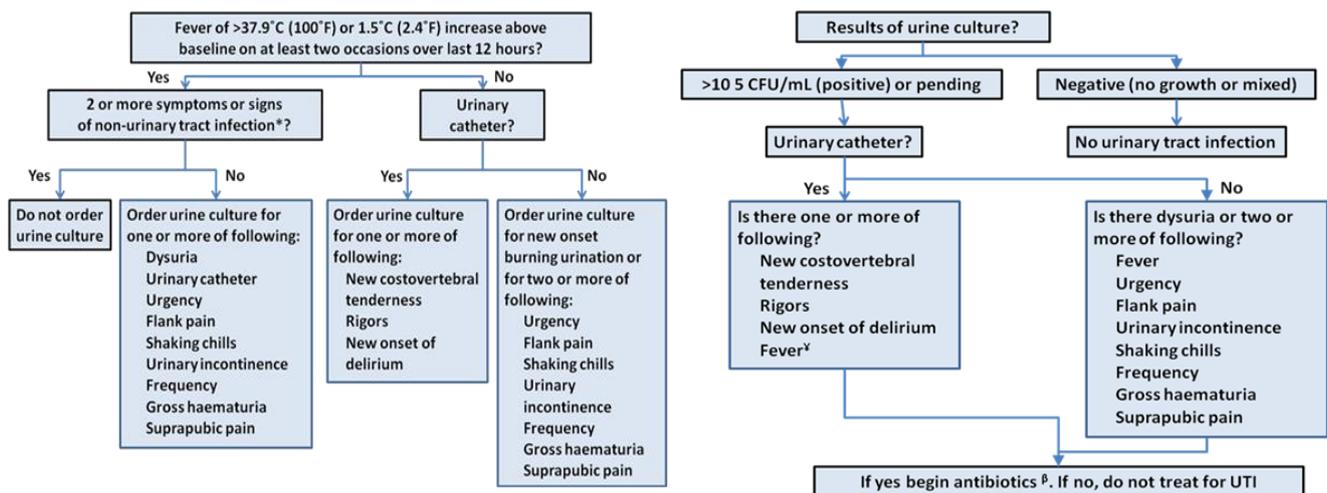
RATIONALE: An expert guideline, aiming to provide both urologists and physicians from other medical specialities with evidence-based guidance regarding the treatment and prophylaxis of urinary tract infections. This guideline states that asymptomatic bacteriuria is seldom associated with adverse outcomes in people with indwelling catheters. Treatment of bacteriuria causes increased short-term frequency of symptomatic infection, and re-infection with organisms of increased antimicrobial resistance. This guideline states that antibiotic treatment shows no benefit in patients with indwelling or supra-pubic catheters with asymptomatic bacteriuria, and antibiotics should only be given in the cases of systemic illness or suspected pyelonephritis. Antibiotics should be given based on local susceptibility patterns, and should be adjusted according to pathogen sensitivity.

3. Loeb M, Brazil K, Lohfeld L, McGeer A, Simor A, Stevenson K et al. Effect of a multifaceted

Management and treatment of common infections-Antibiotic guidance for primary care

intervention on number of antimicrobial prescriptions for suspected urinary tract infections in residents of nursing homes: cluster randomised controlled trial. *BMJ*. 2005 Sep; 331(7518):669. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1226247/>.

RATIONALE: A cluster randomised controlled trial in 24 nursing homes in Ontario, Canada, and Idaho, United States, with 12 allocated to a multifaceted intervention, and 12 allocated to usual care. A diagnostic and treatment algorithm was implemented in the multifaceted intervention, suggesting that urine cultures should only be ordered if there is a fever of >37.9°C, or a 1.5°C increase above baseline on at least two occasions over the previous 12 hours, and one or more of the following: dysuria; urinary catheter; urgency; flank pain; shaking chills; urinary incontinence; frequency; gross haematuria; suprapubic pain. Advice is given on when to order a urine culture if there is a urinary catheter in situ, including: new costovertebral tenderness; rigors; new onset of delirium; new onset burning urination, or two or more of: urgency; flank pain; shaking chills; urinary incontinence; frequency; gross haematuria; suprapubic pain. Antibiotics should only be prescribed in cases of systemic symptoms of infection with an in situ catheter. Fewer courses of antimicrobials were prescribed in the intervention nursing homes than in the usual care homes (weighted mean difference -0.49; 95% CI -0.93 to -0.06). Antimicrobials for suspected UTIs represented 28.4% of all courses of drugs prescribed in the intervention nursing homes, compared with 38.6% prescribed in the usual care homes.



4. National Institute for Health and Care Excellence (NICE). Healthcare-associated infections: prevention and control in primary and community care. 2012 Mar. Available from: <https://www.nice.org.uk/guidance/cg139?unlid=296483106201684204532>.

RATIONALE: A NICE guideline advising that, when changing catheters in patients with a long-term indwelling urinary catheter, antibiotic prophylaxis should not be routinely offered. Antibiotic prophylaxis should be considered for patients who have a history of symptomatic urinary tract infection after catheter change, or in patients who experience trauma during catheterisation. This guideline defines trauma during insertion of a urinary catheter as frank haematuria after catheterisation, or two or more efforts to insert the catheter in one attempt.

5. Lusardi G, Lipp A, Shaw C. Antibiotic prophylaxis for short-term catheter bladder drainage in

Management and treatment of common infections-Antibiotic guidance for primary care

adults (Review). *Cochrane Database Syst Rev*. 2013 Jul; 3(7):1-38. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005428.pub2/epdf>.

RATIONALE: A systematic review and meta-analysis reviewing six parallel-group randomised controlled trials and 789 participants, to compare antibiotic prophylaxis against no prophylaxis to prevent UTI. One study (n=78) compared antibiotic prophylaxis in patients at catheterisation only, versus antibiotic prophylaxis throughout the catheterisation period in patients with asymptomatic bacteriuria. Antibiotics at catheterisation resulted in significantly fewer cases of bacteriuria than giving prophylaxis throughout the catheterisation period (RR 0.29; 71% reduction; 95% CI 0.09 to 0.91). Secondary data of pyuria were provided by two surgical studies (n=255). When studies were pooled, pyuria occurred in significantly fewer cases in the prophylactic antibiotic group (RR 0.23; 77% reduction; 95% CI 0.13 to 0.42). In one study, the number of gram-negative isolates in patients' urine just before catheter removal (RR 0.05; 95% reduction; 95% CI 0 to 0.79), and six weeks after hospital discharge (RR 0.36; 64% reduction; 95% CI 0.23 to 0.56) were significantly lower. Pooled data from two studies showed significantly reduced febrile morbidity in those receiving antibiotic prophylaxis compared to those not (RR 0.53; 47% reduction; 95% CI 0.31 to 0.89). Although all studies assessed micro-organisms isolated from urine specimens, the data was too heterogeneous to pool in a meta-analysis. The authors conclude that there is some limited evidence to show that receiving prophylactic antibiotics may reduce the rate of bacteriuria and other signs of infection. As the benefits were limited to certain groups, and prophylaxis is associated with increased antibiotic resistance, antibiotics should only be used if there is a history of trauma during urinary catheterisation, or in those with symptoms of a UTI.

6. Kandel R, Doron S, Salen-Schatz S, McElroy N, Griswold P, DeMaria A. Antimicrobial stewardship in long-term care facilities: an urgent need. 2016 Mar (*unpublished*). Available from: <http://www.macoalition.org/evaluation-and-treatment-uti-in-elderly.shtml>.

RATIONALE: A collaborative program over two separate nine month learning collaboratives, using a framework supported by both technical and adaptive learning and change frameworks, for participant engagement and improvement in long-term care facilities. Four clinician materials were used: a checklist-based worksheet in practice to guide decisions and communication about testing urine and treating UTIs in long-term care, adapted from the Loeb criteria; a clinician education sheet; a mnemonic poster for assessing change in mental status; talking with families about UTIs, bacteriuria and antibiotics. Several brochures were also developed for residents and families to educate them about the problem of antibiotic overuse and resistance, and appropriate diagnosis of UTIs. 36 facilities participated with 17 submitting data (47%) in the first collaborative, and 32 facilities participated with 25 submitting data (78%) in the second collaborative. Statistically significant decreases in urine culture and UTI diagnosis rates were seen over the course of both the first and second collaboratives. There was a downward trend over all time periods for rates of UTIs diagnosed that did not meet criteria for symptomatic UTIs as set forth by the collaboratives. There was also a trend toward decreased *Clostridium difficile* rates over the course of the study, but this was not statistically significant. The authors conclude that this current study adds to the literature demonstrating behaviour

Management and treatment of common infections-Antibiotic guidance for primary care

change with a multifaceted educational program directed at long-term care facilities, including multiple venues for teaching and support, literature for distribution to staff and families, and a practical algorithm adapted from the Loeb criteria.

7. Hawkey P, Enoch D, McNulty C, Livermore DM, Warren R, Otter J et al. Joint working party on multi-resistant gram-negative infection: treatment. 2016 Jun (*unpublished*). Available from: <http://bsac.org.uk/national-consultation-joint-working-party-on-multi-resistant-gram-negative-infection-treatment/>.

RATIONALE: A review by the British Society for Antimicrobial Chemotherapy, recommending that clinicians should only start empirical antibiotics and send urine for culture in elderly patients if they have two or more signs of infection, in particular: dysuria; fever over 38°C; new incontinence. The authors advise that differentiating urinary tract infection from asymptomatic bacteriuria (ASB) can be particularly challenging in elderly patients with dementia, as they cannot always accurately describe their symptoms. The authors also state that a positive urine culture or dipstick test will not differentiate between UTI or ASB. Patients with asymptomatic bacteriuria may have white blood cells in the urine, just as in true infection. In older patients, including those with dementia, diagnosis should be based on a full clinical assessment, including vital signs.

UTI in pregnancy:

1. Scottish Intercollegiate Guidelines Network (SIGN). Management of suspected bacterial urinary tract infection in adults: a national clinical guideline. 2012 Jul. Available from: <http://www.sign.ac.uk/assets/sign88.pdf>.

RATIONALE: A SIGN guideline, demonstrating that antibiotic treatment of asymptomatic bacteriuria in pregnancy reduces the risk of upper urinary tract infections, pre-term delivery, and low birth weight babies. This guideline recommends that an MSU should be performed routinely for pregnant women at the first antenatal visit. If bacteriuria is reported, it should be confirmed with a second MSU. Dipstick testing is not sufficiently sensitive to be used for screening for bacteriuria in pregnant women. This guideline also states that antibiotic treatment should be started in women with symptomatic and asymptomatic bacteriuria.

2. Spencer RC, Moseley DJ, Greensmith MJ. Nitrofurantoin modified release versus trimethoprim or co-trimoxazole in the treatment of uncomplicated urinary tract infection in general practice. *J Antimicrob Chemother.* 1994 May; 33(1):121-129. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/7928829>.

RATIONALE: A non-blinded randomised controlled trial (n=538), which found that nitrofurantoin MR had equivalent clinical cure rates to co-trimoxazole and trimethoprim. The rate of gastrointestinal adverse effects was similar between the co-trimoxazole and trimethoprim groups (7.3% to 8.8%), but was reportedly less in the nitrofurantoin m/r group (5.6%). A seven day treatment regimen was used with each antibiotic.

3. UK Teratology Information Service (UKTIS). Use of nitrofurantoin in pregnancy. 2015 Nov.

Management and treatment of common infections-Antibiotic guidance for primary care

Available from: <http://www.medicinesinpregnancy.org/bumps/monographs/USE-OF-NITROFURANTOIN-IN-PREGNANCY/>.

RATIONALE: A UKTIS guideline, suggesting that there is no strong evidence of an association between in utero nitrofurantoin exposure and an overall increased risk of congenital malformation. Individual studies have suggested a possible increased risk of hypoplastic left heart syndrome, talipes, hypospadias, microphthalmia, ASD, and cleft lip/palate. However, these findings have not been confirmed, and the increase in risk of congenital malformations following exposure to nitrofurantoin is likely to be small, especially given the low risk of systemic absorption and transfer to the foetus. No increased risk of intrauterine death, low birth weight, or preterm delivery has been identified, although an increased incidence of neonatal jaundice has been observed in infants exposed to nitrofurantoin in the month preceding delivery. Nitrofurantoin use is generally avoided in pregnant patients during labour and delivery, due to the theoretical possibility of haemolytic anaemia in the foetus, or in the neonate, due to immature erythrocyte enzyme systems. This guideline suggests that, where possible, antibiotic choice should be informed by culture and sensitivity tests. However, if treatment is required urgently or before test results are available, nitrofurantoin may be considered where clinically appropriate. Any risks to the foetus from the antimicrobials used to treat maternal UTI should be weighed against the potential adverse effects for the mother and foetus from untreated infection. The decision as to which antimicrobial is chosen should be based on the clinical condition of the pregnant woman, and local prescribing guidelines and resistance rates. Exposure to nitrofurantoin at any stage in pregnancy would not usually be regarded as medical grounds for termination of pregnancy. However, other risk factors may be present in individual cases, which may independently increase the risk of adverse pregnancy outcomes, and should be considered by clinicians.

4. UK Teratology Information Service (UKTIS). *UKTIS – UK Teratology Information Service.*

Available from: <http://www.uktis.org/> [Accessed: 6th March, 2017].

RATIONALE: A UKTIS webpage, providing details of the effects of different antimicrobials when used as infection treatment during pregnancy. It is important to ensure adequate treatment of maternal infection, as failure to treat may lead to adverse maternal and foetal effects, as a consequence of uncontrolled infection or fever. When considering treatment with antimicrobial agents during pregnancy, the following factors should be considered: severity of maternal infection; effects of any fever present; effects of failing to treat the mother; potential fetotoxicity of antimicrobials to be used. This website suggests that, where possible, antibiotic choice should be informed by culture and sensitivity tests. Penicillins, along with cephalosporins, may be used in pregnancy if considered clinically appropriate. The use of trimethoprim has been linked to a risk of neural tube defects due to folate deficiency. Therefore, folate supplementation is required if trimethoprim is prescribed in pregnancy. Treatment with any antimicrobial listed (nitrofurantoin; trimethoprim; pivmecillinam; cephalosporins) at any stage in pregnancy would not usually be regarded as medical grounds for termination of pregnancy.

5. Ruxton CHS, Derbyshire E. Women's diet quality in the UK. *Nutrition Bulletin.* 2010 May;

Management and treatment of common infections-Antibiotic guidance for primary care

35(2):126-137. Available from: <http://onlinelibrary.wiley.com/doi/10.1111/j.1467-3010.2010.01828.x/abstract>.

RATIONALE: A national bulletin providing data from national diet and nutrition surveys, showing that women's dietary intake of iron, vitamin D, calcium, and folate remain below recommended levels. It is therefore appropriate to provide supplementary folate, particularly in women prescribed trimethoprim for UTI.

6. Roupheal NG, O'Donnell JA, Bhatnagar J, Lewis F, Polgreen PM, Beekmann S et al. *Clostridium difficile*-associated diarrhea: an emerging threat to pregnant women. *Am J Obstet Gynecol*. 2008 Jun; 198(6):635-640. Available from:

<http://www.sciencedirect.com/science/article/pii/S0002937808001361>.

RATIONALE: A series of ten case studies, demonstrating that most cases of peripartum *Clostridium difficile*-associated diarrhoea are associated with antibiotic use. Seven of the women in these studies were admitted to intensive care; three of the infants were stillborn, and three women died. This article also states that, even a single dose of an antimicrobial such as a beta-lactam and cephalosporin given prior to caesarean section for the prevention of group B streptococcus disease, or for asymptomatic bacteriuria, may result in *Clostridium difficile*-associated diarrhoea.

7. Huttner A, Verhaegh EM, Harbarth S, Muller AE, Theuretzbacher U, Mouton JW. Nitrofurantoin revisited: a systematic review and meta-analysis of controlled trials. *J Antimicrob Chemother*. 2015 Sep; 70(9):2456-2464. Available from:

<http://www.ncbi.nlm.nih.gov/pubmed/26066581>.

RATIONALE: A systematic review and meta-analysis of 27 controlled clinical trials and 4,807 patients, to assess nitrofurantoin's efficacy and toxicity in the treatment of lower UTI. This review sites one open-label randomised trial, which compares three day regimens of high-dose nitrofurantoin (100mg four times daily), trimethoprim/sulfamethoxazole (200mg twice daily), cefadroxil (500mg twice daily), and amoxicillin (500mg three times daily). Results indicated that, at six weeks post-therapy, nitrofurantoin's clinical efficacy is only 61%. Results confirmed that nitrofurantoin appears to have good clinical and microbiological efficacy for UTI caused by common uropathogens, with clinical cure rates varying between 79% and 92%. The most methodologically robust studies indicated an overall equivalence between nitrofurantoin, when given for five or seven days, and trimethoprim/sulfamethoxazole, ciprofloxacin and amoxicillin. Meta-analyses of randomised controlled trials confirmed equivalence in clinical cure, but indicated a slight advantage to comparator drugs in microbiological efficacy (RR 0.93, 7% advantage; 95% CI 0.89 to 0.97). If given for only three days, nitrofurantoin's clinical efficacy was diminished (61% to 70%); toxicity was infrequent (5% to 16%), mild, reversible, and predominantly gastrointestinal. The authors conclude that nitrofurantoin appears to have clinical efficacy equivalent to that of trimethoprim/sulfamethoxazole, ciprofloxacin and amoxicillin, although meta-analyses for microbiological cure indicate a slightly more favourable effect for comparators. Nitrofurantoin appears to achieve therapeutic concentrations only in the lower urinary tract, restricting its indication to the treatment of lower UTI. Acquisition of resistance to nitrofurantoin is still relatively rare,

Management and treatment of common infections-Antibiotic guidance for primary care

although it is likely to rise given recent increases in consumption. It is important to note that treatment durations of at least five days do appear to optimise efficacy. However, this review does not include any studies that directly compare three to five days' nitrofurantoin.

8. UK Teratology Information Service (UKTIS). Use of cephalosporins in pregnancy. 2017 Jun. Available from: <http://www.medicinesinpregnancy.org/bumps/monographs/USE-OF-CEPHALOSPORINS-IN-PREGNANCY/>.

RATIONALE: A UKTIS guideline, stating that the majority of available data on the use of cephalosporins in pregnancy do not suggest that therapeutic doses of these drugs are associated with an increased risk of spontaneous abortion or congenital abnormalities. However, two studies have identified a possible association between in utero cephalosporin exposure and cardiovascular defects in exposed offspring, with single studies also suggesting an increased risk of oral clefts and anorectal atresia. Therefore, cefalexin should only be given during pregnancy when need has been clearly established.

9. Delzell JE, Lefevre ML. Urinary tract infections during pregnancy. *Am Fam Physician*. 2000 Feb; 61(3):713-720. Available from: <http://www.aafp.org/afp/2000/0201/p713.html>.

RATIONALE: An editorial, examining the pathogenesis and bacteriology of UTIs during pregnancy, as well as patient-orientated outcomes. The authors state that pregnant women should be treated when bacteriuria is identified, with the choice of antibiotic addressing the most common infection organism. Antibiotic choices are listed as: nitrofurantoin 50mg to 100mg four times daily, or cephalexin 250mg four times daily, or 500mg twice daily. It is also stated that a seven to 10 day course of antibiotic treatment is usually sufficient to eradicate the infection organisms.

10. European Association of Urology. Guidelines on urological infections. 2015 Mar. Available from: http://uroweb.org/wp-content/uploads/19-Urological-infections_LR2.pdf.

RATIONALE: An expert guideline suggesting that seven days of antibiotics should be used to treat urinary tract infections during pregnancy. Short courses of antimicrobial therapy can also be considered for the treatment of cystitis in pregnancy, but these should be given based on local susceptibility patterns, after culture results are available, and should be adjusted according to pathogen sensitivity. This guideline notes that not all antibiotics are suitable during pregnancy.

Acute prostatitis:

1. Rees J, Abrahams M, Doble A, Cooper A, Prostatitis Expert Reference Group (PERG). Diagnosis and treatment of chronic bacterial prostatitis and chronic prostatitis/chronic pelvic pain syndrome: a consensus guideline. *BJU Int*. 2015 Sep; 116:509-525. Available from: <http://www.bashh.org/documents/bju%20prostatitis%202015.pdf>.

RATIONALE: A BASHH guideline stating that acute prostatitis is a severe illness, and that it is important that an MSU is sent for culture and sensitivities to ensure that an appropriate antibiotic is prescribed. For men with acute prostatitis who are suitable for oral antibiotic treatment, ciprofloxacin 500mg BD for 28 days, or ofloxacin 200mg BD for 28

Management and treatment of common infections-Antibiotic guidance for primary care

days will provide adequate bacteriocidal concentrations within the prostate gland.

Trimethoprim 200mg BD for 28 days is a suitable alternative for men who are intolerant or allergic to quinolones. Expert opinion is that a four week course of antibiotics is required to reduce the risk of developing chronic bacterial prostatitis.

2. European Association of Urology. Guidelines on urological infections. 2015 Mar. Available from: http://uroweb.org/wp-content/uploads/19-Urological-infections_LR2.pdf.

RATIONALE: An expert guideline advising that acute bacterial prostatitis can be a serious infection. Parenteral administration of high doses of a bacteriocidal antibiotic is usually required, which may include a broad-spectrum penicillin, a third-generation cephalosporin, or a fluoroquinolone. All of these agents can be combined with an aminoglycoside for initial therapy. Treatment is required until fever subsides and normalisation of infection parameters. In less severe cases, a fluoroquinolone may be given orally for ten days; in chronic bacterial prostatitis, preferably a fluoroquinolone should be given for at least four weeks. In case of fluoroquinolone resistance or adverse reactions, trimethoprim can be given orally for a period of four to 12 weeks after the initial diagnosis. The patient should then be reassessed and antibiotics continued if pre-treatment cultures are positive and/or the patient has positive effects. A treatment period of four to six weeks is recommended for optimal bacterial cure.

3. Truven Health Analytics. *Micromedex Solutions*. Available from: <http://micromedex.com/> [Accessed: 22nd August, 2016].

RATIONALE: A Truven Health Analytics website providing information on a wide range of antibiotics, suggesting that trimethoprim reaches good concentrations in prostatic tissue (peak prostate concentration: 2.3mcg/g, 280 minutes after an oral dose, compared with serum levels of 2.2mcg/mL at 125 minutes after an oral dose). Ciprofloxacin reaches high concentration in prostatic fluid, often exceeding serum concentrations (prostatic fluid concentrations: 0.02 to 5.5mcg/mL two to four hours following oral administration, compared with serum concentrations of 1 to 2.5mcg/mL). Ofloxacin also reaches high concentration in prostatic fluid (prostatic fluid concentrations: 3.22 to 4.25mcg/g one to four hours following oral administration).

UTI in children:

1. National Institute for Health and Care Excellence (NICE). Urinary tract infection in under 16s: diagnosis and management. 2007 Aug. Available from:

<https://www.nice.org.uk/guidance/cg54/evidence/full-guideline-pdf-196566877>.

RATIONALE: A NICE guideline stating that children under the age of three months with suspected UTI should be admitted, as this ensures optimal care for those with serious infection. It also states that imaging during the acute episode is only necessary for atypical UTI or for children under the age of six months, as there is an increased risk of recurrent UTI in this age group. This guideline cites a range of studies, that suggest that all infants and children who have bacteriuria and either fever of 38°C or higher, or loin pain/tenderness, should be considered to have acute pyelonephritis/upper urinary tract

Management and treatment of common infections-Antibiotic guidance for primary care

infection. All other infants and children who have bacteriuria, but no systemic symptoms or signs, should be considered to have cystitis/lower urinary tract infection. To confirm diagnosis and susceptibility, a pre-treatment MSU should be taken and sent for culture, and antibiotics should be started. This guideline identifies three randomised controlled trials comparing trimethoprim to other antibiotics for lower UTI in children, and one systematic review comparing short- and long-course antibiotics, including studies assessing trimethoprim, nitrofurantoin, and amoxicillin. Findings indicated that shorter courses of antibiotics (seven to 10 days) improved compliance, decreased antibiotic-related adverse events, and diminished the emergence of resistant organisms. One systematic review into children with lower UTI found no difference in efficacy between short-course (two to four days) and long-course (seven to 14 days) of antibiotics. As a result, this guideline recommends three days trimethoprim, nitrofurantoin, amoxicillin, or cefalexin, for empirical treatment of lower UTI in children. For upper UTI, one systematic review combined two studies of co-amoxiclav treatment for ten to 14 days compared with IV antibiotic treatment; no difference in efficacy was found, therefore seven to ten days treatment is recommended.

Acute pyelonephritis:

1. European Association of Urology. Guidelines on urological infections. 2015 Mar. Available from: http://uroweb.org/wp-content/uploads/19-Urological-infections_LR2.pdf.
RATIONALE: An expert guideline suggesting that admission should be arranged for more severe cases of acute uncomplicated pyelonephritis (dehydration; inability to take oral medication; pregnancy; patients with diabetes mellitus), if complicating factors cannot be ruled out by available diagnostic procedures, and/or the patient has clinical signs and symptoms of sepsis. This guideline also recommends that advice should be sought for people with acute pyelonephritis if there is no response to antibiotics within 24 hours, as the complications of acute pyelonephritis can be life-threatening. Lack of response to treatment is likely to be due to antibiotic resistance.
2. Shields J, Maxwell AP. Acute pyelonephritis can have serious complications. *Practitioner*. 2010 Apr; 254(1728):23-24. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/20486480>.
RATIONALE: A review article, discussing the causes of and risk factors for uncomplicated acute pyelonephritis. Recommended treatment is also discussed, in which it is stated that ciprofloxacin 500mg twice daily for seven days, or co-amoxiclav 500mg/125mg for 14 days are reasonable initial treatments. Failure to respond to antibiotic treatment within 24 hours should prompt consideration of an alternative diagnosis or the development of complications. Hospital admission is therefore advisable for patients who fail to respond.
3. Hawkey P, Enoch D, McNulty C, Livermore DM, Warren R, Otter J et al. Joint working party on multi-resistant gram-negative infection: treatment. 2016 Jun (*unpublished*). Available from: <http://bsac.org.uk/national-consultation-joint-working-party-on-multi-resistant-gram-negative-infection-treatment/>.
RATIONALE: A review by the British Society for Antimicrobial Chemotherapy, advising

Management and treatment of common infections-Antibiotic guidance for primary care

that, generally, antibiotic resistance in the community is still quite uncommon. Prospective and retrospective epidemiological studies identify a number of risk factors for carriage risk of ESBL *E. coli*. The authors advise that patients are at increased risk if they have: recurrent urinary infection; persistent urinary symptoms after initial antibiotics; over seven days' hospital admission in the last six months; residence in a care home; recent travel, and especially healthcare in a country with increased antimicrobial resistance (outside North America, Northern Europe, and Australasia); previous known urinary tract infection resistant to co-amoxiclav, cephalosporins, or quinolones, or recent treatment with any of these antimicrobial agents.

4. Chapman AL, Seaton RA, Cooper MA, Hedderwick S, Goodall V, Reed C et al. Good practice recommendations for outpatient parenteral antimicrobial therapy (OPAT) in adults in the UK: a consensus statement. *J Antimicrob Chemother*. 2012 May; 67(5):1053-1062. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/22298347>.

RATIONALE: A consensus statement suggesting that, if intravenous treatment is needed for an antibiotic resistant organism, outpatient-based treatment can reduce hospitalisation and spread of antibiotic resistant pathogens. This statement also covers best practice when providing an OPAT service.

5. Talan DA, Stamm WE, Hooton TM, Moran GJ, Burke T, Irvani A et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis in women: a randomized trial. *JAMA*. 2000 Mar; 283(12):22-29. Available from: <http://jama.jamanetwork.com/article.aspx?articleid=192526>.

RATIONALE: A double-blind randomised controlled trial, which found that seven days of ciprofloxacin 500mg BD was as effective as 14 days co-trimoxazole. In this study, it was demonstrated that, in 1999, 100% of *E. coli* isolates were susceptible to ciprofloxacin. The authors conclude that both ciprofloxacin and co-amoxiclav can be used for the treatment of acute pyelonephritis. This is based on the need to cover the broad spectrum of pathogens that cause acute pyelonephritis, and their excellent kidney penetration. Although they are associated with an increased risk of *Clostridium difficile*, MRSA, and other antibiotic resistant infections, this has to be balanced against the risk of treatment failure and consequent serious complications. Expert consensus is that trimethoprim may be used if the causative organism is known to be susceptible to this antibiotic.

6. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*. 2011 Mar; 52(5):103-120. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/21292654>.

RATIONALE: An international guideline and consensus statement based on a meta-analysis of evidence from 1998. This guideline states that, in patients suspected of having pyelonephritis, a urine culture and susceptibility test should always be performed, and initial empirical therapy should be tailored appropriately on the basis of the infecting uropathogen. Oral ciprofloxacin (500mg BD) for seven days is an appropriate choice.

Management and treatment of common infections-Antibiotic guidance for primary care

Previous guidelines have suggested that β -lactams are less effective than other available agents for the treatment of pyelonephritis, but they have been less well studied. The authors state that optimal therapy for acute pyelonephritis depends on the severity of illness at presentation and local resistance patterns, as well as specific host factors. Strategies for optimising empirical therapy when local resistance patterns are unknown include: using an initial intravenous dose of a long-acting parenteral antimicrobial; starting with a broader-spectrum agent; narrowing therapy when laboratory results are available. However, broad-spectrum antimicrobial coverage should be tailored, as appropriate, on the basis of urine culture and susceptibility results.

7. Eliakim-Raz N, Yahav D, Paul M, Leibovici L. Duration of antibiotic treatment for acute pyelonephritis and septic urinary tract infection – 7 days or less versus longer treatment: systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother.* 2013 Oct; 68(10):2183-2191. Available from:
<https://www.ncbi.nlm.nih.gov/pubmed/23696620>.

RATIONALE: A systematic review and meta-analysis of eight randomised controlled trials and 2,515 patients, which found that a shorter seven day course of quinolones or beta-lactam antibiotics was as clinically effective as a 14 day course (RR 0.63; 37% effectiveness; 95% CI 0.33 to 1.18; $I^2=41\%$). There was no direct comparison of seven versus 14 days of trimethoprim/co-trimoxazole; 14 days treatment should be prescribed.

Recurrent UTI in non-pregnant women:

1. Scottish Antimicrobial Prescribing Group (SAPG). Guidance on management of recurrent urinary tract infection in non-pregnant women. 2016 Jun. Available from:
https://www.scottishmedicines.org.uk/files/sapg1/Management_of_recurrent_lower_UTI_in_non-pregnant_women.pdf.

RATIONALE: An SAPG guideline, providing a thorough overview of the current management of recurrent urinary tract infections. This guideline provides advice about initial simple measures to limit recurrent UTI, including: better hydration; urge initiated voiding and postcoital voiding; cranberry products; stand-by antibiotics; intra-vaginal or oral oestrogens for post-menopausal women. This guideline also stresses the importance of confirming UTI diagnoses, and investigating underlying causes if simple measures are not effective, such as: checking MSU to confirm diagnosis and establish sensitivities; consider renal tract ultrasound and post-void bladder residual volume scan; prescribing low-dose prophylactic antibiotics as per local guidance for a three to six month period. This guideline states that cranberry products help prevent bacteria from adhering to epithelial cells that line the wall of the bladder, which may indicate its use in patients with recurrent UTI. Trimethoprim 100mg to be taken within two hours of intercourse is also recommended, for patients with recurrent cystitis associated with sexual intercourse.

2. Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI). 5th Annual Report, April 2013 – March 2014. 2015 Feb. Available from:
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/405295/ARHAI

Management and treatment of common infections-Antibiotic guidance for primary care _annual_report.pdf.

RATIONALE: An ARHAI report, noting that mandatory surveillance over the past ten years has demonstrated a sustained increase in *E. coli* bacteraemia, that is unexplained by improved diagnosis. The analysis demonstrates that only a small proportion of infections are related to urinary catheterisation. Other risk factors, such as repeated urinary tract infections treated by sub-optimal antibiotic prescribing, and inadequate hydration, have a significant impact. The surveillance report shows that *E. coli* bacteraemia peaks in the summer months, which may also be due to poor urine output associated with dehydration.

3. National Institute for Health and Care Excellence (NICE). Acute kidney injury: prevention, detection and management. 2013 Aug. Available from:
<https://www.nice.org.uk/guidance/cg169>.

RATIONALE: A NICE guideline, including hypoalbuminaemia and limited access to fluid as risk factors for acute kidney injury. It was strongly felt that there was a need to include these, as it is widely recognised from clinical experience that dehydration and volume depletion can lead to AKI. Furthermore, these risk factors are modifiable, and would be key targets if a risk assessment tool was deployed in AKI prevention. The Guideline Development Group felt it particularly important to draw specific attention to those who may have limited access to fluids, due to neurological or cognitive impairment, as being at particular risk of dehydration due to their reliance on others to maintain adequate fluid intake. These may include: the frail; elderly; people with dementia in care homes; physically disabled people.

4. Bleidorn J, Gagyor I, Kochen MM, Wegscheider K, Hummers-Pradier E. Symptomatic treatment (ibuprofen) or antibiotics (ciprofloxacin) for uncomplicated urinary tract infection? – Results of a randomized controlled pilot trial. *BMC Med*. 2010 May; 8(30):1-8. Available from:
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2890534/pdf/1741-7015-8-30.pdf>.

RATIONALE: A double-blind randomised controlled pilot trial across 29 German general practices. 80 otherwise healthy women aged between 18 and 85 years presenting with at least one common symptom of UTI (dysuria; frequency) were randomly assigned to one of two treatment arms: ibuprofen 3 x 400mg orally for three days; ciprofloxacin 2 x 250mg (plus one placebo) orally for three days. 79 participants were analysed (ibuprofen n=40; ciprofloxacin n=39). On day four, 21 of 36 (58.3%) of patients in the ibuprofen group were symptom free, versus 17 of 33 (51.5%) of patients in the ciprofloxacin group. Patients receiving ibuprofen also reported fewer symptoms of UTI than patients receiving ciprofloxacin (PP analysis -0.33; 95% CI -1.13 to 0.47). Between days zero and nine, 12 out of 36 (33%) patients in the ibuprofen treatment arm received secondary antibiotic treatment due to ongoing or worsening symptoms, compared to six out of 33 (18%) patients in the ciprofloxacin treatment arm, but these results were not significant. The authors conclude that their results support the assumption of non-inferiority of ibuprofen compared to ciprofloxacin for treatment of symptomatic uncomplicated UTI in women.

5. Gagyor I, Bleidorn J, Kochen MM, Schmiemann G, Wegscheider K, Hummers-Pradier E. Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: randomised controlled trial. *BMJ*. 2015 Dec; 23(351):1-11. Available from:

Management and treatment of common infections-Antibiotic guidance for primary care

<http://www.bmj.com/content/bmj/351/bmj.h6544.full.pdf>.

RATIONALE: A randomised controlled trial across 42 German general practices, aiming to determine if treatment of symptoms of uncomplicated UTI with ibuprofen can reduce the rate of antibiotic prescriptions without a significant increase in symptoms, recurrences, or complications. 494 women aged between 18 and 65 with typical symptoms of uncomplicated UTI were included and randomly assigned to one of two treatment arms: a single dose of fosfomycin 3g for three days (n=246), or ibuprofen 3 x 400mg for three days (n=248). In both groups, additional antibiotic treatment was subsequently prescribed as necessary for persistent, worsening, or recurrent symptoms. Out of the 248 women in the ibuprofen group, two thirds treated symptomatically recovered without any antibiotics. Recurrent UTIs were more common in the fosfomycin group, suggesting that antimicrobial treatment may result in recurrent UTIs. The authors conclude that, although they cannot generally recommend ibuprofen as first line treatment for uncomplicated UTI in women, the treatment option can be discussed with women with mild to moderate symptoms in a shared decision making approach, or within a strategy of delayed or back-up prescribing.

6. Public Health England Expert Panel. In a conversation with the British Infection Association Expert Panel (oral communication, June 2012).

RATIONALE: Cranberry juice has been found to potentially prevent infection by interfering with the attachment of bacteria to uroepithelial cells. There are many other compounds found in cranberries that have yet to be explored for their potential adherence activity, but A-type proanthocyanidins have been shown to potentially inhibit the adherence of P-fimbriated *Escherichia coli* to the urogenital mucosa. Without adhesion, *E. coli* cannot infect the mucosal surface of the urinary tract. Cranberry capsules may be more convenient than juice, due to better compliance, and high strength capsules may be most effective. Women should be advised about the relative benefits and risks of daily prophylactic antibiotics, versus post-coital antibiotics, versus stand-by antibiotics and cranberry products, so that they can make an informed decision. Patients taking warfarin should be advised against cranberry products, unless the health benefits are considered to outweigh any potential risks.

7. Wang CH, Fang CC, Chen NC, Liu SS, Yu PH, Wu TY et al. Cranberry-containing products for prevention of urinary tract infections in susceptible populations: a systematic review and meta-analysis of randomized controlled trials. *Arch Intern Med*. 2012 Jul; 172(13):988-996. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/22777630>.

RATIONALE: A systematic review and meta-analysis of ten randomised controlled trials and 1,494 participants. Administration of cranberry-containing products differed significantly in form, daily dosage, proanthocyanidins content, and dosing frequency. Cranberry-containing products seemed to be more effective in women with recurrent UTIs (RR 0.53; 47% effectiveness; 95% CI 0.33 to 0.83; $I^2=0\%$); female populations (RR 0.49; 51% effectiveness; 95% CI 0.34 to 0.73; $I^2=34\%$); children (RR 0.33; 67% effectiveness; 95% CI 0.16 to 0.69; $I^2=0\%$); cranberry juice users (RR 0.47; 53% effectiveness; 95% CI 0.30 to 0.72; $I^2=2\%$); people using cranberry-containing products more than twice daily (RR 0.58; 42% effectiveness; 95% CI 0.40 to 0.84; $I^2=18\%$). The authors conclude that

Management and treatment of common infections-Antibiotic guidance for primary care

cranberry-containing products are associated with a protective effect against UTIs. The results should be interpreted in the context of substantial heterogeneity across trials.

8. Jepson RG, Williams G, Craig JC. Cranberries for preventing urinary tract infections (Review). *Cochrane Database Syst Rev*. 2012 Oct; 17(10):1-82. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/23076891>.

RATIONALE: A systematic review of 24 studies and 4,473 participants, comparing cranberry products with control or alternative treatments. There was a small trend towards fewer UTIs in people taking cranberry products, compared to placebo or no treatment, but this was not a significant finding. Many participants stopped drinking the juice, suggesting it may not be an acceptable intervention. In the long-term, cranberry products were ineffective, possibly due to the lack of potency of the active ingredient. Four of the five studies in women with recurrent UTI (n=594), which included a placebo group, provided data that could be combined in a meta-analysis. Results demonstrated a small, non-significant reduction in the risk of repeat symptomatic UTI with cranberry treatment, compared to placebo or no treatment (RR 0.74; 26% reduction; 95% CI 0.42 to 1.31). Two studies in women with recurrent UTI, and one study in children, compared cranberry capsules or syrup with antibiotic prophylaxis. Meta-analysis of the two studies in women showed that cranberry products, compared to antibiotics, were equally as effective in reducing the risk of repeat UTI (RR 1.31; 95% CI 0.85 to 2.02). The study in children also showed that the cranberry products, compared to antibiotics, were as effective in reducing the risk of repeat symptomatic UTI (RR 0.69; 31% effectiveness; 95% CI 0.32 to 1.51).

9. Albert X, Huertas I, Pereiro II, Sanfelix J, Gosalbes V, Perrota C. Antibiotics for preventing recurrent urinary tract infection in non-pregnant women (Review). *Cochrane Database Syst Rev*. 2004 Jul; 3:1-72. Available from:

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001209.pub2/epdf>.

RATIONALE: A systematic review of 19 studies, involving 1,120 participants. One study of 500mg post-coital ciprofloxacin compared with 500mg ciprofloxacin prophylaxis found no significant difference on the rate of UTI, or side-effects between the two regimens (MRPY 0.46 versus 0.42, respectively; p=0.8). Two trials explored a range of one-off antibiotic doses versus placebo (ciprofloxacin 500mg; nitrofurantoin 100mg; nitrofurantoin 50mg; cotrimoxazole 40-200mg; cephalexin 125mg), and found that continuous antibiotic prophylaxis for six to 12 months does reduce the rate of UTI. Eight trials compared prophylactic antibiotics, one of which demonstrated that 100mg nitrofurantoin had higher efficacy than 100mg trimethoprim, but there were no significant differences in terms of clinical outcome (RR 0.54; 95% CI 0.23 to 1.24).

10. European Association of Urology. Guidelines on urological infections. 2015 Mar. Available from: http://uroweb.org/wp-content/uploads/19-Urological-infections_LR2.pdf.

RATIONALE: An expert guideline, suggesting that the same antibiotics and same doses used for nightly prophylaxis can be used as a stat dose for post-coital prophylaxis of UTI. Antimicrobial prophylaxis can be given continuously for longer periods of time (three to six months). Continuous or post-coital antimicrobial prophylaxis for prevention of recurrent

Management and treatment of common infections-Antibiotic guidance for primary care

UTIs should be considered only after counselling and behavioural modification has been attempted, and when non-antimicrobial measures have been unsuccessful. This guideline recommends that urological examination should always be carried out for recurrent UTIs.

11. Lee BS, Bhuta T, Simpson J, Craig JC. Methenamine hippurate for preventing urinary tract infections. *Cochrane Database Syst Rev.* 2012 Oct; 17(10):1-46. Available from:

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003265.pub3/epdf>.

RATIONALE: An updated systematic review of 13 randomised and quasi-randomised trials, in which 2,032 patients were included. Subgroup analyses suggested that methenamine hippurate may have some benefit in patients without renal tract abnormalities (symptomatic UTI: RR 0.24; 76% effectiveness; 95% CI 0.07 to 0.89; bacteriuria: RR 0.56; 44% effectiveness; 95% CI 0.37 to 0.83). No benefits were reported in patients with renal tract abnormalities (symptomatic UTI: RR 1.54; 95% CI 0.38 to 6.20; bacteriuria: RR 1.29; 95% CI 0.54 to 3.07). This review found that there was a significant reduction in symptomatic UTI in those without renal tract abnormalities, when used for short-term treatment duration (RR 0.14; 86% effectiveness; 95% CI 0.05 to 0.38), and the rate of adverse events was low. The authors conclude that methenamine hippurate may be effective for preventing UTIs in patients without renal tract abnormalities, particularly when used for short-term prophylaxis, but does not appear to work in those with neuropathic bladder or in patients who have renal tract abnormalities.

Meningitis

Suspected meningococcal disease:

1. National Institute for Health and Care Excellence (NICE). Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management. 2010 Jun. Available from: <https://www.nice.org.uk/guidance/CG102>.

RATIONALE: A NICE guideline stating that primary healthcare professionals should transfer children and young people with suspected bacterial meningitis or suspected meningococcal septicaemia to secondary care as an emergency. This guideline recommends that, if urgent transfer to hospital is not possible, parenteral antibiotics should be administered immediately (either intravenous or intramuscular benzylpenicillin, cefotaxime, or ceftriaxone). Intramuscular administration can provide a satisfactory clinical outcome in patients with limited intravenous access. This guideline also recommends that benzylpenicillin should only be withheld in children and young people who have a clear history of anaphylaxis; a history of a rash following penicillin is not a contraindication.

2. Scottish Intercollegiate Guidelines Network (SIGN). Management of invasive meningococcal disease in children and young people: a national clinical guideline. 2008 May. Available from: <http://www.sign.ac.uk/assets/sign102.pdf>.

RATIONALE: A SIGN guideline suggesting that antibiotics should be administered to reduce the risk of mortality. Parenteral antibiotics (either benzylpenicillin or cefotaxime)

Management and treatment of common infections-Antibiotic guidance for primary care

should be administered, if time, before hospital admission, and a non-blanching rash.

Antibiotics should not be delayed pending investigation, but should be administered as soon as invasive meningococcal disease is suspected.

3. Sudarsanam T, Rupali P, Tharyan P, Abraham OC, Thomas K. Pre-admission antibiotics for suspected cases of meningococcal disease (Review). *Cochrane Database Syst Rev*. 2008 Jan; 23(1):1-40. Available from:

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005437.pub2/epdf>.

RATIONALE: A systematic review of randomised controlled trials aiming to study the effectiveness and safety of pre-admission antibiotics versus no pre-admission antibiotics or placebo, and different pre-admission antibiotic regimens in decreasing mortality, clinical failure, and morbidity in people with suspected meningococcal disease. The authors state that meningococcal disease can lead to disability or death within hours after onset. Pre-admission antibiotics aim to reduce the risk of serious disease and death by preventing delays in starting therapy before confirmation of the diagnosis. No RCTs were found that compared pre-admission antibiotics versus no pre-admission antibiotics or placebo. One open-label, non-inferiority RCT, conducted during an epidemic in Niger, evaluated a single-dose of intramuscular ceftriaxone versus a single-dose of intramuscular long-acting chloramphenicol. Ceftriaxone was not inferior to chloramphenicol in reducing mortality (RR 1.2; 95% CI 0.6 to 2.6; n=503, 308 with confirmed meningococcal meningitis and 26 deaths), clinical failures (RR 0.8; 92% effectiveness; 95% CI 0.3 to 2.2; n=477, 18 clinical failures), or neurological sequelae (RR 1.3; 95% CI 0.6 to 2.6; n=477, 29 with sequelae). No adverse effects of treatment were reported, and estimated treatment costs were similar. No data was available on disease burden due to sequelae. The authors conclude that there is no reliable evidence to support or refute the use of pre-admission antibiotics for suspected cases of non-severe meningococcal disease. Evidence of moderate quality from one RCT indicated that single intramuscular injections of ceftriaxone and long-acting chloramphenicol were equally effective, safe, and economical in reducing serious outcomes. The choice between these antibiotics should be based on affordability, availability and patterns of antibiotic resistance. Further RCTs comparing different pre-admission antibiotics, accompanied by intensive supportive measures, are ethically justifiable in participants with severe illness, and are needed to provide reliable evidence in different clinical settings.

4. Saeed K. 'One for all' concerns regarding NICE antibiotic guidelines on suspected bacterial meningitis. *Br J Gen Pract*. 2011 Oct; 61(591):606. Available from:

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3177115/pdf/bjgp61-606.pdf>.

RATIONALE: A review article of NICE antibiotic guidelines stating that, in children or young people with suspected bacterial meningitis or meningococcal septicaemia, transfer to hospital is the priority, and intravenous benzylpenicillin should be given at the earliest opportunity if a non-blanching rash is present. This article recommends benzylpenicillin because it covers meningococcal septicaemia, which causes the highest mortality, and it is the most frequently used antibiotic in primary care. However, following prompt admission, evaluation of a more definitive choice of antimicrobials can be made. Although

Management and treatment of common infections-Antibiotic guidance for primary care

the scope of the NICE guideline is for children, the author states that it seems reasonable to extrapolate the advice to older age groups.

- Andes DR, Craig WA. Pharmacokinetics and pharmacodynamics of antibiotics in meningitis. *Infect Dis Clin North Am*. 1999 Sep; 13(3):595-618. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/10470557>.

RATIONALE: A review article, stating that, for the antibiotics administered in bacterial meningitis, it is the duration of time that antibiotic concentrations in the cerebrospinal fluid exceed the minimum bactericidal concentration for that antibiotic that determines the rate of bactericidal activity. Taking this into consideration, the following dosages are recommended for IV or IM administration (if a vein cannot be accessed). For benzylpenicillin, a child under one year should be given a stat dose of 300mg, a child between one and nine years should be given a stat dose of 600mg, and an adult or child over the age of 10 should be given a stat dose of 1.2g. In true penicillin allergy, cefotaxime should be given at a dose of 50mg/kg for children under 12 years, and a dose of 1g should be given for adults or children over the age of 12.

Gastrointestinal Tract Infections

Oral candidiasis:

- Zhang LW, Fu JY, Hua H, Yan ZM. Efficacy and safety of miconazole for oral candidiasis: a systematic review and meta-analysis. *Oral Dis*. 2016 Apr; 22(3):185-195. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26456226>.

RATIONALE: A systematic review and meta-analysis of 17 studies involving 2,273 patients, aiming to assess the efficacy and safety of miconazole for treating oral candidiasis. 355 patients with thrush, 306 patients with cancer, 1,020 patients with HIV, 454 patients with denture stomatitis, and 138 patients with unidentified conditions were included. Results indicated that miconazole was superior to nystatin in clinical and mycological outcomes (clinical OR 13; 95% CI 3.05 to 55.29; mycological OR 6.40; 95% CI 1.38 to 29.6). For HIV-infected patients, there were no significant differences in the efficacy between miconazole and other antifungals. The heterogeneity among trials was acceptable (clinical outcome I^2 0%; mycological outcome I^2 32%). A fixed-effect model was used for the meta-analysis, and no statistical differences were found in clinical or mycological efficacy between miconazole and the other antifungals (clinical OR 0.75; 25% difference; 95% CI 0.53 to 1.06; mycological OR 1.01; 95% CI 0.74 to 1.38). For cancer-associated oral candidiasis, one trial compared miconazole buccal tablets with miconazole oral gel. No clinical differences were found between the two formulations. For denture stomatitis, five trial data were pooled to compare miconazole and natural substances: two trials for evaluating clinical outcome; three for evaluating mycological outcome. The heterogeneity between trials was acceptable (clinical I^2 31%; mycological I^2 0%), and a fixed-effect model was used for the meta-analysis. Results indicated that miconazole was clinically more efficacious than the natural substances (OR 3.01; 95% CI 1.35 to 6.72),

Management and treatment of common infections-Antibiotic guidance for primary care

whereas no statistical differences were found for mycological outcome (OR 1.5; 95% CI 0.72 to 3.12). No significant differences were found in the safety evaluation between miconazole and other treatments, but the relapse rate of miconazole oral gel may be lower than that of other formulations. The authors conclude that miconazole may be an optimal choice for the treatment of oral candidiasis, and that miconazole oral gel may be more effective than other formulations with regard to long-term results.

2. Farah CS, Ashman RB, Challacombe SJ. Oral candidosis. *Clin Dermatol*. 2000 Sep; 18(5):553-562. Available from:

<http://www.sciencedirect.com/science/article/pii/S0738081X0001450?via%3Dihub>.

RATIONALE: A review article, suggesting that the advent of HIV and AIDS has resulted in a resurgence of oral *Candida* infections that were formerly seen mainly in immunocompromised patients, or in persons at the extreme ends of the age spectrum. The authors state that, if oral candidiasis is present in an immunocompetent adult, clinicians should consider investigations for an underlying comorbidity or immunosuppressive illness, including HIV. Treatment regimens are provided, including 100,000 U/mL nystatin oral suspension, or oral fluconazole in severe or resistant cases.

3. Nelson M, Dockrell DH, Edwards S. British HIV Association and British Infection Association guidelines for the treatment of opportunistic infection in HIV-seropositive individuals 2011. *HIV Medicine*. 2011 May; 12(2):1-5. Available from:

http://www.bhiva.org/documents/Guidelines/OI/hiv_v12_is2_Iss2Press_Text.pdf.

RATIONALE: A BHIVA guideline recommending oral fluconazole for the treatment of oral candidiasis in HIV-positive patients. Patients with extensive/severe candidiasis, or with a background of HIV, should receive oral fluconazole therapy at a dose of 50-100mg/day. If patients are systemically unwell, or have not responded to oral fluconazole, consider referral to secondary care.

4. Clinical Knowledge Summaries (CKS). *Candida – oral*. 2013 Jul. Available from

<http://cks.nice.org.uk/candida-oral#>.

RATIONALE: A CKS guideline recommending that, for localised or mild oral candida infection, topical treatment for seven days should be prescribed, and advice should be given for the person to continue treatment for two days after symptoms resolve. This guideline advises that for adults and children over the age of 2 years, miconazole oral gel (24mg/ml) 2.5ml QDS should be offered as first line treatment, or 1ml nystatin suspension 100,000units/mL QDS, if miconazole is not tolerated. Oral fluconazole 50mg OD should be prescribed in extensive or severe cases, or 100mg OD for HIV or immunosuppression. All treatment should be prescribed for seven days, and continued for a further 7 days (miconazole) or 2 days (nystatin) if candida infection is persistent. The recommendations provided for the assessment and treatment of oral candida infection are in line with expert opinion, as there is a lack of direct evidence from randomised controlled trials to support the use of topical miconazole or nystatin, or oral fluconazole in the treatment of oral candidiasis in otherwise healthy adults. However, their use is supported by pharmacological principles, historical use, and extrapolation of clinical data from trials in other groups (infants; immunosuppression).

Management and treatment of common infections-Antibiotic guidance for primary care

5. Bensadoun RJ, Daoud J, El Gueddari B, Bastit L, Gourmet R, Rosikon A et al. Comparison of the efficacy and safety of miconazole 50-mg mucoadhesive buccal tablets with miconazole 500mg gel in the treatment of oropharyngeal candidiasis: a prospective, randomized, single-blind, multicentre, comparative, phase 3 trial in patients treated with radiotherapy for head and neck cancer. *Cancer*. 2008 Jan; 112(1):204-211. Available from:

<http://www.ncbi.nlm.nih.gov/pubmed/18044772>.

RATIONALE: A randomised controlled trial of cancer patients, in whom oral candidiasis was effectively treated by both tablet and gel formulations of miconazole. Clinical success was achieved in 56% of 141 patients who received 14 days 50mg mucoadhesive buccal tablet administration miconazole, and 49% of 141 patients who received 14 days of the 500mg gel preparation, administered in four equal doses. Other end-points of this study were largely non-significant, but 29% of patients who used buccal preparation experienced side-effects, versus 27% in the gel preparation group. However, fewer participants dropped out of the study due to adverse events (three versus six, respectively) when using the buccal preparation.

6. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016 Jan; 62(4):1-50. Available from:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4725385/>.

RATIONALE: An international consensus document providing the following recommendations. For mild disease, clotrimazole lozenges, 10mg five times daily, or miconazole mucoadhesive buccal, 50mg tablets applied to the mucosal surface over the canine fossa, once daily for seven to 14 days, are recommended. Alternatives for mild disease include nystatin suspension (100,000U/mL) 4-6mL four times daily, or 1-2 nystatin pastilles (200,000U each) four times daily, for seven to 14 days. For moderate to severe disease, oral fluconazole, 100-200mg daily, for seven to 14 days, is recommended. For fluconazole-refractory disease, itraconazole solution, 200mg once daily, or posaconazole suspension, 400mg twice daily for three days, then 400mg daily for up to 28 days, are recommended. Alternatives for fluconazole-refractory disease include voriconazole, 200mg twice daily, or AmB deoxycholate oral suspension, 100mg/mL four times daily. If required for patients who have recurrent infection, fluconazole, 100mg three times weekly, is recommended. For HIV-infected patients, antiretroviral therapy is strongly recommended to reduce the incidence of recurrent infections. For denture-related candidiasis, disinfection of the denture, in addition to antifungal therapy, is recommended. The authors state that the use of effective antiretroviral therapy has dramatically decreased the incidence of oesophageal candidiasis in HIV-infected patients.

7. Flynn PM, Cunningham CK, Kerkering T, San Jorge AR, Peters VB, Pitel PA. Oropharyngeal candidiasis in immunocompromised children: A randomized, multicenter study of orally administered fluconazole suspension versus nystatin. *J Pediatr*. 1995 Aug; 127(2):322-328.

Available from: <http://www.sciencedirect.com/science/article/pii/S0022347695703217>.

RATIONALE: A randomised controlled trial, demonstrating 14 day cure in 91% of patients treated with fluconazole suspension 2 to 3mg/kg per day, compared with 51% of patients

Management and treatment of common infections-Antibiotic guidance for primary care

treated with nystatin 400,000 units per day in a QDS regimen, both for 14 days.

Mycologically, there was organism eradication in 76% of patients on fluconazole, versus 11% on nystatin. Both regimens were tolerated well, with similar relapse rates.

8. Pons V, Greenspan D, Lozada-Nur F, McPhail L, Gallant JE, Tunkel A et al. Oropharyngeal candidiasis in patients with AIDS: randomized comparison of fluconazole versus nystatin oral suspensions. *Clin Infect Dis*. 1997 Jun; 24(6):1204-1207. Available from:

<http://cid.oxfordjournals.org/content/24/6/1204.long>.

RATIONALE: A randomised controlled trial of fluconazole versus nystatin oral suspensions. Cure was achieved at day 14 in 87% of 83 HIV-positive patients who were treated with fluconazole 100mg once daily, and 52% of 84 patients who received nystatin 500,000 units per day. Mycological clearance was achieved in 60% of the fluconazole group, and 6% of the patients treated with nystatin. 18% of patients relapsed with fluconazole, compared with 44% on nystatin, at day 28. Gastrointestinal side-effects were comparable, but two patients in the fluconazole group developed deranged liver function tests, and one had to withdraw.

Helicobacter pylori:

1. Ford AC, Delaney B, Forman D, Moayyedi P. Eradication therapy for peptic ulcer disease in *Helicobacter pylori* positive patients (Review). *Cochrane Database Syst Rev*. 2011 Apr; 1:1-121. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003840.pub4/pdf>.

RATIONALE: A systematic review and meta-analysis examining duodenal ulcer healing in 3,910 patients across 34 trials. Findings indicated that *H. pylori* eradication therapy was superior to ulcer healing drugs (UHDs) (RR of ulcer persisting 0.66; 34% superiority; 95% CI 0.58 to 0.76) and no treatment (two trials; 207 patients; RR 0.37; 63% superiority; 95% CI 0.26 to 0.53). In gastric ulcer healing, no significant differences were detected between eradication therapy and UHDs (15 trials; 1,974 patients; RR 1.23; 95% CI 0.90 to 1.68). In preventing duodenal ulcer recurrence, no significant differences were detected between eradication therapy and maintenance therapy with UHDs (4 trials; 319 patients; RR 0.73; 27% difference; 95% CI 0.42 to 1.25), but eradication therapy was superior to no treatment (27 trials; 2,509 patients; RR 0.20; 80% superiority; 95% CI 0.15 to 0.26). In preventing gastric ulcer recurrence, eradication therapy was superior to no treatment (12 trials; 1,476 patients; RR 0.31; 69% superiority; 95% CI 0.22 to 0.45), therefore, test and treat for *H. pylori* is advised in patients with a past history of gastric ulcers.

2. National Institute for Health and Care Excellence (NICE). Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. 2014 Sep. Available from:

<https://www.nice.org.uk/guidance/cg184>.

RATIONALE: A NICE guideline recommending that patients of any age with gastro-oesophageal symptoms that are unexplained or unresponsive to treatment should be referred to a specialist. Unexplained is defined as “a symptom(s) and/or sign(s) that has not led to a diagnosis being made by the primary care professional after initial assessment of the history, examination and primary care investigations”. Clinicians should offer *H.*

Management and treatment of common infections-Antibiotic guidance for primary care

pylori test and treat to patients with dyspepsia. Clinicians should leave a two week washout period after PPI use before testing for *H. pylori* with a urea breath test or stool antigen test. NICE recommend that patients with reflux-like symptoms should be treated in a similar way to those with dyspepsia, using full dose PPI for four weeks, before considering treatment for *H. pylori*. Clinicians should offer patients who need long-term management of dyspepsia symptoms an annual review of their condition, and should encourage them to try stepping down or stopping treatment (unless there is an underlying condition or co-medication that needs continued treatment). Clinicians should test for *H. pylori* using a carbon-¹³urea breath test or stool antigen test, or laboratory-based serology where performance has been locally validated. Clinicians should not use office-based serology tests for *H. pylori*, as their performance is routinely inadequate. Clinicians should discuss treatment adherence with the patient and should emphasise its importance. Clinicians should offer patients who test positive for *H. pylori* a seven day, twice daily course of treatment with a PPI, amoxicillin, and either clarithromycin or metronidazole. Choose the treatment regimen with the lowest acquisition cost and take into account previous exposure to clarithromycin and metronidazole. All triple regimens have similar outcomes and are slightly better than quadruple regimens. Offer patients who are allergic to penicillin a seven day, twice daily course of treatment with a PPI, clarithromycin and metronidazole. Offer patients who are allergic to penicillin and who have had previous exposure to clarithromycin a seven day, twice daily course of treatment with a PPI, metronidazole and levofloxacin. Offer patients who still have symptoms after first line eradication treatment a seven day, twice daily course of treatment with a PPI, amoxicillin and either clarithromycin or metronidazole (whichever was not used first line). Offer patients who have had previous exposure to clarithromycin and metronidazole a seven day, twice daily course of treatment with a PPI, amoxicillin and a quinolone or tetracycline. Offer patients who are allergic to penicillin (and who have not had previous exposure to a quinolone) a seven day, twice daily course of treatment with a PPI, metronidazole and levofloxacin. Offer patients who are allergic to penicillin and who have had previous exposure to a quinolone a PPI, a bismuth salt (tripotassium dicitratobismuthate or bismuth subsalicylate), metronidazole and tetracycline. NICE document evidence from one study, stating that increasing the duration of PPI/amoxicillin/quinolones from seven to 10 days results in improved second line *H. pylori* eradication when using standard or double dosing for the 10 day regimen. Evidence from other studies has shown that increasing the duration of a quadruple regimen from seven to 14 days does not improve second line *H. pylori* eradication. Clinicians should consider referral for those patients who have *Helicobacter pylori*, which has not responded to second line eradication therapy.

3. Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F et al. Management of *Helicobacter pylori* infection – the Maastricht IV/Florence Consensus Report. *Gut*. 2012 Feb; 61:646-664. Available from: <http://gut.bmj.com/content/61/5/646.full.pdf>.

RATIONALE: A consensus report providing expert opinion on the most appropriate management and diagnostic tests for *Helicobacter pylori*. The report advises that younger patients without alarm symptoms should be offered test and treat for *H. pylori* if local prevalence is over 20%, and also states that *H. pylori* eradication is most beneficial in

Management and treatment of common infections-Antibiotic guidance for primary care

patients with gastro-duodenal ulcer disease. Both *H. pylori* infection and NSAID use are independent risk factors for the development of peptic ulcer disease and associated bleeding. These conditions are uncommon in those who do not have either risk factor, but there is an increased risk when both factors are present. In naïve users of NSAIDs, it is clearly beneficial to eradicate *H. pylori*, but there is no clear benefit for those who are already long-term users. However, results from a meta-analysis showed that eradication seems less effective than *H. pylori* treatment with a maintenance PPI for preventing NSAID-associated ulcers. Clinicians should test for *H. pylori* in patients with unexplained iron-deficiency anaemia, idiopathic thrombocytopenic purpura, and vitamin B12 deficiency. Two meta-analyses have supported the association between these conditions, with one illustrating a clear link between *H. pylori* infection and iron-deficiency anaemia, and the other showing that *H. pylori* eradication increases haemoglobin levels in patients with this condition. Systematic reviews have demonstrated that an overall platelet response has been recorded in more than 50% of patients successfully treated for *H. pylori* infection, and response rates are increasing in countries with a high prevalence of *H. pylori* infection in background populations. This report states that there is a negative association between the prevalence of *H. pylori* and GORD. The sequelae of GORD, such as Barrett's oesophagus and oesophageal adenocarcinoma, are less common in infected individuals, and eradication of *H. pylori* in populations of infected patients, on average, neither causes nor exacerbates symptoms of GORD. Therefore, the presence of GORD should not dissuade practitioners from *H. pylori* eradication treatment, where indicated. Long-term treatment with PPIs in *H. pylori* positive patients is associated with the development of corpus-predominant gastritis. This accelerates the process of losing specialised glands, leading to atrophic gastritis. Eradication of *H. pylori* in patients receiving long-term PPI treatment heals gastritis and prevents the progression to atrophic gastritis. However, there is no evidence that this reduces the risk of gastric cancer. Finally, this report emphasises that urea breath tests (UBTs) and stool helicobacter antigen tests (SATs) are the most accurate tests and should be used in preference to serology.

4. Moayyedi P, Soo S, Deeks J, Delaney B, Harris A, Innes M et al. Eradication of *Helicobacter pylori* for non-ulcer dyspepsia. *Cochrane Database Syst Rev*. 2006 Apr; 19(2):1-42. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002096.pub4/epdf>.
RATIONALE: A systematic review and meta-analysis of 17 randomised controlled trials (n=3,566), which found that there was a 10% relative risk reduction in dyspepsia symptoms in people with non-ulcer dyspepsia when randomised to receive *H. pylori* eradication (95% CI 6% to 14%), compared to placebo. The NNT to cure one case of dyspepsia was 14 (95% CI 10 to 25).
5. Fischbach L, Evans EL. Meta-analysis: the effect of antibiotic resistance status on the efficacy of triple and quadruple first line therapies for *Helicobacter pylori*. *Aliment Pharmacol Ther*. 2007 Aug; 26(3):343-357. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17635369>.
RATIONALE: A systematic review and meta-analysis of 10 studies, including 10,178 participants, demonstrating pooled data that found that the efficacy of a PPI and clarithromycin and metronidazole was reduced more by resistance to clarithromycin, than

Management and treatment of common infections-Antibiotic guidance for primary care

it was by resistance to metronidazole. Metronidazole resistance reduced efficacy by 18%, whilst clarithromycin resistance was estimated to reduce efficacy by 35%. Clarithromycin resistance reduced the efficacy of PPI and clarithromycin and amoxicillin by 66%.

6. McNulty CA, Lassetter G, Shaw I, Nichols T, D'Arcy S, Lawson AJ et al. Is *Helicobacter pylori* antibiotic resistance surveillance needed and how can it be delivered? *Aliment Pharmacol Ther.* 2012 May; 35(10):1221-1230. Available from:

<http://www.ncbi.nlm.nih.gov/pubmed/22469191>.

RATIONALE: A 2009/2010 study of *Helicobacter pylori* antibiotic resistance surveillance in three centres across England and Wales. Biopsy specimens were taken from endoscopy patients in Gloucester, England and Bangor, Wales. Of 1,153 biopsy specimens in Gloucester, 11% were tested positive for *H. pylori* on culture or biopsy urease test, and 9% were tested positive by serology. Antibiotic resistance to amoxicillin, rifabutin and tetracycline remained very low, whereas each course of clarithromycin, metronidazole and levofloxacin was related to a 50% increase in resistance.

7. Gisbert JP, de la Morena F. Systematic review and meta-analysis: levofloxacin-based rescue regimens after *Helicobacter pylori* treatment failure. *Aliment Pharmacol Ther.* 2006 Jan; 23(1):35-44. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16393278>.

RATIONALE: A systematic review and meta-analysis of 149 studies demonstrating an 80% mean eradication rate with levofloxacin 250mg BD containing regimens. 10 day regimens were more effective than seven days, and side-effects were lower than with bismuth treatment. However, the authors conclude that this regimen should not be used if there has been previous use of a quinolone, as quinolone resistance develops easily.

8. Malfertheiner P, Bazzoli F, Delchier JC, Celinski K, Giguere M, Riviere M et al. *Helicobacter pylori* eradication with a capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline given with omeprazole versus clarithromycin-based triple therapy: a randomised, open-label, non-inferiority, phase 3 trial. *Lancet.* 2011 Mar; 377(9769):905-913. Available from: <http://www.sciencedirect.com/science/article/pii/S0140673611600202>.

RATIONALE: A randomised controlled trial, in which 339 patients across the UK, Germany, France, Ireland, Poland, and Spain were allocated to either 10 days omeprazole 20mg BD plus three capsules containing bismuth 140mg, metronidazole 125mg, and tetracycline hydrochloride 125mg QDS after meals, or seven days omeprazole 20mg BD plus 500mg amoxicillin and 500mg clarithromycin, all taken four times daily. According to intention to treat criteria, *H. pylori* eradication was successful in 92% of patients on quadruple therapy, and 69% of patients on triple therapy. In clarithromycin resistance, eradication was reduced to 8% of patients on triple therapy, but it did not influence quadruple therapy. Quadruple therapy is effective as a second line treatment, and should be considered if there is a past history of clarithromycin use.

9. O'Connor A, Fischbach W, Gisbert JP, O'Morain C. Treatment of *Helicobacter pylori* infection 2016. *Helicobacter.* 2016 Sep; 21(1):55-61. Available from:

<https://www.ncbi.nlm.nih.gov/pubmed/27531541>.

Management and treatment of common infections-Antibiotic guidance for primary care

RATIONALE: A review of all previously published trials regarding the treatment of *H. pylori*. This review states that outcomes for standard triple therapy have been generally poor, and the most promising results have come from bismuth and non-bismuth containing quadruple therapies. The findings also indicate that levofloxacin-based therapies have performed well as both first- and second line eradication regimens, and show promise when used in combination as a second line treatment. However, issues regarding resistance and availability may limit the adoption of these agents in treatment protocols.

10. Nocon M, Kuhlmann A, Leodolter A, Roll S, Vauth C, Willich SN et al. Efficacy and cost-effectiveness of the ¹³C-urea breath test as the primary diagnostic investigation for the detection of *Helicobacter pylori* infection compared to invasive and non-invasive diagnostic tests. *GMS Health Technol Assess*. 2009 Oct; 21(5):1-12. Available from:

<http://www.ncbi.nlm.nih.gov/pubmed/21289901>.

RATIONALE: A systematic review of 30 studies (3,415 patients) directly comparing the ¹³C-UBT and other non-invasive tests to biopsy-based tests as the gold standard for *H. pylori* testing. The ¹³C-UBT showed higher sensitivity and specificity than IgG serology in 18 studies, and showed higher sensitivity and specificity than SATs in 13 studies (a 100% sensitive test correctly identifies all patients with *H. pylori*, and a 100% specific test correctly identifies all patients without *H. pylori*). Sensitivity and specificity higher than 90% was found in 84% of the studies for the ¹³C-urea breath test. Sensitivity and specificity higher than 90% was found in 62% of the studies for the stool antigen test, and 56% sensitivity and 44% specificity for the IgG test. Nine health economic evaluations were included in this Health Technology Assessment (HTA) report. Test and treat strategies using the ¹³C-UBT were more cost-effective than serology-based strategies in three of the nine, and was dominated by a test and treat strategy using the SAT in one of those three.

11. Gisbert JP, de la Morena F, Abaira V. Accuracy of monoclonal stool antigen test for the diagnosis of *H. pylori* infection: a systematic review and meta-analysis. *Am J Gastroenterol*. 2006 Aug; 101(8):1921-1930. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16780557>.

RATIONALE: A systematic review of 22 studies (2,499 patients) showing *H. pylori* monoclonal stool antigen tests as having a sensitivity of 94% (95% CI, 93 to 95), and specificity of 97% (95% CI, 96 to 98), with LR+ and LR- being 24 (15 to 41) and 0.07 (0.04 to 0.12), respectively. Monoclonal tests were more sensitive than polyclonal tests (pooled sensitivity of 95% for monoclonal tests, and 83% for polyclonal tests). Post-treatment, the monoclonal stool antigen tests were evaluated in 957 patients, with a sensitivity of 93% (95% CI 89 to 96) and a specificity of 96% (95% CI 94 to 97), respectively. Pooled positive and negative LR were 17 (12 to 23) and 0.1 (0.07 to 0.15).

12. Xin Y, Manson J, Govan L, Harbour R, Bennison J, Watson E, Wu O. Pharmacological regimens for eradication of *Helicobacter pylori*: an overview of systematic reviews and network meta-analysis. *BMC Gastroenterol*. 2016 Jul; 16(1):80-98. Available from:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4962503/>.

RATIONALE: A meta-analysis of 30 systematic reviews with pairwise meta-analysis, involving, 66,037 patients, which analyses the effectiveness of different pharmacological

Management and treatment of common infections-Antibiotic guidance for primary care

regimens to treat proven *H. pylori* infection. The results demonstrated the benefits of adding proton pump inhibitor (PPI) medication to an *H. pylori* eradication treatment regimen. Seven studies evaluated the impact of different PPIs within a triple therapy regimen on *H. pylori* eradication rate. The reported eradication rates ranged from 77% (data from nine RCTs relating to rabeprazole-based triple therapy) to 94% (data from one RCT relating to esomeprazole-based triple therapy). Three studies also compared the effectiveness of PPI versus H₂RA within a triple therapy. One systematic review based on 20 RCTs with 2374 patients showed PPI was associated with greater effectiveness than H₂RA (OR 1.31; 95%CI 1.09 to 1.58).

13. Dore MP, Lu H, Graham DY. Role of bismuth in improving *Helicobacter pylori* eradication with triple therapy. *Gut*. 2016 Feb; 1:1-9. Available from:

<http://gut.bmj.com/content/early/2016/02/04/gutjnl-2015-311019.full.pdf>.

RATIONALE: A literature review describing the increasing antibiotic resistance to *H. pylori* worldwide, and the added value of using bismuth (subsalicylate and nitrate) in areas where resistance is high. This review states that the addition of bismuth to form quadruple therapy can increase *H. pylori* eradication by 30-40% in populations with high resistance.

14. O'Connor A, Gisbert JP, McNamara D, O'Morain C. Treatment of *Helicobacter pylori* infection 2011. *Helicobacter*. 2011 Sep; 16(1):53-58. Available from:

<http://onlinelibrary.wiley.com/doi/10.1111/j.1523-5378.2011.00881.x/pdf>.

RATIONALE: A review of all previously published trials regarding the treatment of *H. pylori*. Seven studies were cited describing the successful use of levofloxacin 250mg to 500mg with amoxicillin or clarithromycin and a proton pump inhibitor as first line treatment for *H. pylori* (85% eradication). Rifabutin 150mg BD with amoxicillin 1g BD achieved 79 to 85% eradication in patients who had failed other treatment regimens. A study of a bismuth, omeprazole 20mg to 40mg, amoxicillin 1g BD and clarithromycin regimen showed superior eradication of 94% in a group treated for 14 days, compared with 80% for a group treated for 7 days. In a further study of patients unsuccessfully treated with triple therapy, eradication rates of 77% were obtained for one week of bismuth-based quadruple therapy, and 94% for two weeks.

15. Chey WD, Wong BC, Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2007 Aug; 102(8):1808-1825. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/17608775>.

RATIONALE: An ACOG guideline, providing details of first line regimens for *Helicobacter pylori* eradication. Post-treatment testing has demonstrated that, for penicillin allergic patients, bismuth subsalicylate at a dose of 525mg QDS should be given alongside a PPI, tetracycline hydrochloride 500mg QDS, and metronidazole 250mg QDS or 500mg BD. This guideline also provides standard doses for a range of PPIs, including: lansoprazole 30mg; omeprazole 20mg; pantoprazole 40mg; rabeprazole 20mg; esomeprazole 40mg.

16. Yuan Y, Ford AC, Khan KJ, Gisbert JP, Forman D, Leontiadis GI et al. Optimum duration of

Management and treatment of common infections-Antibiotic guidance for primary care

regimens for *Helicobacter pylori* eradication (Review). *Cochrane Database Syst Rev*. 2013 Dec; 12:1-421. Available from:

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008337.pub2/epdf>.

RATIONALE: A systematic review and meta-analysis of 75 studies from around the world, suggesting that the optimal duration for *Helicobacter pylori* eradication therapy is controversial, with recommendations ranging from seven to 14 days. The authors conclude that increasing the duration of PPI-based triple therapy increases *H. pylori* eradication rates (72.9% versus 81.9%; RR 0.66; 95% CI 0.60 to 0.74; NNT 11). For PPI, clarithromycin, and amoxicillin (PCA), prolonging treatment duration from seven to ten, or from ten to 14 days is associated with a significantly higher eradication rate (75.7% versus 79.9%; RR 0.80; 95% CI 0.72 to 0.89; NNT 21). The optimal duration of therapy for PCA and PAN (PPI, amoxicillin, and nitroimidazole) appears to be at least 14 days. The authors suggest that there was no statistically significant difference between regions. However, for conditions in which eradication is critical, as in MALToma, a longer eradication regimen of 14 days is recommended.

17. Buzas GM, Jozan J. Nitrofurantoin-based regimens for the eradication of *Helicobacter pylori* infection. *J Gastroenterol Hepatol*. 2007 Oct; 22(10):1571-1581. Available from:

<http://onlinelibrary.wiley.com/doi/10.1111/j.1440-1746.2007.05082.x/epdf>.

RATIONALE: A systematic review and meta-analysis of 51 studies and 4,946 patients, examining furazolidone- and nitrofurantoin-based regimens in the eradication of infection. There have been some studies with small numbers of patients examining the effectiveness of furazolidone with amoxicillin (60% eradication) and furazolidone with levofloxacin (83% eradication) in patients on rescue treatment. The overall eradication rate of third-line rescue therapies was 65.5%, but side-effects of the regimens containing furazolidone were more frequent than in standard therapies. ($p=0.02$). The authors conclude that primary triple regimens containing furazolidone are slightly less efficient than the standard primary combinations, and that it is the duration of treatment, not the dose, that has the largest influence on the treatment outcome.

Infectious diarrhoea:

1. Independent Investigation Committee. Review of the major outbreak of *E. coli* 0157 in Surrey, 2009: An evaluation of the outbreak and its management, with a consideration of the regulatory framework and control of risks relating to open farms. 2010 Jun. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/342361/Review_of_major_outbreak_of_e_coli_o157_in_surrey_2009.pdf.

RATIONALE: An evaluation of the 2009 outbreak of *E. coli* 0157 and its management, with a consideration of the regulatory framework and control of risks relating to open farms. *E. coli* 0157 infection is relatively uncommon but, because the illness it causes can be severe or fatal, it remains a serious public health issue. *E. coli* 0157 should be suspected in any child presenting with bloody or painful diarrhoea.

2. Farthing M, Feldman R, Finch R, Fox R, Leen C, Mandal B et al. The management of

Management and treatment of common infections-Antibiotic guidance for primary care

infective gastroenteritis in adults. A consensus statement by an expert panel convened by the British Society for the Study of Infection. *J Infect.* 1996 Nov; 33(3):143-152. Available from: [http://www.journalofinfection.com/article/S0163-4453\(96\)92057-5/abstract](http://www.journalofinfection.com/article/S0163-4453(96)92057-5/abstract).

RATIONALE: An expert consensus statement suggesting that empirical treatment for patients well enough to be managed in primary care should not be recommended, as the majority of illnesses seen in the community do not have an identifiable bacterial cause. In addition, an RCT of quinolones as empiric therapy found no benefit in patients whose stool cultures were negative for bacterial infection.

3. Public Health England (PHE). Managing suspected infectious diarrhoea. Quick reference guide for primary care: for consultation and local adaptation. 2015 Jan. Available from: <https://www.gov.uk/government/publications/infectious-diarrhoea-microbiological-examination-of-faeces>.

RATIONALE: A PHE guideline, recommending that, if campylobacter is strongly suspected as the cause of diarrhoea, empirical treatment with clarithromycin 250-500mg BD for five to seven days should be considered. Quinolones are not recommended as there is increasing resistance of campylobacter to quinolones, and broad-spectrum antibiotics are not recommended for empirical treatment due to an increased risk of *Clostridium difficile*, MRSA, and antibiotic-resistant UTIs.

4. Ternhag A, Asikainen T, Giesecke J, Ekdahl K. A meta-analysis on the effects of antibiotic treatment on duration of symptoms caused by infection with Campylobacter species. *Clin Infect Dis.* 2007 Mar; 44(5):696-700. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/17278062>.

RATIONALE: A meta-analysis of 11 randomised controlled trials, involving 479 patients, which provides evidence that, when compared with placebo, treating diarrhoea caused by campylobacter with erythromycin, norfloxacin, or ciprofloxacin, shortens the duration of diarrhoea by 1.32 days (95% CI 0.64 to 1.99; $p < 0.001$). Duration of symptoms was 41 hours shorter (2.4 versus 4.1 days) if treated within three days of the start of symptoms, in comparison to commencement of treatment after three days.

Clostridium difficile:

1. Debast SB, Bauer MP, Kuijper EJ, European Society of Clinical Microbiology and Infectious Diseases. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection. *Clin Microbiol Infect.* 2014 May; 20(2):1-26. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24118601>.

RATIONALE: A European guideline, evaluating the available literature categorising *Clostridium difficile* infection severity. This guideline offers the following recommendations: antiperistaltic agents and opiates should be avoided; in general, strive to use antibiotics covering a spectrum no broader than necessary, and narrow the antibiotic spectrum of treatment after results of cultures and/or susceptibility tests become known; mild CDI (stool frequency < 4 times daily; no signs of severe colitis), clearly induced by the use of antibiotics, may be treated by stopping the inducing antibiotic. Patients should be

Management and treatment of common infections-Antibiotic guidance for primary care

observed closely for any signs of clinical deterioration and placed on therapy immediately if this occurs. If oral therapy is possible, non-severe cases should be prescribed metronidazole 500mg three times daily orally for ten days; severe cases should be prescribed vancomycin 125mg four times daily for ten days. If oral therapy is not possible, non-severe cases should be prescribed metronidazole 500mg three times daily, intravenously, for ten days. If severe cases unable to take oral treatment, metronidazole 500mg three times daily, intravenously, for ten days, should be prescribed, plus intracolonic vancomycin 500mg in 100mL of normal saline every four to twelve hours (C-III) and/or vancomycin 500mg four times daily by nasogastric tube.

2. Public Health England (PHE). Updated guidance on the management and treatment of *Clostridium difficile* infection. 2013 May. Available from:

<https://www.gov.uk/government/publications/clostridium-difficile-infection-guidance-on-management-and-treatment>.

RATIONALE: A PHE guideline suggesting that supportive care should be given to patients with *Clostridium difficile*, including attention to hydration, electrolytes, and nutrition. Antiperistaltic agents should be avoided in acute infection, due to the theoretical risk of precipitating toxic megacolon by slowing the clearance of *C. difficile* toxin from the intestine. The precipitating antibiotic should be stopped wherever possible; agents with less risk of inducing CDI can be substituted if an underlying infection still requires treatment. Patients with mild disease may not require specific *C. difficile* antibiotic treatment. If treatment is required, oral metronidazole is recommended (400-500mg TDS for 10 to 14 days), as it has been shown to be as effective as oral vancomycin in mild to moderate CDI. For patients with moderate disease, a ten to 14 day course of oral metronidazole is the recommended treatment (400-500mg TDS). This is because it is cheaper than oral vancomycin and there is concern that overuse of vancomycin may result in the selection of vancomycin-resistant enterococci. For patients with severe CDI oral vancomycin is preferred (125mg QDS for 10 to 14 days). This is because of relatively high failure rates of metronidazole and a slower clinical response to metronidazole, compared with oral vancomycin treatment. Two double-blind randomised studies reported that vancomycin is superior to metronidazole in severe cases of CDI. A pooled analysis of these two phase 3 studies has shown that metronidazole was overall inferior to vancomycin. The following symptoms should be used to indicate severe CDI: WCC $>15 \times 10^9/L$; acutely rising blood creatinine (eg more than 50% increase above baseline); temperature $>38.5^\circ C$; evidence of severe colitis (abdominal signs; radiology). Recurrent disease may occur in up to 20% of patients, up to half of which may be reinfections, rather than relapse. The same antibiotic can be used for a second course of treatment. After a first recurrence, the risk of further recurrences is higher. For recurrent disease, a tapering course of vancomycin may be considered after the initial treatment course. There are various regimens for vancomycin: 125mg QDS for one week; 125mg TDS for one week; 125mg BD for one week; 125mg OD for one week; 125mg on alternate days for one week; 125mg every third day for one week. Clearly, this may provide a considerable selective pressure for vancomycin resistance, eg in enterococci. Fidaxomicin should also be considered for patients with severe CDI who are considered at high risk for recurrence;

Management and treatment of common infections-Antibiotic guidance for primary care

these include elderly patients with multiple comorbidities who are receiving concomitant antibiotics. Fidaxomicin is very expensive and may not be of additional benefit for some strains of *C. difficile* (eg ribotype 0157). Its role in multiple recurrences is unclear. Local cost-effective decision making should determine its use.

- Howell MD, Novack V, Grgurich P, Soulliard D, Novack L, Pencina M et al. Iatrogenic gastric acid suppression and risk of nosocomial *Clostridium difficile* infection. *Arch Intern Med*. 2010 May;170(9):784-789. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20458086>.
RATIONALE: A pharmacoepidemiologic cohort study, presenting increasing evidence that acid-suppressing medications, in particular proton pump inhibitors, may be a risk factor for CDI. The authors report a correlation between the degree of acid suppression and risk of CDI (ie a 'dose response' effect), which ranged from none (OR 1), to H₂ receptor antagonists (OR 1.53; 95% CI 1.12 to 2.10), to once daily PPI (OR 1.74; 95% CI 1.39 to 2.18), to more frequent PPI (OR 2.36; 95% CI 1.79 to 3.11). It remains possible that these associations are confounded by other CDI risk factors. However, given that acid suppression drugs, especially PPIs, may be over-prescribed and frequently not reviewed to determine if long-standing prescriptions are still justifiable, consideration should be given to stopping or reviewing the need for PPIs in patients with, or at high risk of, CDI.
- Belmares J, Gerding DN, Parada JP, Miskevics S, Weaver F, Johnson S. Outcome of metronidazole therapy for *Clostridium difficile* disease and correlation with a scoring system. *J Infect*. 2007 Dec; 55(6):495-501. Available from: <http://www.sciencedirect.com/science/article/pii/S0163445307007840>.
RATIONALE: A retrospective study of 102 patients given a five day course of metronidazole for *Clostridium difficile* infection. This study found that 70.6% responded to treatment by the end of the five day course. 21 of the remaining 30 patients eventually responded to metronidazole, but needed a longer course of treatment (14 days; overall response rate = 91%). The mean CDD score at presentation was higher among true failures (2.89 + 1.4) than among all metronidazole responders (0.77 + 1.0; p<0.0001). The CDD score (0-7) included variables previously suggested in the literature, to correlate with a higher disease severity: fever $\geq 38^{\circ}\text{C}$; ileus; hypotension (each scored one); leucocytosis; specific CT abnormalities (weighted as one or two depending on WBC and CT findings).
- National Institute for Health and Care Excellence (NICE). *Clostridium difficile* infection: fidaxomicin. 2012 Jul. Available from: <https://www.nice.org.uk/advice/esnm1/chapter/Introduction>.
RATIONALE: A NICE guideline suggesting that, until recently, there were only two main options for the treatment of CDI (metronidazole or vancomycin). Oral fidaxomicin was approved for the treatment of CDI in Europe in 2012, and has been reviewed by both NICE and the SMC. Two phase 3, multi-centred, randomised, double-blind studies with almost identical designs compared oral fidaxomicin (200mg BD for ten to 14 days) with oral vancomycin (125mg QDS for ten to 14 days). Fidaxomicin was non-inferior to vancomycin in the initial clinical cure of CDI (RR 0.88; 12% difference; 95% CI 0.64 to

Management and treatment of common infections-Antibiotic guidance for primary care

1.19; $p=0.396$), but was superior in reducing recurrence (RR 0.54; 46% superiority; 95% CI 0.42 to 0.71; $p<0.001$), and sustained clinical cure (RR 0.68; 32% difference; 95% CI 0.56 to 0.81; $p<0.001$). The side-effect profile of fidaxomicin appears similar to that of oral vancomycin. The acquisition cost of fidaxomicin is considerable higher than vancomycin, which is more expensive than metronidazole. Decision makers need to take into account the benefits versus increased costs.

Traveller's diarrhoea:

1. Centers for Disease Control and Prevention (CDC). Travelers' Diarrhea. 2015 Jul. Available from: <http://wwwnc.cdc.gov/travel/yellowbook/2016/the-pre-travel-consultation/travelers-diarrhea>.

RATIONALE: A CDC chapter stating that high-risk countries for traveller's diarrhoea are defined as: most of Asia; the Middle-East; Africa; Mexico; Central and Southern America. Bismuth subsalicylate can be used for prophylaxis, when prescribed at a dose of two tablets, four times daily: one study found it reduced the incidence of traveller's diarrhoea from 40% to 14%. However, adverse effects are common, and due to its salicylate content, bismuth subsalicylate has several contraindications. The use of prophylactic antibiotics is also discussed. The author concludes that prophylactic antibiotics should not be recommended for most travellers. Prophylactic antibiotics afford no protection against nonbacterial pathogens and can remove normally protective microflora from the bowel. A traveller relying on prophylactic antibiotics will need to carry an alternative antibiotic to use in case diarrhoea develops, despite prophylaxis. Additionally, the use of antibiotics may be associated with allergic or adverse reactions in a certain percentage of travellers, and may potentially contribute to drug resistance. The use of prophylactic antibiotics should be weighed against the result of using prompt, early self-treatment with antibiotics when traveller's diarrhoea occurs, as this can limit the duration of illness to six to 24 hours in most cases. Prophylactic antibiotics may be considered for short-term travellers who are high-risk hosts or who are taking critical trips during which even a short bout of diarrhoea could affect it. The authors suggest azithromycin 500mg per day for one to three days for effective treatment of traveller's diarrhoea.

2. Clinical Knowledge Summaries (CKS). Diarrhoea – prevention and advice for travellers. 2013 May. Available from: <https://cks.nice.org.uk/diarrhoea-prevention-and-advice-for-travellers#!topicsummary>.

RATIONALE: A CKS guideline, listing high risk zones for traveller's diarrhoea as: Africa; Latin America; the Middle East; most parts of Asia. This guideline also lists groups of people who are at higher risk of developing traveller's diarrhoea, including: young children and babies, and elderly or frail people; people with reduced immunity (such as those with HIV infection or AIDS); people with severe cardiac or renal disease; people with inflammatory bowel disease; people with reduced acidity in the stomach, which is a risk factor for infection with acid-sensitive organisms, such as *Salmonella* and *Campylobacter*. This guideline states that azithromycin 500mg daily for three days can be prescribed for stand-by treatment of traveller's diarrhoea, and that a short two day course of bismuth

Management and treatment of common infections-Antibiotic guidance for primary care

subsalsicylate (two tablets twice a day) can also be considered as stand-by treatment if the person is travelling to an area where quinolone resistance is high.

- de Bruyn G, Hahn S, Borwick A. Antibiotic treatment for travellers' diarrhoea (Review). *Cochrane Database Syst Rev*. 2000 Jul; 20(3):1-29. Available from:

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002242/epdf>.

RATIONALE: A systematic review of 20 randomised controlled trials, ten of which evaluated short-courses of quinolones, three of which evaluated stat doses of quinolones, and one of which evaluated azithromycin for traveller's diarrhoea. The authors conclude that antibiotic treatment is effective in reducing the duration of post-treatment diarrhoea, and severity of diarrhoea. However, this is at the price of an increased chance of side-effects from antibiotic treatment.

- Committee to Advise on Tropical Medicine and Travel (CATMAT). Statement on travellers' diarrhoea. An advisory committee statement (ACS). 2015 Apr. Available from:

<http://www.phac-aspc.gc.ca/tmp-pmv/catmat-ccmtmv/diarrhea-diarrhee-eng.php>.

RATIONALE: A CATMAT statement, in which the authors recommend that bismuth subsalsicylate 2.1g to 4.2g per day be considered as an option for preventing traveller's diarrhoea for adults at significant risk, and who are willing to accept multiple doses per day. The authors also suggest that a lower dosage of bismuth subsalsicylate (1.05g per day) could be used to prevent traveller's diarrhoea in situations where a higher dose is not feasible. These recommendations are based on four randomised controlled trials investigating the use of bismuth subsalsicylate versus placebo. The authors found that, overall, a strong protective effect is found after three to four weeks' follow-up (RR 0.50; 50% effectiveness; 95% CI 0.44 to 0.67), resulting in 250 fewer cases of traveller's diarrhoea per 100 travellers treated. This strong effect was similarly found when restricted to those receiving a high (4.2g per day) or low (1.05g per day) dosage of bismuth subsalsicylate (RR 0.51; 49% effectiveness; 95% CI 0.39 to 0.65, and RR 0.65; 35% effectiveness; 95% CI 0.50 to 0.86, respectively). Similarly, there was no difference in effect found when comparing high to low dosage (RR 0.87; 13% difference; 95% CI 0.63 to 1.22). The authors state that the use of bismuth subsalsicylate is permitted in the case of certain children aged two years and older, based on an individual assessment of risks and benefits. Bismuth subsalsicylate is not recommended in children younger than two years.

Threadworm:

- Clinical Knowledge Summaries (CKS). Threadworm. 2011 Dec. Available from:

<http://cks.nice.org.uk/threadworm#!topicsummary>.

RATIONALE: A CKS guideline, suggesting that all household members should be treated at the same time if threadworm is present. This guideline states that there is no good trial evidence regarding the efficacy of anthelmintics in the treatment of threadworm, and the limited data available is from relatively old, small studies, comparing mebendazole with either placebo, or with drugs that are not available in the UK. Mebendazole does not kill eggs, which survive for three weeks; therefore, adequate personal and environmental

Management and treatment of common infections-Antibiotic guidance for primary care

Hygiene is essential to prevent reinfestation from recently swallowed eggs, or eggs already in the environment. Hygiene measures include: washing the perianal area first thing in the morning; washing or wet-wiping at three hourly intervals during the day; changing underwear every morning; bathing or showering immediately on rising each morning, and washing around the anus to remove any eggs laid by the worms during the night; hand hygiene; washing sleepwear, bed linen, towels, and cuddly toys at normal temperatures, and rinsing well; thoroughly vacuuming and dusting, paying particular attention to the bedrooms, including vacuuming mattresses. Thorough hygiene measures should be continued for two weeks in people who have taken an anthelmintic, and for six weeks in people who are using hygiene measures alone, as adults survive for six weeks. A one-off dose of mebendazole can be prescribed in children over six months, but hygiene measures alone should be used in children under six months for at least six weeks. Mebendazole should be avoided in the first trimester of pregnancy and hygiene is the preferred method of treatment for this group.

- Ibarra J. Threadworms: a starting point for family hygiene. *Br J Community Nurs*. 2001 Aug; 6(8):414-420. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/11865209>.
RATIONALE: A review article, emphasising the importance of thorough hygiene measures in cases of threadworm infestation. The most important of these is good hand hygiene, which is also key to preventing the spread of many other more serious infections.
- Lohiya G-S, Tan-Figueroa L, Crinella FM, Lohiya S. Epidemiology and control of enterobiasis in a developmental center. *West J Med*. 2000 May; 172(5):305-308. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1070873/pdf/wjm17200305.pdf>.
RATIONALE: A population-based study in a USA long-term care facility for 1,000 residents with developmental disabilities, and high rates of threadworm (*Enterobius vermicularis*). All cases of *Enterobius* and all 30 residents living in the same unit were treated with a single dose of mebendazole 100mg, which was repeated at 14 days. Prevalence of *Enterobius* fell from 31% to 1% over three years in ambulatory patients. The authors state that mebendazole only kills the adult worm, not the eggs or larvae, by inhibiting its microtubule formation and glucose synthesis. The surviving eggs and larvae in a host's intestines can mature to new adults within 14 days. A second dose, 14 days after the first, is crucial to kill these new adults. A second dose sooner than 14 days would leave the later-maturing adults unaffected and, after 14 days, the new adults would already have produced eggs. Contacts can be infected with larvae or adult worms without visible perianal eggs, which is the mainstay of diagnosis by sellotape slides and strips.

Genital Tract Infections

STI screening:

- British Association for Sexual Health and HIV (BASHH). Standards for the management of sexually transmitted infections (STIs). 2014 Jan. Available from: <http://www.medfash.org.uk/uploads/files/p18dtqli8116261rv19i61rh9n2k4.pdf>.
RATIONALE: A BASHH guideline stating that people with needs relating to STIs should

have a medical and sexual history taken which includes questions about sexual behaviour and other risk factors. Those with symptoms should be offered a genital examination. The minimum investigations, even if asymptomatic, are tests for chlamydia, gonorrhoea, syphilis, and HIV, and should include samples from extra-genital sites if indicated by the sexual history. People with needs relating to STIs should have their care managed by an appropriately skilled healthcare professional, and people needing to be referred to another service for ongoing STI management, such as GUM, should have this arranged for them quickly and easily.

2. Public Health England (PHE). Sexually transmitted infections and chlamydia screening in England, 2015. 2016 Jul. Available from: <https://www.gov.uk/government/statistics/national-chlamydia-screening-programme-ncsp-data-tables>.

RATIONALE: A PHE report stating that, in 2015, there were approximately 435,000 diagnoses of sexually transmitted infections made in England. This report recommends that: prevention should focus on groups at highest risk, including young adults, men who have sex with men, and black ethnic minorities; consistent and correct use of condoms can significantly reduce the risk of infection; rapid access to treatment and partner notification can reduce infection spread; regular testing for HIV and STIs is essential for good sexual health; anyone under 25 who is sexually active should be screened for chlamydia annually, and on change of sexual partner; men who have sex with men should be tested annually for HIV and STIs, and every three months if having condomless sex with new or casual partners. This guideline also suggests that health promotion and education for the general public should be implemented.

Chlamydia trachomatis/urethritis:

1. Public Health England (PHE). Sexually transmitted infections and chlamydia screening in England, 2015. 2016 Jul. Available from: <https://www.gov.uk/government/statistics/national-chlamydia-screening-programme-ncsp-data-tables>.

RATIONALE: A PHE report stating that, in 2015, the most commonly diagnosed STI was chlamydia, with over 1.5 million chlamydia tests carried out, and over 129,000 chlamydia diagnoses made among young people aged 15 to 24 years. This report recommends that: prevention should focus on groups at highest risk, including young adults, men who have sex with men, and black and ethnic minorities; anyone under 25 who is sexually active should be opportunistically screened for chlamydia, screened annually, and on change of sexual partner; MSM should be tested annually for HIV and STIs, and every three months if having condomless sex with new or casual partners; consistent and correct use of condoms can significantly reduce the risk of infection; rapid access to treatment and partner notification can reduce infection spread; regular testing for HIV and STIs is essential for good sexual health. This report also states that all patients treated for chlamydia should have a repeat TOC three to six months after treatment. In pregnancy, a repeat TOC should be conducted no earlier than three weeks after treatment.

2. Scottish Intercollegiate Guidelines Network (SIGN). Management of genital *Chlamydia*

Management and treatment of common infections-Antibiotic guidance for primary care

trachomatis infection: a national clinical guideline. 2009 Mar. Available from:

<http://www.sign.ac.uk/assets/sign109.pdf>.

RATIONALE: A SIGN guideline advising that the treatment of partners prior to resuming sexual intercourse is the strongest predictor for preventing re-infection with *Chlamydia trachomatis*. Sexual partners of chlamydia-positive individuals are at risk of infection and subsequent morbidity; treating them will also reduce the risk of re-infection of the index case. The prevalence of infection in sexual partners of chlamydia-positive cases has been shown to be 60 to 75%. Sexual partners of those with conditions for which chlamydia is a frequent cause, such as PID or epididymo-orchitis, are also at risk of infection. This guideline recommends either doxycycline 100mg BD for seven days, or azithromycin 1g stat as first line treatment for *Chlamydia trachomatis* in pregnant women, as cure rates for both treatments are over 90%. However, the authors advise that, taking compliance with therapy into account, uncomplicated genital chlamydial infection should be treated with azithromycin 1g as a single oral dose.

3. Nwokolo NC, Dragovic B, Patel S, Tong CYW, Barker G, Radcliffe K. 2015 UK national guideline for the management of infection with *Chlamydia trachomatis*. *Int J STD AIDS*. 2015 Oct; 27(4):251-267. Available from:

<http://www.bashh.org/documents/UK%20Chlamydia%20Guidelines%202015.pdf>.

RATIONALE: A UK national guideline stating that partners should also be treated for *Chlamydia trachomatis* infection, as there is a concordance rate of up to 75%. A test of cure is not routinely recommended, but should be performed in pregnancy, or where non-compliance or re-exposure is suspected. The higher rate of positive tests after treatment during pregnancy is attributed to either: a less efficacious treatment regimen; non-compliance; re-infection. A test of cure should be repeated no earlier than three weeks after the end of treatment, as treatment failure with azithromycin has been reported at 8%, questioning its effectiveness. This is recommended especially where poor compliance is suspected, or if symptoms persist after the end of treatment. This guideline recommends the following treatment regimens: for uncomplicated urogenital infection, doxycycline 100mg BD for seven days (contraindicated in pregnancy); azithromycin 1g orally as a single dose. Alternative regimens (if either of the above is contraindicated) include erythromycin 500mg BD for ten to 14 days, or ofloxacin 200mg BD/400mg OD for seven days. Following an extensive review of the evidence and a professional and public consultation, in August 2013, the National Chlamydia Screening Programme (NCSP) in England issued a recommendation that young people under the age of 25 who test positive for chlamydia should be offered a repeat test around three months after treatment of the initial infection. This is based on evidence that young adults who test positive for chlamydia are two to six times more likely to have a subsequent positive test, and that repeated chlamydia infection is associated with an increased risk of complications, such as PID and tubal infertility.

4. Rose SB, Garrett SM, Stanley J, Pullon SRH. Retesting and repeat positivity following diagnosis of *Chlamydia trachomatis* and *Neisseria gonorrhoea* in New Zealand: a retrospective cohort study. *BMC Infect Dis*. 2017 Jul; 17(1):526. Available from:

<https://www.ncbi.nlm.nih.gov/pubmed/28754106>.

Management and treatment of common infections-Antibiotic guidance for primary care

RATIONALE: A retrospective cohort study in Wellington, New Zealand, involving the analysis of laboratory data for chlamydia and gonorrhoea tests performed in primary care and sexual health clinics between July 2012 and July 2015. Overall, 29.4% (1,919/6,530) were retested between six weeks and six months, with 18% (347/1,919) of those retested returning positive results. Lower odds of retesting were observed for males (OR 0.4; 95% CI 0.34 to 0.48). Factors associated with higher odds of repeat positivity on retesting included those aged between 15 and 19 years (OR 1.78; 95% CI 1.32 to 2.41), and those with chlamydia/gonorrhoea co-infection (OR 1.6; 95% CI 1.32 to 4.35). The authors conclude that greater priority needs to be placed on increasing retesting, and reducing rates of reinfection. Therefore, repeat test of cures should be repeat three to six months after completing a course of treatment for chlamydial or gonococcal infection.

5. Lau CY, Qureshi AK. Azithromycin versus doxycycline for genital chlamydial infections: a meta-analysis of randomized clinical trials. *Sex Transm Dis.* 2002 Sep; 29(9):497-502. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12218839>.

RATIONALE: A meta-analysis of 12 randomised controlled trials (n=1,543), reporting that microbiological cure was achieved in 97% of people taking azithromycin 1g once, and 98% of those taking doxycycline 100mg BD for seven days (p=0.296; no significant difference). The authors conclude that azithromycin and doxycycline are equally efficacious in achieving microbial cure and have similar tolerability, with azithromycin being the most effective antimicrobial in pregnancy. Further trials comparing these antibiotics are unnecessary.

6. UK Teratology Information Service (UKTIS). *Maternal exposure*. Available from: http://www.uktis.org/html/maternal_exposure.html [Accessed: 30th August, 2016].

RATIONALE: A UKTIS webpage stating that there are few published trials on the use of azithromycin in pregnancy; however, the data currently available does not indicate that the use of azithromycin in pregnancy is associated with an increased risk of malformations. An increased risk of cardiovascular defects and pyloric stenosis have been suggested for macrolides as a class, although causality has not been established conclusively. For erythromycin, the majority of studies do not support an association between erythromycin exposure and any malformation or any adverse foetal effect. However, associations have been made with an increased incidence of cardiovascular defects and pyloric stenosis, although causality has not been conclusively established. For amoxicillin, there is no evidence to suggest that penicillins are associated with an increased risk of malformations or other forms of foetal toxicity in human pregnancy.

7. Pitsouni E, Iavazzo C, Athanasiou S, Falagas ME. Single-dose azithromycin versus erythromycin or amoxicillin for *Chlamydia trachomatis* infection during pregnancy: a meta-analysis of randomised controlled trials. *Int J Antimicrob Agents.* 2007 Sep; 30(3):213-221. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/17596917>.

RATIONALE: A systematic review and meta-analysis of eight RCTs, involving 587 pregnant women, aiming to compare data regarding the effectiveness and safety of azithromycin with alternative regimens in the treatment of pregnant women with *Chlamydia trachomatis* infection. In all included studies, 1g azithromycin stat was compared with erythromycin 500mg OD three or four times daily for seven days, or

Management and treatment of common infections-Antibiotic guidance for primary care

amoxicillin 500mg three times daily for seven days. Results indicated that there was no difference between azithromycin and erythromycin regarding treatment success (OR 2.66; 95% CI 0.69 to 10.29), but azithromycin was associated with fewer adverse events (OR 0.11; 95% CI 0.07 to 0.18). The authors conclude that azithromycin is associated with similar effectiveness, but less adverse events, when compared with erythromycin or amoxicillin in the treatment of pregnant women with *C. trachomatis* infection, so should be considered as a first line agent.

8. Brocklehurst P, Rooney G. Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy (Review). *Cochrane Database Syst Rev*. 2013 Oct; 2(4):1-33. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000054/epdf>.

RATIONALE: A systematic review and meta-analysis of 11 randomised controlled trials. Pooled data from four RCTs reported that 8% of women taking azithromycin 1g stat (11/145) failed to achieve microbiological cure, compared with 19% of women taking erythromycin 500mg four times daily for seven days (27/145; OR 0.38; 62% difference; 95% CI 0.19 to 0.74). Pooled data from three RCTs found that 9% of women taking amoxicillin 500mg three times daily for seven days (17/199) failed to achieve microbiological cure, compared with 15% of women taking erythromycin (28/191; OR 0.54; 46% difference; 95% CI 0.28 to 1.02). The authors conclude that amoxicillin is an acceptable alternative therapy for the treatment of genital chlamydial infections in pregnancy when compared with azithromycin or erythromycin. Clindamycin 450mg four times daily for 14 days may be considered if azithromycin, erythromycin and amoxicillin are contraindicated or not tolerated.

9. British Association for Sexual Health and HIV (BASHH). The use of antibiotics to treat genital infections in pregnant women. 2017 Aug. Available from:

<https://www.bashhguidelines.org/media/1151/ceg-statement-antibiotics-in-pregnancy.pdf>.

RATIONALE: A BASHH statement on the release of a paper by Muanda et al, which found an association between the use of a number of antibiotics in pregnancy and spontaneous abortion. This paper is a retrospective, case-control study, and an association does not prove causation. In the case of chlamydial infection in pregnant women, it may be considered that amoxicillin or erythromycin may be preferable to azithromycin, given that Muanda et al did not find an association with those two antibiotics. However, azithromycin is better tolerated, and more effective than erythromycin in treating chlamydial infection in pregnancy. Therefore, avoiding azithromycin means using a less effective treatment, which may result in a greater chance of pregnancy loss due to inadequately treated infection. BASHH see no reason at the present time to change the recommendations in its current guidelines for treating genital infections in pregnancy. Good clinical practice remains to discuss the uncertainties, and the potential risks and benefits of the treatment options, with the patient, and to document the discussion in the clinical notes. This is especially important, given that the use of these antibiotics in pregnancy is 'off-label'.

Epididymitis:

Management and treatment of common infections-Antibiotic guidance for primary care

1. Street E, Joyce A, Wilson J. 2010 United Kingdom national guideline for the management of epididymo-orchitis. 2011 Jun. Available from: <http://www.bashh.org/documents/3546.pdf>.
RATIONALE: A UK national guideline stating that, in men over 35 years, the cause is most often non-sexually transmitted Gram-negative enteric organisms. Particular risks include recent instrumentation and catheterisation. In men under 35 years, epididymo-orchitis is most often caused by a sexually transmitted pathogen, such as *Chlamydia trachomatis* or *Neisseria gonorrhoeae*. These men should be referred to a GUM clinic for definitive diagnosis and treatment. There is crossover between these groups, and complete sexual history is imperative. If clinicians decide that the infection is likely to be due to chlamydia or other non-gonococcal organisms (ie where gonorrhoea is considered unlikely, as microscopy is negative for Gram-negative intracellular diplococci and there are no risk factors for gonorrhoea identified), the authors advise that doxycycline 100mg BD for ten to 14 days, ofloxacin 200mg BD for 14 days, or ciprofloxacin 500mg BD for 10 days should be prescribed.
2. Public Health England Expert Panel. In a conversation with the British Infection Association Expert Panel (oral communication, May 2016).
RATIONALE: Expert consensus, noting that most of the studies of epididymitis have studied ofloxacin, with very few that have studied ciprofloxacin, and none that have directly compared the two. In men over 35 years old, ofloxacin 200mg BD for 14 days or ciprofloxacin 500mg BD for 10 days should be used. In men under 35 years old or STI risk, consider non-gonococcal chlamydia and refer to GUM, or consider treatment with doxycycline 100mg BD for 10 to 14 days, or ofloxacin 200mg BD for 14 days. If thought to be due to an enteric organism, ciprofloxacin 500mg BD for 10 days, or ofloxacin 200mg BD for 14 days should be used.
3. BMJ Clinical Evidence. Doxycycline or tetracycline (multiple-dose regimens) for men and non-pregnant women. 2015 Apr. Available from: <http://bestpractice.bmj.com/best-practice/evidence/intervention/1607/0/sr-1607-i1.html>.
RATIONALE: A BMJ Best Practice systematic review of nine RCTs of treatment for uncomplicated genital chlamydial infection, involving 1,970 men and non-pregnant women. Results indicated that, at three weeks follow-up, microbiological cure was 70/72 (97%) with doxycycline 100mg twice daily for seven days, and 65/71 (92%) with ciprofloxacin 1.5 to 2g daily (p=0.03 and p=0.14, respectively). The authors conclude that cure rates are high for all antibiotics assessed, and support the use of multiple-dose doxycycline as first line in the treatment of uncomplicated genital chlamydial infection for men and non-pregnant women.

Vaginal candidiasis:

1. British Association for Sexual Health and HIV (BASHH). United Kingdom national guideline on the management of vulvovaginal candidiasis (2007). 2007 Aug. Available from: <http://www.bashh.org/documents/1798.pdf>.
RATIONALE: A BASHH guideline suggesting that, since all topical and oral azole therapies give a clinical and mycological cure rate of over 70% in uncomplicated acute vulvovaginal candidiasis, choice should be a matter of personal preference, availability,

Management and treatment of common infections-Antibiotic guidance for primary care

and affordability/cost. Nystatin preparations give a 70 to 90% cure rate in patients with vulvovaginal candidiasis. Topical azole therapies can cause vulvovaginal irritation, so this should be considered if symptoms persist or worsen, or in pregnancy. This guideline lists the potential dosing regimens of both oral azoles and nystatin. For uncomplicated vulvovaginal candidiasis, the following options are recommended: clotrimazole 500mg pessary stat, or 10% cream 5g stat; oral fluconazole 150mg stat; miconazole pessary 100mg for 14 nights. For recurrent vulvovaginal candidiasis, oral fluconazole 150mg every 72 hours for three doses induction, followed by 150mg once a week for six months maintenance is recommended.

2. Nurbhai M, Grimshaw J, Watson M, Bond C, Mollison J, Ludbrook A. Oral versus intra-vaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (thrush) (Review). *Cochrane Database Syst Rev*. 2007 Oct; 17(4):1-57. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002845.pub2/epdf>.

RATIONALE: A systematic review and meta-analysis of 19 studies, aiming to assess the clinical cure of oral versus intravaginal antifungal comparisons, in the treatment of uncomplicated vaginal candidiasis. No statistically significant differences were observed in clinical cure rates of azole antifungals administered by the oral or intravaginal route. At short-term follow-up, 74% cure was achieved with oral azole treatment, compared with 73% cure with intravaginal treatment (OR 0.94; 6% difference; 95% CI 0.75 to 1.17). The decision to prescribe or recommend the purchase of an antifungal for oral or intravaginal administration should take into consideration safety, cost, and preference.

3. UK Teratology Information Service (UKTIS). *Use of fluconazole in pregnancy*. Available from: <http://www.medicinesinpregnancy.org/bumps/monographs/USE-OF-FLUCONAZOLE-IN-PREGNANCY/> [Accessed: 6th September, 2016].

RATIONALE: A UKTIS webpage stating that fluconazole is a triazole antifungal commonly used in the treatment of candidiasis. Standard fluconazole therapy generally comprises a single 150mg oral dose, and is not recommended during pregnancy. However, vaginal candidiasis is common in pregnancy, and as fluconazole is sometimes prescribed to treat candidiasis that has not responded to topical clotrimazole treatment, exposure during pregnancy is not uncommon. Where fluconazole use is considered necessary in pregnancy, the risks and benefits of treatment should be discussed with the patient, to support evidence-based shared decision making. Data on the outcomes of over 8,000 fluconazole-exposed pregnancies, the majority of which were exposed to a 150mg single oral dose, showed no increase in the incidence of overall malformation rate. One case-control and one large cohort study reported a significant association between conotruncal defects and in utero exposure to standard doses of fluconazole during the first trimester; however, the absolute risk to the foetus is still likely to be very small (<0.1%). An increased risk of spontaneous abortion following maternal exposure to fluconazole has been reported in a recent large study, but a causal association remains to be confirmed. Rates of stillbirth, prematurity, and low birth weight have not been shown to be elevated in standard dose fluconazole-exposed pregnancies. No studies have evaluated whether neurodevelopmental outcomes are altered in infants exposed to fluconazole in utero.

Management and treatment of common infections-Antibiotic guidance for primary care

4. Young GL, Jewell D. Topical treatment for vaginal candidiasis (thrush) in pregnancy (Review). *Cochrane Database Syst Rev*. 2001 Oct; 4:1-21. Available from:

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000225/epdf>.

RATIONALE: A systematic review and meta-analysis of ten studies, aiming to assess the effects of different methods for treating vaginal candidiasis in pregnancy. Findings indicate that topical imidazole is significantly more effective than nystatin when treating vaginal candidiasis in pregnancy, (OR 0.21; 79% increase; 95% CI 0.16 to 0.29), and topical treatment for only four days was less effective than treatment for seven days (OR 11.7; 95% CI 4.21 to 29.15). The authors conclude that topical imidazoles and not nystatin, should be used if possible for treatment of symptomatic vaginal candidiasis in pregnancy. There is no evidence to suggest that asymptomatic women need to be treated.

5. Faculty of Sexual and Reproductive Healthcare Clinical Guidance. Management of vaginal discharge in non-genitourinary medicine settings. 2012 Feb. Available from:

<https://www.guidelines.gov/summaries/summary/36683>.

RATIONALE: A national guideline, discussing the causes, management, and treatment of abnormal vaginal discharge. Information is provided on how to manage recurrent vaginal candidiasis, which is defined as more than four episodes in a year, and suggests that, based on observational studies, an induction and maintenance regimen may be used for six months. This involves oral fluconazole 150mg every 72 hours for three doses induction, followed by 150mg once a week for another six months. It is also suggested that clotrimazole pessaries can be used as treatment for vaginal candidiasis.

Bacterial vaginosis:

1. Joesoef MR, Schmid GP, Hillier SL. Bacterial vaginosis: review of treatment options and potential clinical indications for therapy. *Clin Infect Dis*. 1999 Jan; 28(1):57-65. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10028110>.

RATIONALE: A meta-analysis of six randomised controlled trials in 1,698 non-pregnant and pregnant women, reviewing the data on the treatment of bacterial vaginosis, published from 1993 to 1996. For non-pregnant women, the authors suggest the use of metronidazole (500mg orally, twice daily, for seven days), clindamycin vaginal cream (2%, once daily, for seven days), or metronidazole vaginal gel (0.75%, twice daily, for five days), as the preferred treatment for bacterial vaginosis. For pregnant, high-risk women (women with a prior preterm birth), the objective of the treatment is to prevent adverse outcomes in pregnancy, in addition to the relief of symptoms. Thus, systemic therapy for possible subclinical upper genital tract infection, as well as medication that has been studied in pregnant women, are preferable. For pregnant, low-risk women (women without a prior preterm birth) with symptomatic disease, the main objective of the treatment is to relieve symptoms. Data does not support the routine treatment of male sexual partners. Pooled data found no significant difference between cumulative cure rates five to ten days after finishing treatment for oral metronidazole 400mg BD for seven days (86%), intravaginal metronidazole 5g BD for five days (81%), or intravaginal clindamycin 5g at night for seven days (85%). One study reported on the use of a single 2g dose of metronidazole, and found that a higher cumulative cure rate was recorded with the seven day metronidazole regimen than with the single dose regimen (88% versus 54%,

Management and treatment of common infections-Antibiotic guidance for primary care

respectively). The authors therefore recommend metronidazole 250mg orally three times daily for seven days, when treating pregnant, low-risk women with bacterial vaginosis.

2. Majeroni BA. Bacterial vaginosis: an update. *Am Fam Phys.* 1998 Mar; 57(6):1285-1289. Available from: <http://www.aafp.org/afp/1998/0315/p1285.html>.

RATIONALE: A review article, stating that metronidazole can be prescribed in women with bacterial vaginosis as 500mg twice daily for seven days, or as a 2g stat dose, with the seven day course resulting in less relapses. The costs of the recommended antimicrobials are listed, and it is demonstrated that oral treatment is cheaper than topical treatment. The author recommends the following topical treatment: clindamycin 2% vaginal cream, 5g at bedtime for seven days; metronidazole vaginal gel, 5g at bedtime for five days. Although this article recommends metronidazole 500mg four times daily, the authors do state that this can be reduced and still result in a high cure rate (84 to 96%).

3. McDonald HM, Brocklehurst P, Gordon A. Antibiotics for treating bacterial vaginosis in pregnancy (Review). *Cochrane Database Syst Rev.* 2007 Jan; 24(1):1-90. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000262.pub3/epdf>.

RATIONALE: A systematic review and meta-analysis of 21 trials, involving 7,847 pregnant women diagnosed with bacterial vaginosis or intermediate vaginal flora. The antibiotics included were: oral metronidazole 400mg BD for two days; erythromycin 300mg TDS for 14 days; clindamycin 300mg BD for five days; amoxicillin 500mg TDS for 14 days; vaginal metronidazole 0.75% gel at night for five nights; intravaginal clindamycin 5g for seven nights. Antibiotic therapy was shown to be effective in eradicating bacterial vaginosis during pregnancy (RR 0.42; 58% effectiveness; 95% CI 0.31 to 0.56; ten trials, n=4,403; random-effect $T^2=0.19$; $I^2=91\%$). Antibiotic treatment also reduced the risk of late miscarriage (RR 0.20; 80% reduction; 95% CI 0.05 to 0.76; two trials, n=1,270; fixed-effect $I^2=0\%$). The overall risk of pre-term birth was not significantly reduced. The authors conclude that antibiotic treatment can eradicate bacterial vaginosis in pregnancy; however, this review provides little evidence that screening and treating all pregnant women with bacterial vaginosis will prevent pre-term birth and its consequences. When screening criteria were broadened to include women with abnormal flora, there was a 47% reduction in pre-term birth.

4. UK Teratology Information Service (UKTIS). *Best use of medicines in pregnancy: metronidazole*. Available from: <http://www.medicinesinpregnancy.org/Medicine--pregnancy/Metronidazole/> [Accessed: 6th September, 2016].

RATIONALE: A UKTIS webpage stating that, where oral treatment is deemed appropriate, the manufacturer advises against a single high-dose regimen of metronidazole during pregnancy. Metronidazole was shown to be mutagenic and carcinogenic in some animal studies. However, available data, which is almost exclusively based on oral exposure, does not indicate an increased risk of congenital malformations or adverse foetal effects associated with metronidazole use in human pregnancy. Pre-term delivery has been reported in women with bacterial vaginosis or trichomoniasis; however, the relative contribution of the underlying maternal infection and metronidazole exposure to pregnancy outcome is uncertain, and recent studies have not found an association between metronidazole use and pre-term delivery. Where possible, the results of culture and

Management and treatment of common infections-Antibiotic guidance for primary care

sensitivity tests should be available before making a treatment choice.

Exposure to metronidazole at any stage in pregnancy would not usually be regarded as medical grounds for termination of pregnancy, or any additional foetal monitoring.

However, other risk factors may be present in individual cases, which may independently increase the risk of adverse pregnancy outcomes. Clinicians are reminded of the importance of consideration of such factors when performing risk assessments.

5. British Association for Sexual Health and HIV (BASHH). UK national guideline for the management of bacterial vaginosis 2012. 2012 Jan. Available from:

<http://www.bashh.org/documents/4413.pdf>.

RATIONALE: A BASHH guideline offering recommendations on diagnosis, treatment regimens, and health promotion principles needed for the effective management of bacterial vaginosis, covering both the management of the initial presentation, and recurrence. This guideline discusses findings from two studies, in which it was found that no reduction in relapse rates were reported when male partners of women with bacterial vaginosis were treated with metronidazole 400mg twice daily for five to seven days, tinidazole 2g single dose, or clindamycin 300mg twice daily for seven days.

Genital herpes:

1. British Association for Sexual Health and HIV (BASHH). 2014 UK national guideline for the management of anogenital herpes. 2014 Aug. Available from:

<https://www.bashh.org/documents/HSV%20Final%20guidelines%20with%20ref%20sorted.pdf>.

RATIONALE: A BASHH guideline, advising that all patients with a first episode of genital herpes are given general advice about saline bathing, analgesia, and anaesthetic agents, eg lidocaine ointment). These may be useful to apply, especially prior to micturition. Although the sensitisation exists in the use of topical anaesthetic agents, lidocaine is a rare sensitiser and can be used safely in genital herpes in the form of gel or ointment. Oral antiviral drugs are indicated within five days of the start of the episode, while new lesions are still forming, or if systemic symptoms persist. Aciclovir 400mg three times daily, valaciclovir 500mg twice daily, and famciclovir 250mg three times daily, for 5 days, all reduce the severity and duration of episodes. Antiviral therapy does not alter the natural history of the disease in that frequency or severity of subsequent recurrences remains unaltered. Topical agents are less effective than oral agents. Combining oral and topical treatment is of no additional benefit over oral treatment alone. Intravenous therapy is indicated only when the patient cannot swallow or tolerate oral medication because of vomiting. There are no comparative studies to show benefit from therapy longer than five days. However, it may still be prudent to review the patient after five days and continue therapy if new lesions are still appearing at this time, or if systemic symptoms are still present, or if complications have occurred. For recurrent genital herpes, this guideline advises that recurrences are self-limiting and generally cause minor symptoms. Management decisions should be made in partnership with the patient. Strategies include: supportive therapy only; episodic antiviral treatments; suppressive antiviral therapy. The best strategy for managing an individual patient may change over time, according to recurrence frequency, symptom severity, and relationship status. Patients should again be given general advice about using saline bathing, Vaseline, analgesia, and 5% lidocaine

Management and treatment of common infections-Antibiotic guidance for primary care

ointment. For episodic antiviral treatment, short-course therapies offer more convenient and cost-effective strategies for managing genital herpes episodically, and should be regarded as first line options. Oral aciclovir 800mg three times daily for two days, valaciclovir 500mg twice daily for three days, and famciclovir 1g twice daily for one day are recommended. The reduction in duration is a median of one to two days. Head-to-head studies show no advantage of one therapy over another, or the advantage of extended five day treatment over short-course therapy. Prodrugs (such as valaciclovir and famciclovir) offer simplified twice a day dosing. Aborted lesions have been documented in up to a third of patients with early treatment. Patient initiated treatment started early in an episode is most likely to be effective, as treatment prior to the development of papules is of greatest benefit. Patients who have taken part in trials of suppressive therapy have had to have at least six recurrences per annum. Such patients have fewer or no episodes on suppressive therapy. Patients with lower rates of recurrence will probably also have fewer recurrences with treatment. Patients should be given full information on the advantages and disadvantages of suppressive therapy. The decision to start suppressive therapy is a subjective one, balancing the frequency of recurrence with the cost and inconvenience of treatment. Patients suffering from psychological morbidity for who the diagnosis causes significant anxiety may benefit from suppressive therapy. Patient safety and resistance data for long-term suppressive therapy with aciclovir now extends to over 20 years of continuous surveillance. This confirms that aciclovir is an extremely safe compound requiring no monitoring in previously well patients, and only a dose adjustment in those with severe renal disease. Recommended suppressive regimens for treatment include: aciclovir 400mg twice daily; famciclovir 250mg twice daily; valaciclovir 500mg once daily, all for one year. These doses can be increased if breakthrough recurrences occur.

2. Clinical Knowledge Summaries (CKS). Herpes simplex – genital. 2012 Sep. Available from: <http://cks.nice.org.uk/herpes-simplex-genital#!topicsummary>.

RATIONALE: A CKS guideline stating that all people with suspected genital herpes should be referred to a GUM specialist for diagnosis, treatment, screening for sexually transmitted infections, counselling, and follow-up. This guideline recommends that treatment with oral aciclovir (200mg five times a day for five days) should be started within five days of the start of the episode, or while new lesions are forming. Management of recurrent episodes is included, and recommends self-care measures, including topical anaesthesia and increasing fluid intake to produce dilute urine, episodic antiviral treatment for infrequent attacks (oral aciclovir 200mg five times a day for five days), and suppressive antiviral treatment for frequent attacks (oral aciclovir 400mg twice daily for six to 12 months). Suppressive antiviral treatment should particularly be considered if the condition is causing psychological distress, or is affecting the individual's social life.

3. Heslop R, Roberts H, Flower D, Jordan V. Interventions for men and women with their first episode of genital herpes (Review). *Cochrane Database Syst Rev*. 2016 Aug; 30(8):1-171. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010684.pub2/epdf>.

RATIONALE: A systematic review and meta-analysis of 26 trials and 2,084 participants, aiming to determine the effectiveness and safety of the different existing treatments for first-episode genital herpes on the duration of symptoms and time to recurrence. Aciclovir, valaciclovir, and famciclovir are competitive inhibitors of viral DNA polymerase, resulting in

Management and treatment of common infections-Antibiotic guidance for primary care

inhibition of viral DNA synthesis. The drugs have an excellent margin of safety because they are converted by viral thymidine kinase to the active drug only inside virally infected cells. The results from this review demonstrated that aciclovir does reduce the duration of symptoms in individuals undergoing their first episode of genital herpes (mean days reduction -3.22 days; 95% CI -5.91 to -0.54). Oral valaciclovir also showed a similar length of symptom duration when compared to aciclovir. There was however no evidence found to demonstrate that topical aciclovir reduces symptoms (mean days reduction -0.61 days; 95% CI -2.16 to 0.95; three RCTs; n=195; $I^2=56\%$), suggesting that topical antivirals do not reduce symptom duration for patients undergoing their first episode of genital herpes.

4. Le Cleach L, Trinquart L, Do G, Meruani A, Lebrun-Vignes B, Ravaud P et al. Oral antiviral therapy for prevention of genital herpes outbreaks in immunocompetent and nonpregnant patients (Review). *Cochrane Database Syst Rev*. 2014 Aug; 8:1-112. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009036.pub2/epdf>.

RATIONALE: A systematic review and meta-analysis of 26 randomised controlled trials, aiming to compare the effectiveness and safety of three oral antiviral drugs (aciclovir, famciclovir, and valaciclovir) prescribed to suppress genital herpes outbreaks in non-pregnant parties. In placebo-controlled trials, there was low quality evidence that the risk of having at least one clinical recurrence was reduced with aciclovir (RR 0.48; 52% reduction; 95% CI 0.39 to 0.58; nine trials; n=2,049), valaciclovir (RR 0.41; 59% reduction; 95% CI 0.24 to 0.69; four trials; n=1,788), or famciclovir (RR 0.57; 43% reduction; 95% CI 0.50 to 0.64; two trials; n=732). The authors conclude that aciclovir, valaciclovir, and famciclovir are strong antimicrobials for the treatment of genital herpes, but there is no superiority of one drug over another when used as suppressive antiviral therapy in patients experiencing at least four recurrences of genital herpes per year.

Gonorrhoea:

1. Public Health England (PHE) GRASP Steering Committee and the British Association for Sexual Health and HIV (BASHH). CEG position statement on the treatment of gonorrhoea. 2015 Dec. Available from: <https://www.evidence.nhs.uk/document?id=1629273&returnUrl=Search%3Fpa%3D2%26ps%3D40%26q%3Dtest%2Bof%2Bcure%2Bchlamydia&q=test+of+cure+chlamydia>.

RATIONALE: A PHE and BASHH position statement on the treatment of gonorrhoea in the United Kingdom. This statement states that antibiotic resistance is now very high, and recommends that dual treatment with ceftriaxone 500mg intramuscularly plus azithromycin 1g orally is advised for the treatment of all gonorrhoea cases, irrespective of the results of chlamydia testing, in order to mitigate against the selection of gonococci with reduced susceptibility to cephalosporins. It is difficult for an organism to develop simultaneous resistance to two different antimicrobial classes, meaning that dual treatment creates a pharmacological barrier to the emergence of isolates exhibiting resistance to one component of the recommended therapy. This strategy is used in the treatment of several other infections, eg HIV and TB. GRASP data shows that current resistance rates to azithromycin are low (1.6%), whereas tetracycline/doxycycline resistance rates remain high (72.9%). Therefore, ceftriaxone plus doxycycline does not reliably give the double coverage sought, allowing for easier selection of ceftriaxone resistance. For co-infection

Management and treatment of common infections-Antibiotic guidance for primary care

with rectal chlamydia, this statement recommends specific treatment of each infection, ie ceftriaxone combined with azithromycin for gonorrhoea, with the addition of doxycycline for concurrent rectal chlamydia. Of 15,758 reported cases of pelvic inflammatory disease in 2013, only 323 (2%) involved gonococci. Therefore, it is reasonable to continue the use of ceftriaxone and doxycycline in this patient group, as it is unlikely to impact on measures to delay the development of widespread ceftriaxone resistance. This statement stresses the importance of test of cure for all patients, but particularly for those not treated with dual gonococcal therapy.

2. Public Health England (PHE). Surveillance of antimicrobial resistance to *Neisseria gonorrhoeae*: Key findings from the 'Gonococcal resistance to antimicrobials surveillance programme' (GRASP) and related surveillance data. 2015 Nov. Available from:

<https://www.gov.uk/government/publications/gonococcal-resistance-to-antimicrobials-surveillance-programme-grasp-report>.

RATIONALE: A PHE report describing trends in, and epidemiology of, antimicrobial resistance and decreased susceptibility in gonococcal infection in England and Wales. In 2014, in England, the number of new gonorrhoea diagnoses increased by 21.4% (especially among men who have sex with men, and young adults). Ciprofloxacin resistance is now endemic in England and Wales, accounting for 25% of all gonorrhoea isolates tested in 2014. 5.6% of isolates exhibited decreased susceptibility to cefixime, only three isolates showed decreased susceptibility to ceftriaxone (MIC >0.125mg/L). If gonorrhoea is suspected, IM ceftriaxone is the cephalosporin of choice.

3. Bignell C, Fitzgerald M, Guideline Development Group, British Association for Sexual Health and HIV UK. UK national guideline for the management of gonorrhoea in adults, 2011. *Int J STD AIDS*. 2011 Oct; 22(10):541-547. Available from:

<http://www.ncbi.nlm.nih.gov/pubmed/21998172>.

RATIONALE: A guideline offering advice on diagnosis, treatment, and health promotion for anogenital and pharyngeal gonorrhoea. Nucleic acid amplification tests (NAATs) are being used more for diagnosis, and are increasing detection rates in the pharynx and rectum. First line treatment using ceftriaxone with azithromycin is advised, along with routine test of cure. The aim is to slow the spread of resistant gonorrhoea, now that fewer antibiotics remain effective. This guideline recommends that: all patients treated for gonorrhoea should be recommended to have a TOC; all patients with gonorrhoea should be screened for genital infection with *Chlamydia trachomatis*, or receive presumptive treatment for this infection; all patients identified with gonorrhoea should have partner notification carried out; all patients identified with gonorrhoea should be offered written information about STIs and their prevention; all patients with gonorrhoea should receive first line treatment, or the reasons for not doing so should be documented.

4. Wetten S, Mohammed H, Yung M, Mercer CH, Cassell JA, Hughes G. Diagnosis and treatment of chlamydia and gonorrhoea in general practice in England 2000-2011: a population-based study using data from the UK Clinical Practice Research Datalink. *BMJ Open*. 2015 Apr; 5(5):1-9. Available from:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4452740/pdf/bmjopen-2015-007776.pdf>.

Management and treatment of common infections-Antibiotic guidance for primary care

RATIONALE: A retrospective, population-based study, demonstrating the relative contribution of GPs to the diagnosis of chlamydia and gonorrhoea in England. GPs make an important contribution to the diagnosis and treatment of bacterial STIs in England. While most patients diagnosed with chlamydia were managed appropriately, many of those treated for gonorrhoea received antimicrobials no longer recommended for use. The authors recommend that confirmed cases of gonorrhoea should be referred to GUM, and that stat doses of ceftriaxone and azithromycin are the antimicrobials of choice. The authors conclude that, given the global threat of antimicrobial resistance, GPs should remain aware of national guidelines, and remain alert to treatment failure in their patients.

Trichomoniasis:

1. Sherrard J, Ison C, Moody J, Wainwright E, Wilson J, Sullivan A. United Kingdom national guideline on the management of *Trichomonas vaginalis* 2014. *Int J STD AIDS*. 2014 Feb; 25(8):541-549. Available from: https://www.bashh.org/documents/TV_2014%20IJSTDA.pdf.

RATIONALE: A BASHH guideline suggesting that current partners, and any partners within the four weeks prior to presentation, should be screened for the full range of STIs and treated for TV irrespective of the results of investigations. This guideline suggests that systemic antibiotic therapy is required to effect a permanent cure of *Trichomonas vaginalis*, due to the high frequency of infection of the urethra and paraurethral glands in females. A systematic review of 54 trials found that almost any nitroimidazole drug given as a single dose, or over a longer period, results in parasitological cure in >90% of cases. Oral single-dose treatment with any nitroimidazole drug seems to be effective in achieving short-term parasitological cure, but is associated with more frequent side-effects than either longer oral, or intravaginal treatment. Intravaginal treatment showed parasitological cure rates around 50%, which is unacceptably low. There is a spontaneous cure rate in the order of 20 to 25%. This guideline recommends metronidazole 2g orally in a single dose, or metronidazole 400 to 500mg twice daily for five to seven days.

2. Gulmezoglu AM, Azhar M. Interventions for trichomoniasis in pregnancy (Review). *Cochrane Database Syst Rev*. 2011 May; 11(5):1-18. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000220.pub2/epdf>.

RATIONALE: A systematic review and meta-analysis of two trials, including 842 pregnant women. In both trials, around 90% of women were cleared of trichomonas in the vagina after treatment. In the United States trial, women with asymptomatic trichomoniasis between 16 and 23 weeks were treated with 2g metronidazole as a stat dose on two occasions, at least two weeks apart. The trial was stopped before reaching its target recruitment, because metronidazole was not effective in reducing pre-term birth, and there was a likelihood of harm (RR 1.78; 95% CI 1.19 to 2.66). The South African trial recruited women later in pregnancy, but did not address adverse clinical outcomes. The authors conclude that metronidazole, given as a 2g single dose, is likely to provide parasitological cure for trichomoniasis, but it is not known whether or not this treatment will have any effect on pregnancy outcomes. The cure rate could probably be higher if more partners were treated. Due to the increased risk of harm, a lower dose of metronidazole should be used, or clotrimazole can be used for symptom relief. A high dose of metronidazole is

Management and treatment of common infections-Antibiotic guidance for primary care

effective against trichomoniasis infection during pregnancy, but may increase the risk of preterm and low birthweight babies.

3. UK Teratology Information Service (UKTIS). *Best use of medicines in pregnancy: metronidazole*. Available from: <http://www.medicinesinpregnancy.org/Medicine--pregnancy/Metronidazole/> [Accessed: 8th September, 2016].

RATIONALE: A UKTIS webpage stating that, where oral treatment is deemed appropriate, the manufacturer advises against a single high-dose regimen of metronidazole during pregnancy. Metronidazole was shown to be mutagenic and carcinogenic in some animal studies. However, available data, which is almost exclusively based on oral exposure, does not indicate an increased risk of congenital malformations or adverse foetal effects associated with metronidazole use in human pregnancy. Pre-term delivery has been reported in women with bacterial vaginosis or trichomoniasis; however, the relative contribution of the underlying maternal infection and metronidazole exposure to pregnancy outcome is uncertain, and recent studies have not found an association between metronidazole use and pre-term delivery. Where possible, the results of laboratory tests should be available before making a treatment choice. Exposure to metronidazole at any stage in pregnancy would not usually be regarded as medical grounds for termination of pregnancy, or any additional foetal monitoring. Other risk factors may be present in individual cases, which may independently increase the risk of adverse pregnancy outcomes. Clinicians are reminded of the importance of consideration of such factors.

4. duBouchet L, Spence MR, Rein MF, Danzig MR, McCormack WM. Multicenter comparison of clotrimazole vaginal tablets, oral metronidazole, and vaginal suppositories containing sulphamylamide, aminacrine hydrochloride, and allantoin in the treatment of symptomatic trichomoniasis. *Sex Transm Dis*. 1997 Mar; 24(3):156-160. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9132982>.

RATIONALE: A randomised, open-label trial (n=168), in which clotrimazole vaginal tablets were found not to effectively eradicate trichomoniasis; however, a reduction in symptoms was reported. The numbers of patients who had positive cultures after treatment were 40/45 (88.9%) in the clotrimazole group, 35/43 (81.4%) in the AVC suppository group, and 9/45 (20%) in the metronidazole group (p<0.001).

5. Cudmore SL, Delgaty KL, Hayward-McClelland SF, Petrin DP, Garber GE. Treatment of infections caused by metronidazole-resistant *Trichomonas vaginalis*. 2004 Oct; 17(4):783-793. Available from: <http://cmr.asm.org/content/17/4/783.full>.

RATIONALE: A review article, stating that treatment of trichomoniasis is commonly with metronidazole, with alternative treatments including vaginal clotrimazole, and arsenical pessaries. These preparations provide local symptom relief, but documentation on their effectiveness as cures has been inconsistent. If clotrimazole is prescribed, a daily intravaginal pessary at a dose of 100mg for six days can be given to provide temporary relief. However, limited information about the effects of these drugs make it questionable whether these regimens are curative or merely palliative.

6. Forna F, Gulmezoglu AM. Interventions for treating trichomoniasis in women. *Cochrane*

Management and treatment of common infections-Antibiotic guidance for primary care

Database Syst Rev. 2003 Apr; 2:1-96. Available from:

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000218/epdf>.

RATIONALE: A systematic review and meta-analysis of 54 studies, in which study populations were heterogeneous. Women attending emergency departments, venereal disease clinics, gynaecology outpatient clinics, cancer screening clinics, prisons, and private practices were recruited into different trials. In most trials, single dose treatment with any nitroimidazole drug resulted in parasitological cure rates above 90%. The authors conclude that oral single dose treatment with any nitroimidazole seems to be effective in achieving short-term parasitological cure, in comparison with longer five to seven day courses (12% less effective, but not significant; RR 1.12; 95% CI 0.58 to 2.16). However, although rarely severe, side-effects seem to be relatively common and dose-related, and mainly of a gastrointestinal nature.

Pelvic inflammatory disease:

1. British Association for Sexual Health and HIV (BASHH). UK national guideline for the management of pelvic inflammatory disease 2011. 2011 Jun. Available from:

<http://www.bashh.org/documents/3572.pdf>.

RATIONALE: A BASHH guideline, suggesting that women with suspected PID, and their sexual contacts, should be referred to GUM or a specialist sexual health service. This guideline states that testing for gonorrhoea and chlamydia in the lower genital tract is recommended since a positive result supports the diagnosis of PID. The absence of infection at this site does not exclude PID. The absence of endocervical or vaginal pus cells has a good negative predictive value (95%) against a diagnosis of PID, but their presence is non-specific (poor positive predictive value; 17%). This guideline recommends treatment regimens for outpatient management of PID as either ofloxacin 400mg BD plus metronidazole 400mg BD for 14 days, or a stat dose of IM ceftriaxone 500mg plus metronidazole 400mg BD and doxycycline 100mg BD for 14 days. Ofloxacin should be avoided in women who are at high risk of gonococcal PID, because of increasing quinolone resistance in the UK. Partners should be screened for gonorrhoea and chlamydia. The recommended regimens are broad spectrum to cover *N. gonorrhoeae*, *C. trachomatis*, and anaerobes. Broad spectrum treatment is warranted in PID due to the consequences of untreated infection (ectopic pregnancy; infertility; pelvic pain). Cefoxitin has a better evidence base for the treatment of PID than ceftriaxone, but it is not readily available in the UK. Finally, although the combination of doxycycline and metronidazole has previously been used in the UK to treat PID, there are currently no clinical trials that adequately assess its effectiveness. Therefore, its use is not recommended.

2. Ross JDC, Cronje HS, Paszowski T, Rakoczi I, Vildaite D, Kureishi A et al. Moxifloxacin versus ofloxacin plus metronidazole in uncomplicated pelvic inflammatory disease: results of a multicentre, double blind, randomised trial. *Sex Transm Infect.* 2006 Dec; 82(6):446-451.

Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2563874/>.

RATIONALE: A randomised controlled trial of 564 patients with uncomplicated PID in hospitals from 13 countries, comparing oral metronidazole 500mg twice daily with either oral ofloxacin 400mg twice daily, or moxifloxacin 400mg once daily. Clinical resolution with

Management and treatment of common infections-Antibiotic guidance for primary care

both regimens was 90%, and bacteriological cure was similar. Metronidazole is included in the regimen to improve the coverage for anaerobic bacteria. Anaerobes are of relatively greater importance in patients with severe PID. Ofloxacin and moxifloxacin should be avoided in patients who are at high risk of gonococcal PID, because of increasing quinolone resistance in the UK (eg when the patient's partner has gonorrhoea; in clinically severe disease; following sexual contact abroad). Quinolones should also be avoided as first line empirical treatment for PID in areas where >5% of PID is caused by quinolone resistant *Neisseria gonorrhoeae*.

3. Public Health England (PHE). Surveillance of antimicrobial resistance to *Neisseria gonorrhoeae*: Key findings from the 'Gonococcal resistance to antimicrobials surveillance programme' (GRASP) and related surveillance data. 2015 Nov. Available from:

<https://www.gov.uk/government/publications/gonococcal-resistance-to-antimicrobials-surveillance-programme-grasp-report>.

RATIONALE: A PHE report describing trends in, and epidemiology of, antimicrobial resistance and decreased susceptibility in gonococcal infection in England and Wales. In 2014, in England, the number of new gonorrhoea diagnoses increased by 21.4% (especially among men who have sex with men, and young adults). Ciprofloxacin resistance is now endemic in England and Wales, accounting for 25% of all gonorrhoea isolates tested in 2014. 5.6% of isolates exhibited decreased susceptibility to cefixime; only three isolates showed decreased susceptibility to ceftriaxone (MIC >0.125mg/L). If gonorrhoea is suspected, a stat dose of 500mg IM ceftriaxone should be given.

4. Ison CA, Mouton JW, Jones K, Fenton KA, Livermore DM. Which cephalosporin for gonorrhoea? *Sex Transm Infect*. 2004 Aug; 80:386-388. Available from:

<http://sti.bmj.com/content/80/5/386.full.pdf+html>.

RATIONALE: A survey report and audit of 179 patients with gonorrhoea attending GUM clinics, using previously published pharmacokinetic data on cefixime, ceftriaxone, and cefuroxime to model the length of time tissue concentrations would be above the MIC (concentration needed to kill 90% of gonorrhoea isolates). Cefuroxime concentrations are too low; ceftriaxone attains the optimal concentrations to prevent the development of step-wise mutations and resistance, and is therefore now the cephalosporin of choice. There is also concern that cefuroxime regimens may select for gonococcal variants of PID.

5. Meads C, Knight T, Hyde C, Wilson J. The clinical effectiveness and cost effectiveness of antibiotic regimens for pelvic inflammatory disease. 2004 May. Available from:
<http://www.birmingham.ac.uk/Documents/college-mds/haps/projects/WMHTAC/REPreports/2004/PelvicInflammatoryDisease.pdf>.

RATIONALE: A systematic review, identifying 34 trials of antibiotic treatment for PID. Most studies were small, open-label, and of poor methodological design. One small trial compared oral ofloxacin plus metronidazole, with clindamycin plus gentamicin. The cure rate was 15/15 for ofloxacin plus metronidazole, and was 17/18 for clindamycin plus gentamicin. This review found one trial of ceftriaxone plus doxycycline, two trials of cefoxitin plus probenecid and doxycycline, and three trials of cefoxitin plus doxycycline, compared to other antibiotics. Meta-analyses of these six studies found no difference in cure rates between IM cephalosporin plus doxycycline and the comparator antibiotics.

Skin and Soft Tissue Infections

General references:

1. Royal College of General Practitioners (RCGP). *Skin Infections*. Available from: <http://www.rcgp.org.uk/learning/online-learning/ole/skin-infections.aspx> [Accessed: 10th March, 2017].
RATIONALE: AN RCGP webpage hosting a free two-hour training module on diagnosing and managing skin infections for continued professional development. This series of training modules includes information on: staphylococcal and streptococcal skin infections; other bacterial skin infections; antibiotics; leg ulcers; pressure sores; acne; viral skin infections, including herpes zoster, warts, and molluscum; fungal and parasitic infections; brief overview of tropical skin conditions. This module equals two hours towards CPD, and can be imported into the RCGP Revalidation portfolio.

Impetigo:

1. Denton M, O'Connell B, Bernard P, Jarlier V, Williams Z, Henriksen AS. The EPISA study: antimicrobial susceptibility of *Staphylococcus aureus* causing primary or secondary skin and soft tissue infections in the community in France, the UK and Ireland. *J Antimicrob Chemother*. 2008 Mar; 61(3):586-588. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18222949>.
RATIONALE: A prospective study stating that, of *Staphylococcus aureus* isolates from the UK, only 75.6% were susceptible to fusidic acid. A diagnosis of impetigo was associated with reduced fusidic acid susceptibility. The authors conclude that differences in the prevalence of certain diagnoses, particularly impetigo, rather than differences in antibiotic consumption may explain some of the observed differences in the susceptibility seen between the three countries included in the study.
2. Public Health England Expert Panel. In a conversation with the British Infection Association Expert Panel (oral communication, June 2012).
RATIONALE: Expert consensus, recommending that oral antibiotics should be used for extensive, severe, or bullous impetigo, and that topical antibiotics should be reserved only for the treatment of very localised lesions. There are concerns that widespread use of topical fusidic acid will lead to increased resistance, rendering its use for severe staphylococcal infections, such as osteomyelitis, or MRSA, ineffective. If a topical antibiotic is used, a short five day course reduces exposure and the risk of resistance. Since few agents are effective against MRSA, mupirocin should be reserved for MRSA, and not used for other topical treatment of impetigo. For empirical treatment of impetigo, flucloxacillin should be used first line, because it is a narrow-spectrum antibiotic that is effective against Gram-positive organisms, including *Staphylococcus aureus*, unless MRSA. It also demonstrates suitable pharmacokinetics, with good diffusion into skin and soft tissue. Clarithromycin is recommended for people with penicillin allergy, as it is also active against most staphylococcal and streptococcal species.

3. Koning S, van der Sande R, Verhagen AP, van Suijlekom-Smit LW, Morris AD, Butler CC et al. Interventions for impetigo (Review). *Cochrane Database Syst Rev*. 2012 Jan; 18(1):1-165. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003261.pub3/epdf>.

RATIONALE: A systematic review and meta-analysis of 68 trials and 5,578 participants, reporting on 50 different treatments, including placebo. Most trials were in primary impetigo, or did not specify. Topical antibiotic treatment showed better cure rates than placebo (RR 2.24; 95% CI 1.61 to 3.13) in six studies with 575 participants. In four studies with 440 participants, when topical antibiotics were compared (mupirocin ointment 2%, three times daily for five to 10 days, and fusidic acid cream gel 2%, two to three times daily for a maximum of 21 days) none were more effective than the others (RR 1.03; 95% CI 0.95 to 1.11). In ten studies with 581 participants, topical mupirocin ointment 2%, three times daily for five to 10 days, was shown to be slightly superior to oral erythromycin 40mg/kg/day, across three doses for seven days (RR 1.07; 95% CI 1.01 to 1.13). There were no significant differences in cure rates from treatment with topical versus other oral antibiotics. There were, however, differences in the outcome from treatment with different oral antibiotics: penicillin V 50mg/kg/day, across four doses for 10 days, was inferior to erythromycin 40mg/kg/day, across four doses for 10 days, in two studies with 79 participants (RR 1.29; 95% CI 1.07 to 1.56), and cloxacillin 250-500mg, four times daily for seven days, in two studies with 166 participants (RR 1.59; 95% CI 1.21 to 2.08). There was a lack of evidence for the benefit of using disinfectant solutions. When two studies with 292 participants were pooled, topical antibiotics were significantly better than disinfecting treatments (RR 1.15; 95% CI 1.01 to 1.32). The reported number of side-effects was low, and most of these were mild. Side-effects were more common for oral antibiotic treatment, compared to topical treatment. Gastrointestinal side-effects accounted for most of the difference. Expert opinion is that, as topical mupirocin is the only topical antibiotic suitable for MRSA, this should be reserved for MRSA-associated infections. The authors conclude that there is good evidence that topical mupirocin and topical fusidic acid are equally, or more, effective than oral treatment. Due to the lack of studies in people with extensive impetigo, it is unclear if oral antibiotics are superior to topical antibiotics in this group. Fusidic acid and mupirocin are of similar efficacy; penicillin is not as effective as most other antibiotics. There is a lack of evidence to support disinfection measures to manage impetigo.

4. Clinical Knowledge Summaries (CKS). Impetigo. 2015 Jul. Available from: <https://cks.nice.org.uk/impetigo#!topicsummary>.

RATIONALE: A CKS guideline, recommending oral flucloxacillin, four times daily for seven days, as first line systemic treatment of impetigo. Oral clarithromycin 250-500mg twice daily for seven days can be used if the patient is allergic to penicillins. This guideline states that, for topical antibiotic treatment, topical fusidic acid can be used alone, or in combination with systemic treatment, and should be applied thinly three to four times daily to uncovered lesions. Less frequent applications may be adequate for covered lesions. The summary states that extensive, severe or bullous infections usually require treatment with an oral antibiotic.

Cold sores:

1. Spurance SL, Nett R, Marbury T, Wolff R, Johnson J, Spaulding T. Acyclovir cream for the treatment of herpes simplex labialis: results of two randomized, double-blind, vehicle-controlled, multicenter clinical trials. *Antimicrob Agents Chemother.* 2002 Jul; 46(7):2238-2243. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC127288/pdf/0797.pdf>.

RATIONALE: Two randomised controlled trials (n=1,385), in which healthy adults with a history of frequent herpes labialis were recruited from the general population, randomised equally to 5% aciclovir cream or vehicle control, given study medication, and told to self-initiate treatment five times daily for four days, beginning within one hour of the onset of a recurrent episode. In study one, the mean duration of episodes was 4.3 days for patients treated with aciclovir cream, and 4.8 days for those treated with the vehicle control (HR 1.23; 95% CI 1.06 to 1.44; p=0.007). In study two, the mean duration of episodes was 4.6 days for patients treated with aciclovir cream, and 5.2 days for those treated with the vehicle control (HR 1.24; 95% CI 1.06 to 1.44; p=0.006). Efficacy was apparent whether therapy was initiated early (prodrome or erythema lesion stage), or late (papule or vesicle stage). The authors conclude that there was a statistically significant reduction in the duration of lesion pain in both studies, and that aciclovir 5% cream reduces the mean duration and pain of an episode by about half a day.
2. Spurance SL, Rea TL, Thoming C, Tucker R, Saltzman R, Boon R. Penciclovir cream for the treatment of herpes simplex labialis. A randomized, multicenter, double-blind, placebo-controlled trial. Topical Penciclovir Collaborative Study Group. *JAMA.* 1997 May; 277(17):1374-1379. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9134943>.

RATIONALE: A randomised controlled study, comparing the safety and efficacy of topical 1% penciclovir cream with vehicle control cream for the treatment of a recurrent episode of herpes simplex labialis in immunocompetent patients. Findings indicated that healing of classical lesions was 0.7 days faster for penciclovir-treated patients, compared with those who received vehicle control cream (median 4.8 days penciclovir versus 5.5 days control; HR 1.33; 95% CI 1.18 to 1.49; p<0.001). Pain (median 3.5 days penciclovir versus 4.1 days control; HR 1.22; 95% CI 1.09 to 1.36; p<.001) and lesion virus shredding (median 3 days versus 3 days; HR 1.35; 95% CI 1.10 to 1.64; p=.003) also resolved more quickly for penciclovir-treated patients compared with patients who applied the vehicle control.
3. Raborn GW, Martel AY, Lassonde M, Lewis MA, Boon R, Spurance SL et al. Effective treatment of herpes simplex labialis with penciclovir cream: combined results of two trials. *J Am Dent Assoc.* 2002 Mar; 133(3):303-309. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11934185>.

RATIONALE: Two randomised controlled trials (n=4,573), in which the efficacy and safety of topical 1% penciclovir cream and a placebo cream was compared. Time to loss of a classical lesion and the percentage of patients who had lost a classical lesion by days six and eight were evaluated. Combined data revealed that penciclovir recipients lost classical lesions 31% faster than did placebo recipients (4.9 versus 5.5 days, respectively; HR 1.31; 95% CI 1.20 to 2.42; p=0.0001), and experienced 28% faster resolution of lesion pain (3.8 versus 4.3 days, respectively; HR 1.28; 95% CI 1.17 to 1.39; p=0.0001). Significant benefits were achieved with penciclovir use when treatment was initiated in the early stages (p=0.001) and later stages (p=0.0055). The authors conclude that penciclovir

Management and treatment of common infections-Antibiotic guidance for primary care

cream positively affects recurrent herpes simplex labialis, and dose frequency is vital to topical treatment. Even when penciclovir was applied late, it was effective in favourably altering the course of recurrent of herpes simplex labialis by a mean duration of one day.

4. Clinical Knowledge Summaries (CKS). Herpes simplex – oral. 2016 Oct. Available from: <https://cks.nice.org.uk/herpes-simplex-oral#!topicsummary>.
RATIONALE: A CKS guideline, stating that oral herpes simplex virus is usually a mild, self-limiting infection that resolves within approximately ten to 14 days, with HSV-1 being the cause in more than 90% of cases. Oral herpes simplex virus can, however, cause severe or life-threatening complications in some cases, particularly in immunocompromised people. This guideline recommends that oral prophylaxis can be prescribed if herpes simplex is frequent, severe or has predictable triggers. In this case, oral aciclovir 500mg five times daily for five days can be prescribed.
5. Arduino PG, Porter SR. Oral and perioral herpes simplex virus type 1 (HSV-1) infection: review of its management. *Oral Dis*. 2006 May; 12(3):254-270. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16700734>.
RATIONALE: A review article in which it is stated that prophylaxis with oral antivirals may be of use for those with frequent, severe episodes, or predictable triggers, eg sunlight, or for immunocompromised individuals, as they are at higher risk of complications. Specialist advice should be sought if long-term prophylaxis is being considered. The authors conclude that systemic aciclovir may be effective in reducing the duration of symptoms of recurrent HSV-1 infection, but the optimal timing and dose of the treatment are uncertain. There is also evidence that prophylactic oral aciclovir may reduce the frequency and severity of recurrent attack of herpetic infection in immunocompromised patients, but the optimal timing and duration of treatment is uncertain and can vary in different situations.
6. Chi C-C, Wang S-H, Delamere FM, Wojnarowska F, Peters MC, Kanjirath PP. Interventions for prevention of herpes simplex labialis (cold sores on the lips). *Cochrane Database Syst Rev*. 2015 Aug; 8:1-173. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010095.pub2/epdf>.
RATIONALE: A systematic review and meta-analysis of 32 randomised controlled trials, and a total of 2,640 immunocompetent participants. The evidence for short-term (less than one month) use of oral acyclovir in preventing recurrent herpes simplex labialis was inconsistent across the doses used in the studies, but was most effective when a 400mg twice daily dose, for five to seven days was used (RR 0.36; 95% CI 0.13 to 0.51; n=177). The authors conclude that the current evidence demonstrates that long-term use of oral antiviral agents can prevent HSL, but the clinical benefit is small. There was no evidence demonstrating an increased risk of adverse events.

Panton-Valentine Leukocidin-positive *Staphylococcus aureus* (PVL-SA):

1. Holmes A, Ganner M, McGuane S, Pitt TL, Cookson BD, Kearns AM. *Staphylococcus aureus* isolates carrying Panton-Valentine leucocidin genes in England and Wales: frequency, characterization, and association with clinical disease. *J Clin Microbiol*. 2005 May; 43(5):2384-2390. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1153723/>.

Management and treatment of common infections-Antibiotic guidance for primary care

RATIONALE: A prospective study in which the Staphylococcus Reference Unit tested 515 UK isolates of *Staphylococcus aureus* for PVL, of which only eight (1.6%) were positive for the PVL locus. However, of 470 *S. aureus* isolates associated with clinical disease, 23 (4.9%) were PVL-positive. In abscesses, 7 of 16 (44%) were positive. The PVL genes were also detected in isolates responsible for community-acquired pneumonia, burn infections, bacteraemia, and scalded skin syndrome. This PVL is relatively rare overall, but much more common in patients with abscesses (20.8 to 46%).

2. Shallcross LJ, Williams K, Hopkins S, Aldridge RW, Johnson AM, Hayward AC. Panton-Valentine leukocidin associated staphylococcal disease: a cross-sectional study at a London hospital, England. *Clin Microbiol Infect.* 2010 Nov; 16(11):1644-1648. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/20969671>.

RATIONALE: A prospective, cross-sectional study, stating that there has been a rapid emergence of highly pathogenic strains of *Staphylococcus aureus*, associated with the toxin Panton-Valentine leukocidin (PVL). The strains are considered to be rare among healthy people, but mainly severe. In this study, 390 clinical *Staphylococcus aureus* isolates were collected from hospital and community specimens, and were investigated for the presence of the PVL genes. Results indicated that MRSA with PVL was rare (0.8% of all isolates), but MSSA with PVL was common (9% of all specimens). Results also suggested that PVL infection was more frequent in males (OR 3; 95% CI 1.3 to 7), and in young adults aged between 20 and 39 years (OR 3.7; 95% CI 1.3 to 10.4). The authors conclude that community-onset PVL-associated disease mainly causes skin and soft tissue infections.

3. Ellington MJ, Ganner M, Smith IM, Perry C, Cookson BD, Kearns AM. Panton-Valentine leucocidin-related disease in England and Wales. *Clin Microbiol Infect.* 2010 Jan; 16(1):86-88. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/19681948>.

RATIONALE: A retrospective study, in which 720 PVL-SA isolates were identified during 2005 (n=224) and 2006 (n=496), demonstrating an almost two-fold increase. PVL-SA was identified in individuals in previously recognised at risk groups, including: school children; nursing home residents; military service personnel; household contacts of individuals with PVL-SA disease; injecting drug users; men who have sex with men. The authors conclude that the data supports an increasing trend in PVL-SA, but this data is likely to reflect an underestimate of PVL-related disease, due to factors influencing case ascertainment.

4. Public Health England (PHE). Guidance on the diagnosis and management of PVL-associated *Staphylococcus aureus* infections (PVL-SA) in England. 2008 Nov. Available from: <https://www.gov.uk/government/publications/pvl-staphylococcus-aureus-infections-diagnosis-and-management>.

RATIONALE: A PHE guideline based on a review of the literature and experiences of colleagues working with PVL-SA in the UK, Europe, the USA, and Canada. This guideline identifies risk factors for the spread of infection, and suggests keeping your skin in good condition to prevent the spread of PVL-SA to others, especially in people who have underlying skin conditions, eg eczema. Suppression therapy is discussed, in which it is stated that suppression of PVL-SA is ineffective if skin lesions are still leaking, so suppression therapy should only be started after the primary infection has resolved.

Eczema:

1. Birnie AJ, Bath-Hextall FJ, Ravenscroft JC, Williams HC. Interventions to reduce *Staphylococcus aureus* in the management of atopic eczema (Review). *Cochrane Database Syst Rev.* 2008 Jul; 16(3):1-60. Available from:

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003871.pub2/epdf>.

RATIONALE: A systematic review and meta-analysis, in which most randomised controlled trials identified were small, of poor quality, and heterogeneous. Oral antibiotics were not associated with benefit in two small trials of people with eczema without visible signs of infection (n=66). Adding antibiotics to topical steroids reduced the numbers of *Staphylococcus aureus* in four trials (n=302), but not in a further nine trials (n=677).

2. National Institute for Health and Care Excellence (NICE). Atopic eczema in under 12s: diagnosis and management. 2016 Jul. Available from:

<https://www.nice.org.uk/Guidance/cg57>.

RATIONALE: A NICE guideline, covering the diagnosis and assessment of the impact of eczema, the management during and between flares, and information and education for children and their parents or carers about the condition. This guideline states that flucloxacillin should normally be the first line treatment for active *Staphylococcus aureus* and streptococcal infections, because it is active against both. Erythromycin or clarithromycin should be used when there is local resistance to flucloxacillin, and in children with penicillin allergy, as it is as effective as cephalosporins, less costly, and less likely to encourage resistance. Topical antibiotics, including those combined with topical corticosteroids, should be used to treat localised overt infection only, and for no longer than two weeks.

Acne:

1. Clinical Knowledge Summaries (CKS). Acne vulgaris. 2014 Sep. Available from:

<http://cks.nice.org.uk/acne-vulgaris#!topicsummary>.

RATIONALE: A CKS guideline, recommending that people with acne should: not wash more than twice daily; use a mild soap or cleanser and lukewarm water; not use vigorous scrubbing when washing acne-affected skin; not attempt to 'clean' blackheads; avoid excessive use of makeup and cosmetics; use fragrance-free, water-based emollient if dry skin is a problem. This guideline states that topical retinoids normalise follicular keratinisation, promote drainage of comedones, and inhibit new comedone formation. They have been used historically mainly to treat comedones, but they are also effective at treating inflammatory lesions by inhibiting microcomedone formation. Benzoyl peroxide is a potent bactericide and significantly reduces the population of *Propionibacterium acnes* in the sebaceous follicle. There is good evidence from placebo-controlled trials that benzoyl peroxide reduces both inflammatory and non-inflammatory lesions. Due to its bactericidal properties, benzoyl peroxide produces rapid improvement in inflammatory lesions and prevents the development of antibiotic resistance. Topical antibiotics are recommended as they are especially effective in reducing the number of inflammatory lesions. There is a lack of evidence from comparative randomised controlled trials to show that any particular

Management and treatment of common infections-Antibiotic guidance for primary care

topical antibiotic has an advantage over another. It is thought that monotherapy with antibiotics can lead to resistance, not only in *Propionibacterium acnes*, but also in other potentially pathogenic bacteria, especially certain strains of *Staphylococcus aureus*, coagulase-negative staphylococci, and Group A streptococci, which can lead to both therapeutic failure of acne and bacterial resistance. Monotherapy with antibiotics should be strongly discouraged; antibiotics should be combined with retinoids and/or benzoyl peroxide. Treatment with a topical antibiotic should be limited to 12 weeks' duration where possible, to reduce the risk of resistance developing. Oral antibiotics are universally recommended by experts for the treatment of severe acne, or extensive acne that would be difficult to treat with a topical drug. Oral tetracyclines are recommended first line as it is effective at reducing lesion counts and severity. Oral erythromycin should be reserved for use when tetracyclines are contraindicated. There is a lack of evidence from placebo-controlled trials to verify the efficacy of erythromycin, although evidence from comparative trials indicate that it is probably as effective as tetracyclines. This guideline indicates that anyone presenting with severe acne should be referred to a specialist, and that treatment with topical retinoids and benzoyl peroxide should be continued for at least six weeks.

2. Primary Care Dermatology Society (PCDS). Acne vulgaris. 2016 Jul. Available from: <http://www.pcds.org.uk/clinical-guidance/acne-vulgaris>.

RATIONALE: A PCDS guideline outlining the aetiology, diagnosis, classification, and treatment regimens for acne vulgaris. This guideline suggests that anyone with severe acne should be referred immediately, and that topical preparations containing benzoyl peroxide and/or topical retinoids are an essential part of treatment. This guideline states that there is little additional benefit in using antibiotics for more than three months, as prolonged use increases the resistance of *Propionibacterium acnes*. It is therefore recommended that antibiotics should be stopped after three months; however, the patient should remain on their topical agent. If the patient does not respond to two types of antibiotics, especially if they are starting to scar, the patient should be referred for consideration of isotretinoin.

3. Purdy S, de Berker D. Acne vulgaris. *BMJ Clin Evid*. 2011 Jan; 1(1714):1-71. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3275168/>.

RATIONALE: A systematic review and meta-analysis of five systematic reviews and 64 randomised controlled trials. The authors advise that topical benzoyl peroxide 5% twice to four times daily or a topical retinoid once daily should be considered as first line treatment in mild acne. Topical benzoyl peroxide 5% and topical azelaic acid 20% reduce inflammatory and non-inflammatory lesions compared with placebo, but can cause itching, burning, stinging, and redness of the skin. Topical antibiotics such as clindamycin 1% and erythromycin 2% (alone or with zinc) reduce inflammatory lesions compared with placebo, but have not been shown to reduce non-inflammatory lesions. This review references several studies indicating development of antibiotic resistance to *Propionibacterium acnes* when using topical application or oral antibiotics for acne treatment. (Cooper AJ. *Systematic review of Propionibacterium acnes resistance to systemic antibiotics. Med J Aust* 1998;169:259–261. Search date 1998. [\[PubMed\]](#) and Simonart T, Dramaix M. *Treatment of acne with topical antibiotics: lessons from clinical studies. Br J Dermatol* 2005;153:395–403. [\[PubMed\]](#)). Tetracycline may reduce overall acne severity, but may

Management and treatment of common infections-Antibiotic guidance for primary care

cause skin discoloration, and should be avoided in pregnant or breastfeeding women. Antimicrobial resistance can develop with the use of topical or oral antibiotics, and their efficacy may decrease over time. Topical preparations of tretinoin 0.025%, adapalene 0.1% daily, and isotretinoin 0.05% may reduce inflammatory and non-inflammatory lesions, but can also cause redness, burning, dryness, and soreness of the skin. Oral antibiotics, including doxycycline 100mg daily, erythromycin 500mg twice daily, minocycline 1, 2, or 3/mg/kg/day, oxytetracycline 500mg twice daily, and tetracycline 500mg twice daily for a maximum of three months are considered useful for people with more severe acne.

4. Tan J, Humphrey S, Vender R, Barankin B, Gooderham M, Kerrouche N et al. A treatment for severe nodular acne: a randomized investigator-blinded, controlled, noninferiority trial comparing fixed-dose adapalene/benzoyl peroxide plus doxycycline vs. oral isotretinoin. *BJD*. 2014 Oct; 171(6):1508-1516. Available from:

<http://onlinelibrary.wiley.com/doi/10.1111/bjd.13191/abstract>.

RATIONALE: A multicentre, randomised controlled trial involving 266 subjects, aiming to compare the efficacy and safety of oral isotretinoin versus doxycycline 200mg plus benzoyl peroxide 2.5% gel in severe nodular acne over 20 weeks. Doxycycline plus benzoyl peroxide showed a significantly earlier onset of action in reducing nodules, pustules, and total lesions at week two, whereas oral isotretinoin was superior at week 20. Doxycycline plus benzoyl peroxide was noninferior to oral isotretinoin in the intent-to-treat population (95% CI 2.7 to 20.8; $p=0.13$) and per-protocol population (95% CI 3.9 to 28.6; $p=0.01$), based on the composite efficacy/safety end point. The authors conclude that doxycycline plus benzoyl peroxide showed a favourable composite efficacy/safety profile compared with oral isotretinoin, and can be used as an alternative in patients intolerant to oral isotretinoin as an option for treatment of severe nodular acne.

Cellulitis and erysipelas:

1. Clinical Resource Efficiency Support Team (CREST). Guidelines on the management of cellulitis in adults. 2005 Jun. Available from:

<http://www.acutemed.co.uk/docs/Cellulitis%20guidelines,%20CREST,%202005.pdf>.

RATIONALE: An expert consensus outlining the most common infective organisms as streptococci and *Staphylococcus aureus*. The consensus is that people with Class I disease (no signs of systemic toxicity and no uncontrolled comorbidities) can usually be managed on an outpatient basis with oral antibiotics. Flucloxacillin 500mg QDS (or clarithromycin 500mg BD for those with penicillin allergy) are suitable oral antibiotics because they cover both staphylococci and streptococci. Clindamycin 300mg QDS is also recommended as a further alternative for people who do not respond to treatment, or have more severe disease, as well as co-amoxiclav 500/125mg three times daily for facial cellulitis. This document states that most cases of uncomplicated cellulitis can be successfully treated within 1-2 weeks of therapy. Consider outpatient antimicrobial therapy (OPAT) with intravenous treatment in those with Class II disease (systemically unwell or co-morbidity). Patients can usually be switched to oral treatment after 3-5 days when signs and symptoms are improving (decreased temperature, change in white cell count, and decreasing erythema and induration). Those with Class III disease (significant

Management and treatment of common infections-Antibiotic guidance for primary care

systemic upset, acute confusion, tachycardia, tachypnoea, hypotension or unstable co-morbidities) or Class IV disease (patients with sepsis syndrome or severe life threatening infections) should be admitted urgently. This consensus also recommends that, if cellulitis is suspected following river or sea water exposure, management and treatment advice should be sought from a specialist.

2. British Lymphology Society. Consensus document on the management of cellulitis in lymphoedema. 2015 Apr. Available from:

<http://www.lymphoedema.org/images/pdf/CellulitisConsensus.pdf>.

RATIONALE: An expert consensus document on the management of cellulitis in lymphoedema. The authors state that flucloxacillin 500mg QDS should be prescribed in the presence of clinical infection (eg pus formation, folliculitis or crusted dermatitis). They also state that if the patient is allergic to penicillin, clarithromycin 500mg BD or clindamycin 300mg QDS should be prescribed. Doxycycline 200mg is recommended as an alternative if the patient is penicillin-hypersensitive and taking statins (eg simvastatin or atorvastatin). Finally, the authors state that advice should be sought from a local microbiologist if the infection fails to respond to these recommendations.

3. Ferreira A, Bolland MJ, Thomas MG. Meta-analysis of randomised trials comparing a penicillin or cephalosporin with a macrolide or lincosamide in the treatment of cellulitis or erysipelas. *Infection*. 2016 Oct; 44(5):607-615. Available from:

<https://www.ncbi.nlm.nih.gov/pubmed/27085865>.

RATIONALE: A systematic review of 15 studies: nine in patients with cellulitis or erysipelas; six in patients with various skin and soft tissue infections. The efficacy of treatment of cellulitis or erysipelas was similar with a beta-lactam and a macrolide or lincosamide (RR 1.24; 95% CI 0.72 to 2.41; p=0.44). Treatment efficacy was also similar for skin or soft tissue infections, including cellulitis and erysipelas (RR 1.28; 95% CI 0.96 to 1.69; p=0.09). Risk of adverse effects were also similar for beta-lactams and macrolides or lincosamides (RR 0.86; 14% difference; 95% CI 0.64 to 1.16; p=0.31).

4. Bruun T, Oppegaard O, Kittang BR, Mylvaganam H, Langeland N, Skrede S. Etiology of cellulitis and clinical prediction of streptococcal disease: a prospective study. *Open Forum Infect Dis*. 2015 Nov; 3(1):181-189. Available from:

<https://www.ncbi.nlm.nih.gov/pubmed/26734653>.

RATIONALE: A prospective study, including 216 patients who were hospitalised with cellulitis and erysipelas. The predominance of bacterial origin was lower extremity (57%), followed by facial (24%), and in cases of facial erysipelas, was usually unilateral. The authors reported that serology, or blood or tissue culture, confirmed beta-haemolytic streptococcal aetiology in 72% of cases. An additional 13% of cases had probably (BHS) infection, indicated by penicillin response or BHS cultures from skin swabs. Beta-haemolytic streptococcal aetiology was predominant in all clinical subgroups, including patients without sharply demarcated erythema. *Staphylococcus aureus* was cultured from swabs as a single pathogen in 24 cases. The authors conclude that beta-haemolytic streptococci were the dominating cause of cellulitis in all clinical subgroups, and Group C or G streptococci were more frequently detected than GAS.

Management and treatment of common infections-Antibiotic guidance for primary care

5. Kilburn SA, Featherstone P, Higgins B, Brindle R. Interventions for cellulitis and erysipelas (Review). *Cochrane Database Syst Rev*. 2010 Jun; 16(6):1-72. Available from:

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004299.pub2/epdf>.

RATIONALE: A systematic review and meta-analysis of 25 studies, with a total of 2,488 participants. It was commonly reported that symptoms were rated by the participant or medical practitioner as symptom-free. No two trials examined the same antibiotics, therefore the review grouped similar types of drugs together. Three studies (n=88) comparing a penicillin for seven days with a cephalosporin for ten days showed no difference in treatment effect (RR 0.99; 1% reduction; 95% CI 0.68 to 1.43). Macrolides (azithromycin or erythromycin 250-500mg for five to seven days)/streptogramins (oral pristinamycin 1g three times daily for 14 days) were found to be more effective than penicillins for seven days (RR 0.84; 16% reduction; 95% CI 0.73 to 0.97). In two trials (n=419), an oral macrolide for five to seven days was compared with intravenous penicillin, which demonstrated that oral therapies can be more effective than IV therapies (RR 0.85; 15% reduction; 95% CI 0.73 to 0.98).

6. Fisher RG, Benjamin DK Jr. Facial cellulitis in childhood: a changing spectrum. *South Med J*. 2002 Jul; 95(7):672-674. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12144069>.

RATIONALE: A retrospective study stating that buccal cellulitis is commonly due to infection with *Haemophilus influenzae*, although rates are decreasing. Trauma was the most common antecedent to facial cellulitis. Co-amoxiclav is recommended for empirical treatment of facial cellulitis, as it is broader spectrum than flucloxacillin, and also covers anaerobes and other less common causes of facial cellulitis.

NB See dental section for advice around dental-associated swelling.

Leg ulcer:

1. Grey JE, Enoch S, Harding KG. Wound assessment. *BMJ*. 2008 Feb; 332(7536):285-288. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1360405/>.

RATIONALE: A review article providing a methodological mechanism for wound assessment, accompanied by photographic examples. This article states that a full clinical history should be taken, including; patient details, history of ulceration, and ulcer characteristics. It also suggests that all open wounds are colonised by bacteria, but routine bacteriological sampling should only be conducted if infection is suspected. This article states that removal of necrotic tissue is key, and reports that antibiotics should only be prescribed in the presence of infection.

2. O'Meara S, Al-Kurdi D, Ologun Y, Ovington LG, Martyn-St James M, Richardson R. Antibiotics and antiseptics for venous leg ulcers (Review). *Cochrane Database Syst Rev*. 2014 Jan; 1:1-156. Available from:

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003557.pub5/pdf/standard>.

RATIONALE: An updated Cochrane review of 45 randomised controlled trials, established to determine the effects of systemic, topical antibiotics and antiseptics on the healing of venous leg ulcers. The authors state that the evidence does not currently support the routine use of systemic antibiotics in venous leg ulcers, especially with the increasing

Management and treatment of common infections-Antibiotic guidance for primary care

problem of bacterial resistance in the community. There is, however, some evidence in support of cadexomer iodine as a topical preparation. This review suggests that all wounds are colonised by bacteria and, at a certain level, some bacteria can cause significant infection and delay healing. The authors conclude that antibacterial preparations should only be used in cases of clinical infection, as bacterial colonisation alone is not considered adverse to healing.

3. Public Health England (PHE). UK standards for microbiological investigations: investigation of skin, superficial and non-surgical wound swabs. 2014 May. Available from:
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/391745/B_11i5.2.pdf.

RATIONALE: A PHE document outlining the standards required for bacteriological investigation and processing of skin, superficial and non-surgical wound swabs. This document suggests that routine swab cultures are of questionable clinical value if there is no sign of infection. It also states that specimens should be collected before antimicrobial therapy is started, and provides details on how to optimise results from a wound swab. The guideline describes how to take a microbiological sample and the importance of using appropriate transport medium and transporting the specimen to the microbiology laboratory as soon as possible.

4. Scottish Intercollegiate Guidelines Network (SIGN). Management of chronic venous leg ulcers: a national clinical guideline. 2010 Aug. Available from:
<http://www.sign.ac.uk/assets/sign120.pdf>.

RATIONALE: A detailed guideline providing evidence-based recommendations on the management of venous leg ulcers. The guideline provides advice on the assessment of the leg, the importance of Doppler studies, and the use of dressings and compression in treating venous leg ulcers. SIGN recommend that ulcerated legs should be washed normally in tap water and carefully dried. This guideline clearly states that routine bacteriological samples should not be taken in the absence of clinical infection (cellulitis; pyrexia; increased pain; rapid extension of area of ulceration; malodour; increased exudate). It is also advised that only patients with a non-healing or atypical venous leg ulcer should be referred for consideration of biopsy, and that colonisation of wounds does not necessarily mean that a wound is infected. Finally, this guideline states that antibiotics should not be started unless there is clear sign of clinical infection.

5. Clinical Resource Efficiency Support Team (CREST). Guidelines on the management of cellulitis in adults. 2005 Jun. Available from:
<http://www.acutemed.co.uk/docs/Cellulitis%20guidelines,%20CREST,%202005.pdf>.

RATIONALE: An expert consensus outlining the most common infective organisms as streptococci and *Staphylococcus aureus*. The consensus is that people with Class I disease (no signs of systemic toxicity and no uncontrolled comorbidities) can usually be managed on an outpatient basis with oral antibiotics. Flucloxacillin 500mg QDS (or clarithromycin 500mg BD for those with penicillin allergy) are suitable oral antibiotics because they cover both staphylococci and streptococci. Clindamycin 300mg QDS is also recommended as a further alternative for people who do not respond to treatment, or have more severe disease, as well as co-amoxiclav 500/125mg three times daily for facial

Management and treatment of common infections-Antibiotic guidance for primary care

cellulitis. This document states that most cases of uncomplicated cellulitis can be successfully treated within 1-2 weeks of therapy. Consider outpatient antimicrobial therapy (OPAT) with intravenous treatment in those with Class II disease (systemically unwell or co-morbidity). Patients can usually be switched to oral treatment after 3-5 days when signs and symptoms are improving (decreased temperature, change in white cell count, and decreasing erythema and induration). Those with Class III disease (significant systemic upset, acute confusion, tachycardia, tachypnoea, hypotension or unstable co-morbidities) or Class IV disease (patients with sepsis syndrome or severe life threatening infections) should be admitted urgently. If cellulitis is suspected following river or sea water exposure, management and treatment advice should be sought from a specialist.

6. Dryden M. Reactive oxygen therapy: a novel therapy in soft tissue infection. *Curr Opin Infect Dis.* 2017 Apr; 30(2):143-149. Available from:
<https://www.ncbi.nlm.nih.gov/pubmed/28225711>.

RATIONALE: An editorial, stating that many chronic, poorly healing lesions get treated with antibiotics, despite the lack of evidence for long-term antimicrobial treatment. One of the only novel agents to reach clinical use is one using reactive oxygen species (ROS), oxygen radicals, as an antimicrobial mechanism. This editorial outlines the following five key points: reactive oxygen species is highly active against Gram-positive and negative organisms, with some viral and fungal activity; ROS can prevent biofilm formation and reduce existing biofilm activity; ROS has significant therapeutic implications for topical treatment of wounds, surgical cavities, respiratory tract and urinary mucosa; ROS is delivered by topical and local application; ROS can support infection prevention and antimicrobial stewardship. The author concludes that early clinical data supports ROS treatment in skin and soft tissue lesions to reduce bacterial bioburden and biofilm in critical colonisation, and in preventing surgical site infection. The approach is that the use of ROS in leg ulceration can reduce unnecessary antimicrobial prescribing for colonisation, and reduce the amount of time community nurses currently spend dressing and treating non-healing leg ulcers.

7. Dryden M, Cooke J, Salib R, Holding R, Pender SLF, Brooks J. Hot topics in reactive oxygen therapy: Antimicrobial and immunological mechanisms, safety and clinical applications. *J Glob Antimicrob Resist.* 2017 Mar; 8:194-198. Available from:
<https://www.ncbi.nlm.nih.gov/pubmed/28219826>.

RATIONALE: An editorial, stating that reactive oxygen species, when combined with various delivery mechanisms, has the potential to become a powerful novel therapeutic agent against difficult-to-treat infections, especially in those involving biofilm. ROS is rapidly active in vitro against all Gram-positive and Gram-negative bacteria tested, and also has antifungal and antiviral properties. ROS has successfully been used in infection prevention, eradication of multiresistant organisms, prevention of surgical site infection, and intravascular line care. For skin and soft tissue infections, one large observational study and five in vitro studies have recorded a reduction in bacterial load and biofilm, and healing has been promoted with the use of ROS. The authors conclude that this antimicrobial mechanism has great potential for the control of bioburden and biofilm at many sites. However, well-designed randomised controlled studies are needed to clearly demonstrate the effectiveness of its use.

Bites:

1. Medeiros I, Saconato H. Antibiotic prophylaxis for mammalian bites (Review). *Cochrane Database Syst Rev*. 2001 Apr; 2:1-20. Available from:

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001738/epdf>.

RATIONALE: A systematic review and meta-analysis, in which only one trial (n=48) analysed human bites. The infection rate in the antibiotic group, who received either cefaclor 250mg three times daily, cefazolin 1g four times daily intravenously, or benzylpenicillin 1.2 million units four times daily intravenously, (0%) was significantly lower than the infection rate in the control group (47%; OR 0.02; 98% lower; 95% CI 0.00 to 0.33). For dog bites, pooled results from six randomised controlled trials (n=463) found that the infection rate was not reduced after the use of prophylactic antibiotics (phenoxymethylpenicillin 250mg four times daily for five days, erythromycin 500mg four times daily for seven days, oxacillin 500mg four times daily for five days, or dicloxacillin 250mg four times daily; 4%) compared with the control group (5.5%; OR 0.74; 26% difference; 95% CI 0.30 to 1.8). For cat bites, one very small study (n=11) reported a lower infection rate in the treatment group who received prophylactic antibiotics (0%) compared with the control group (67%). The authors conclude that there is evidence that the use of antibiotic prophylaxis after bites of the hand reduces infection. Prevention of tetanus and rabies where appropriate, together with adequate cleansing of such wounds, are also universally accepted measures of managing bite wounds.

2. Clinical Knowledge Summaries (CKS). Bites – human and animal. 2015 Jul. Available from: <http://cks.nice.org.uk/bites-human-and-animal#!topicsummary>.

RATIONALE: A CKS guideline stating that thorough irrigation with warm, running water is key for the management of a human or animal bite. Antibiotic prophylaxis should be given for all human bite wounds under 72 hours old, even if there are no signs of clinical infection. Prophylaxis for animal bites is not required unless: it is a bite to the hand, foot, or face; puncture wounds; all cat bites; wounds requiring surgical debridement; wounds involving joints, tendons, ligaments, or suspected fractures; wounds that have undergone primary closure; wounds to people who are at risk of serious wound infection (eg those who are diabetic, cirrhotic, asplenic, immunosuppressed, or people with a prosthetic valve or prosthetic joint). This guideline also provides treatment and dosing regimens for human and animal bites. Co-amoxiclav is recommended for both prophylaxis and treatment of all bites, as it is a broad-spectrum antibiotic, and effective against most bacteria isolated from human and domestic animal bites. For human bites in those with penicillin allergy, metronidazole 400mg three times daily plus clarithromycin 250-500mg twice daily for seven days is recommended. For animal bites, metronidazole 400mg three times daily plus doxycycline 100mg twice daily for seven days is recommended.

3. Public Health England Expert Panel. In a conversation with the British Infection Association Expert Panel (oral communication, June 2012).

RATIONALE: Expert consensus, recommending that the risk of tetanus, rabies, HIV and hepatitis B and C should be assessed in all human bites. Co-amoxiclav 375-625mg three times daily, for seven days, is recommended for the treatment or prophylaxis of human or

Management and treatment of common infections-Antibiotic guidance for primary care

animal bites, because it is a broad-spectrum antibiotic that is effective against the most commonly isolated organisms from bite wounds. For those with human bites and penicillin allergy, metronidazole plus either doxycycline or clarithromycin are recommended. Metronidazole is included to cover anaerobes, and both doxycycline and clarithromycin are active against both staphylococci and streptococci. Doxycycline is also active against *Eikenella* species: another common pathogen isolated from human mouths. For those with animal bites and penicillin allergy, metronidazole plus doxycycline is recommended, as these cover anaerobes, *Pasteurella* species, staphylococci and streptococci. Macrolides are not recommended for animal bites, as they do not adequately cover *Pasteurella* species. Specialist advice should be sought for children under the age of 12 years. People with penicillin allergy should be reassessed at 24 and 48 hours after starting a course of antimicrobial treatment, as the recommended regimen covers the majority, but not all, of the likely pathogens from human and animal bites.

4. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014 Jun; 59(2):10-52.

Available from: <http://cid.oxfordjournals.org/content/early/2014/06/14/cid.ciu296>.

RATIONALE: An IDSA guideline, providing detailed advice on the treatment of human and animal bites, and emphasising the important of promptly diagnosing SSTIs, identifying the pathogen, and administering effective treatments. Where pre-emptive treatment of animal and human bite wounds is concerned, the authors recommendations include pre-emptive early antimicrobial therapy for three to five days for patients who: are immunocompromised; are asplenic; have advanced liver disease; have pre-existing or resultant oedema of the affected area; have moderate to severe injuries, especially to the hands or face; have injuries that may have penetrated the periosteum or joint capsule. Prophylactic or early pre-emptive therapy seems to provide only marginal benefit to wound care for patients with dog bites who present within 12 to 24 hours after injury, particularly in those: with low-risk wounds; that are not associated with puncture wounds; with no history of an immunocompromising disorder or use of immunosuppressive drugs; with wounds not involving the face, hand, or foot. The authors conclude that antibiotics reduce the risk of infection in dog bite wounds but suggest limiting this to 'high risk' wounds. For infected wounds, the authors recommend antimicrobial agents active against both aerobic and anaerobic bacteria, such as amoxicillin-clavulanate. Purulent bite wounds and abscesses are more likely to be polymicrobial, whereas nonpurulent wounds commonly yield staphylococci and streptococci. *Pasteurella* species are commonly isolated from both nonpurulent wounds, with or without lymphangitis, and from abscesses. Unless no alternative agents are available, macrolides should be avoided for prophylaxis and treatment of animal bites, due to variable activity against *Pasteurella multocida* and fusobacteria. Human bites may occur from accidental injuries, purposeful biting, or closed-fist injuries. The bacteriologic characteristics of these wounds are complex, but include aerobic bacteria, such as streptococci, *Staphylococcus aureus*, and *Eikenella corrodens*, as well as with multiple anaerobic organisms, including *Fusobacterium*, *Peptostreptococcus*, *Prevotella*, and *Porphyromonas* species. *Eikenella corrodens* is resistant to first-generation cephalosporins, macrolides, clindamycin, and

Management and treatment of common infections-Antibiotic guidance for primary care

aminoglycosides; therefore, treatment with amoxicillin-clavulanate is recommended. If there is history of hypersensitivity to beta-lactams, a fluoroquinolone, such as ciprofloxacin plus metronidazole is recommended.

Scabies:

1. National Health Service (NHS). Community infection prevention and control guidance for health and social care: scabies. 2015 May. Available from:
<http://www.infectionpreventioncontrol.co.uk/content/uploads/2015/05/19-Scabies-May-2015-Version-1.01.pdf>.

RATIONALE: An NHS guideline stating that topical treatment is best done in the evening, and must be applied all over from the ear downwards, including: in between buttocks; fingers; toes; naval; behind the ears; on the palms of hands; on the soles of feet; under nail edges; genital areas. If the patient is under two years or elderly, the face and scalp should also be treated, avoiding the lips and eye area. This guideline states that the index case, and all members of the household and sexual contacts, should be treated within 24 hours of one another, even in the absence of symptoms, to reduce the risk of reinfestation. Permethrin 5% cream, or malathion 0.5% aqueous liquid, are recommended as first line treatments. Two treatments should be given, seven days apart, for eradication of scabies.

2. Medicines.org. *Lyclear Dermal Cream*. Available from:
<http://www.medicines.org.uk/EMC/medicine/10439/SPC/Lyclear+Dermal+Cream/> [Accessed: 20th September, 2016].

RATIONALE: An EMC webpage stating that Lyclear 5% Dermal Cream is indicated for the treatment of scabies in adults and children over two months of age. Adults and adolescents over 12 years of age should apply up to 30g of cream; children aged from six to 12 years should apply up to 15g of cream; children aged from two months to five years should apply up to 7.5g of cream. Cream should be applied uniformly to the whole body, including the neck, palms of the hands, and soles of the feet. The head and face can be spared, unless scabies efflorescences are present in this region. On application, the areas between the fingers and toes (also under the finger and toenails), the wrists, elbows, armpits, external genitalia, and the buttocks, should be especially carefully treated.

3. Strong M, Johnstone P. Interventions for treating scabies (Review). *Cochrane Database Syst Rev*. 2007 Jul; 18(3):1-74. Available from:
<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000320.pub2/epdf>.

RATIONALE: A systematic review and meta-analysis of 20 studies, involving 2,392 children and adults undergoing drug treatment for scabies. One trial was placebo controlled, 18 compared two or more drug treatments, three compared treatment regimens, and one compared different drug vehicles. 19 of the 22 studies included were conducted in resource-poor countries, although one was a large multicentre trial involving eight centres in Mexico and the USA (four sexually transmitted disease clinics, two dermatology clinics, and two family practice clinics). Results indicated that fewer treatment failures occurred by day seven with oral ivermectin, compared with placebo (n=55); topical permethrin (5% cream) appeared more effective than oral ivermectin 200 µg/kg

Management and treatment of common infections-Antibiotic guidance for primary care

bodyweight single dose (n=140), topical crotamiton (n=194), and topical lindane (n=753); permethrin appeared more effective in reducing itch persistence than crotamiton (n=94), and lindane (n=490); no significant differences were detected between permethrin and a natural pyrethrin-based topical treatment (n=40), or between permethrin and benzyl benzoate (n=53). The authors conclude that topical permethrin is significantly more effective than oral ivermectin, topical crotamiton, and topical lindane (RR 0.32; 68% reduction; 95% CI 0.13 to 0.75; n=735). More research is required on the effectiveness of malathion, particularly when compared with permethrin, as no trials were identified.

Mastitis:

1. Spencer JP. Management of mastitis in breastfeeding women. *Am Fam Phys*. 2008 Sep; 78(6):727-731. Available from: <http://www.aafp.org/afp/2008/0915/p727.pdf>.

RATIONALE: A review article defining mastitis as localised, painful inflammation of the breast, occurring in conjunction with flu-like symptoms. When antibiotics are needed, those effective against *Staphylococcus aureus* are preferred, as this organism is responsible for most cases of mastitis. This article states that, in breastfeeding women, continued breastfeeding should be encouraged in the presence of mastitis, and generally does not pose a risk to the infant. As the mother and infant are usually colonised with the same organisms at the time mastitis develops, breastfeeding can continue during an episode of mastitis without worry of the bacterial infection being transmitted to the infant.

2. Clinical Knowledge Summaries (CKS). Mastitis and breast abscess. 2015 Aug. Available from: <http://cks.nice.org.uk/mastitis-and-breast-abscess#!topicsummary>.

RATIONALE: A CKS guideline defining mastitis as a painful inflammatory condition of the breast, which may or may not be accompanied by infection. This guideline recommends that mastitis should be suspected if a woman has: a painful breast; fever and/or general malaise; a tender, red, swollen, and hard area of the breast, usually in a wedge-shaped distribution. Finally, this guideline recommends the following for first line management of a woman with mastitis not requiring urgent admission or referral: offering reassurance that the breast should return to normal following appropriate treatment; advising on measures to relieve pain and discomfort, such as the use of simple analgesics and applying a warm compress to the breast; encouraging breastfeeding women to continue feeding if possible, including from the affected breast; identifying and managing predisposing factors for mastitis, where possible, including poor infant attachment to the breast, nipple damage, smoking, and/or an underlying breast abnormality; prescribing oral antibiotics if indicated; offering appropriate advice on measures to prevent recurrence, such as encouraging good breastfeeding technique and maintaining good hygiene. The first line treatment regimens suggested for lactating women are: flucloxacillin 500mg four times daily for ten to 14 days, or in penicillin allergy, erythromycin 250-500mg four times daily, or clarithromycin 500mg twice daily for ten to 14 days.

3. Jahanfar S, Ng CJ, Teng CL. Antibiotics for mastitis in breastfeeding women (Review). *Cochrane Database Syst Rev*. 2013 Feb; 28(2):1-29. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005458.pub3/epdf>.

Management and treatment of common infections-Antibiotic guidance for primary care

RATIONALE: A small systematic review and meta-analysis of two trials, aiming to examine the effectiveness of antibiotic therapies in relieving symptoms for breastfeeding women with mastitis. One trial (n=25) compared amoxicillin 500mg three times daily for seven days with cephadrine 500mg three times daily for seven days and found no significant difference between the two antibiotics in terms of symptom relief and abscess formation. Another study (n=213) compared breast emptying versus antibiotic therapy plus supportive therapy, and no therapy. The findings suggest faster clearance of symptoms for women using antibiotics, compared to the other treatment arms.

Dermatophyte infection: skin:

1. Public Health England (PHE). Fungal skin and nail infections: quick reference guide. 2017 Jun. Available from: <https://www.gov.uk/government/publications/fungal-skin-and-nail-infections-diagnosis-and-laboratory-investigation>.

RATIONALE: A PHE guideline emphasising the importance of sending skin scrapings to confirm diagnosis of fungal infections before starting oral antibiotics. The authors recommend terbinafine, as it is fungicidal and has a shorter treatment time, instead of azole, which is fungistatic and takes longer to treat. This guideline also states that scalp infections should be discussed with a specialist.

2. Crawford F, Hollis S. Topical treatments for fungal infections of the skin and nails of the foot (Review). *Cochrane Database Syst Rev*. 2007 Jul; 18(3):1-11. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001434/full>.

RATIONALE: A systematic review and meta-analysis, in which pooled data from 11 randomised controlled trials specifically focussed on fungal skin, not nail, infection (n=962). This review covered three azoles: bifonazole; clotrimazole; miconazole, and two allylamines: naftifine; 1% terbinafine. Where stated, the concentration was 1%, and the frequency of treatment was once or twice daily, for four or more weeks. The pooled relative risk of failure to cure was 0.88 (12% risk; 95% CI 0.78 to 0.99), significantly favouring the allylamines naftifine or terbinafine (12% lower). The authors conclude that, in placebo-controlled trials, allylamines, azoles, and undecenoic acid are efficacious in treating dermatophyte skin infections. At six weeks, in five trials, 1% terbinafine for one week had similar outcomes to 1% clotrimazole and miconazole used for four weeks (RR treatment failure 0.75; 25% difference; 95% CI 0.33 to 1.72). Two trials followed patients for more than 12 weeks, and found that, when measuring treatment failure, terbinafine was favoured (RR 0.47; 53% increase; 95% CI 0.22 to 1.02), but this did not quite reach statistical significance. When 1% terbinafine for four to six weeks was compared with 1% azoles for four to six weeks (8 trials; n=962), there was 37% less treatment failure from terbinafine (RR 0.63; 95% CI 0.42 to 0.94). Longer four week courses of clotrimazole were definitely more effective than one week, but four and one week terbinafine had similar efficacy; the trials were, however, small. All antifungal compounds demonstrated some success in curing athlete's foot. The best results were observed with the use of allylamines (terbinafine), which are now available over the counter. There is a small amount of evidence that butenafine may be similarly good. Azoles are also very effective, and participants should be advised that although all azoles appear to be similarly effective, using an azole cream for four weeks is likely to produce better results than using it for one

Management and treatment of common infections-Antibiotic guidance for primary care

week. Azoles may also be more efficacious than tolnaftate, but they seem no more efficacious than undecenoic acid.

- Bell-Syer SE, Hart R, Crawford F, Torgerson DJ, Tyrell W, Russell I. Oral treatments for fungal infections of the skin of the foot (Review). *Cochrane Database Syst Rev*. 2002 Apr; 2:1-41. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003584/epdf>.
RATIONALE: A systematic review and meta-analysis of 15 trials, involving 1,438 participants. One RCT (n=41) found that oral terbinafine 250mg daily for six weeks, was more effective than placebo for treating athlete's foot. At eight weeks, 65% of the terbinafine group were cured, compared with none of the placebo group (RR of cure with terbinafine 25; 95% CI 2 to 384). One RCT (n=77) found that oral itraconazole 400mg daily for one week, was more effective than placebo. At nine weeks, 55% of the itraconazole group were cured, compared with 8% of the placebo group (RR of cure with itraconazole 7; 95% CI 2 to 20). Pooled data from three RCTs (n=222) found no difference in cure rates between oral terbinafine 250mg daily for two weeks (76% cured), and itraconazole 100mg daily for four weeks (71% cured; RD 5%; 95% CI -6 to 27).
- Medicines.org. *Lamisil AT 1% Cream*. Available from: <http://www.medicines.org.uk/emc/medicine/21036> [Accessed: 20th September, 2016].
RATIONALE: An EMC webpage recommending Lamisil AT 1% Cream for the treatment of tinea pedis (athlete's foot) and tinea cruris (dhotie itch/jock itch), caused by Trichophyton (eg *T. rubrum*; *T. mentagrophytes*; *T. verrucosum*; *T. violaceum*) and *Epidermophyton floccosum*. Terbinafine cream is not licensed for the treatment of candida infection.
- Primary Care Dermatology Society (PCDS). Tinea manuum (hands), pedis (feet), and unguium (nails). 2015 Oct. Available from: <http://www.pcds.org.uk/clinical-guidance/tinea-pedis-feet-manuum-hands-and-unguium-nails>.
RATIONALE: A PCDS guideline on the diagnosis and management of tinea. For tinea manuum, treatment is with a topical antifungal agent, eg terbinafine cream, for one to two weeks, or one of the imidazole creams, such as miconazole, for two to four weeks. Terbinafine is more expensive but slightly more effective. Systemic/oral treatment should be used if there is co-existent nail involvement; in which case, treat as per tinea unguium. For tinea pedis with interdigital involvement or fine scaling, treatment should be the same as for tinea manuum. Topical treatments need to involve the soles of the feet as well as the interdigital spaces. Systemic treatment should be used if there is co-existent nail involvement; in which case, treat as per tinea unguium. Recurrence is common, and patients need to be advised to keep feet well aerated by wearing breathable footwear and leaving shoes off around the home. Prophylactic treatment with topical antifungals used once to twice a week can help.
- Fuller LC, Barton RC, Mohd Mustapa MF, Proudfoot LE, Punjabi SP, Higgins EM. British Association of Dermatologists' guidelines for the management of tinea capitis 2014. *Br J Dermatol*. 2014 Sep; 171(3):454-463. Available from: <http://onlinelibrary.wiley.com/doi/10.1111/bjd.13196/epdf>.
RATIONALE: A British Association of Dermatologists' guideline recommending that oral therapy is generally required to eradicate tinea capitis. The authors suggest that it is

Management and treatment of common infections-Antibiotic guidance for primary care

reasonable to begin treatment on the basis of one or more cardinal signs, whilst awaiting confirmatory mycology. Clear evidence has now emerged to show that the optimal treatment regimen varies according to the dermatophyte involved. Treatment protocols should therefore reflect local epidemiology, and be based on the most likely culprit organism. A prolonged course, or a change of agent, may be required in cases of treatment failure, or if an unexpected fungus is identified on culture. The definitive end point for adequate treatment must be mycological cure, rather than clinical response.

Dermatophyte infection: nail:

1. Roberts DT, Taylor WD, Boyle J, British Association of Dermatologists. Guidelines for treatment of onychomycosis. *Br J Dermatol*. 2003 Mar; 148(3):402-410. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12653730>.

RATIONALE: A British Association of Dermatologists guideline stating that only 50% of cases of nail dystrophy are fungal, and it is not easy to identify these clinically. The length of treatment needed (six to 12 months) is too long for a trial of therapy. Treatment should not be commenced before mycological confirmation of infection, through taking nail clippings. Dermatophytes are by far the commonest causal organisms. Culture of yeasts and non-dermatophyte moulds should be interpreted carefully in each individual case. In the majority of cases, yeasts are likely to be a secondary infection, and non-dermatophyte moulds to be saprophytic in previously damaged nails. Topical nail lacquer treatment is inferior to oral treatment in all but a small number of cases of very distal nail infection. Terbinafine is superior to itraconazole, both in vitro and in vivo, for dermatophyte onychomycosis, and should be considered as first line treatment, with itraconazole as the next best alternative. Terbinafine is licensed at a dose of 250 mg daily for six weeks and 12 weeks in fingernail and toenail infection, respectively. Itraconazole is licensed at a dose of 200 mg daily for 12 weeks continuously, or alternatively at a dose of 400 mg daily for one week per month. It is recommended that two of these weekly courses, 21 days apart, are given for fingernail infections and three courses for toenail disease. Cure rates of 80 to 90% for fingernail infection and 70 to 80% for toenail infection can be expected. In cases of treatment failure, the reasons for such failure should be carefully considered. In such cases, either an alternative drug, or nail removal, in combination with a further course of therapy to cover the period of regrowth, should be considered.

2. Ferrari J. Fungal toenail infections. *BMJ Clin Evid*. 2011 Aug;17(15):1-24. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3275109/pdf/2011-1715.pdf>.

RATIONALE: A systematic review and meta-analysis comparing antifungal treatment for toenail infections. One systematic review pooled data from two randomised controlled trials (n=501). At one-year follow-up, the cure rate following 12 weeks of treatment was greater for people with dermatophyte onychomycosis treated with oral terbinafine 250mg once daily for 12 weeks (69%), compared with oral itraconazole 200mg daily for 12 weeks (48%) (RR 21% reduction; 95% CI 13% to 29%). Four small RCTs were identified that found no statistically significant difference between continuous and pulsed itraconazole for dermatophyte onychomycosis.

3. Chang CH, Young-Xu Y, Kurth T, Orav JE, Chan AK. The safety of oral antifungal treatments

Management and treatment of common infections-Antibiotic guidance for primary care

for superficial dermatophytosis and onychomycosis: a meta-analysis. *Am J Med.* 2007 Sep; 120(9):791-798. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17765049>.

RATIONALE: A systematic review and meta-analysis pooling data from about 20,000 participants, which found that both continuous and pulse therapy with terbinafine, itraconazole, or fluconazole were well tolerated. The risk of having asymptomatic raised liver transaminases was less than 2% for all treatments. The risk of having raised liver transaminases that required treatment discontinuation with continuous treatment ranged from 0.11% (itraconazole 100mg/day) to 1.22% (fluconazole 50mg/day). The risk with pulse treatment ranged from 0.39% (itraconazole 400mg/day) to 0.85% (fluconazole 300-450mg/week).

4. Clinical Knowledge Summaries (CKS). Fungal nail infection. 2014 Sep. Available from:

<http://cks.nice.org.uk/fungal-nail-infection#!topicsummary>.

RATIONALE: A CKS guideline recommending oral terbinafine as first line treatment. 250mg once a day should be prescribed for between six weeks and three months for fingernails, and for three to six months for toenails. Visible improvement can be expected after the end of two months of treatment for fingernails, and after three months of treatment for toenails. Oral itraconazole can be used as an alternative treatment. This should be prescribed as pulsed therapy of 200mg twice a day for one week, with subsequent courses repeated after a further 21 days. Fingernail infections require two pulsed courses, and toenail infections require at least three pulsed courses. Specialist advice should be sought for children, as fungal nail infection is rare, and the preferred treatments are not licensed for use in children.

5. Crawford F, Hollis S. Topical treatments for fungal infections of the skin and nails of the foot (Review). *Cochrane Database Syst Rev.* 2007 Jul; 18(3):1-11. Available from:

<http://www.ncbi.nlm.nih.gov/pubmed/17636672>.

RATIONALE: A systematic review and meta-analysis, concluding that there is little evidence that topical antifungals are effective in the management of onychomycosis, or fungally infected toenails. The majority of available data demonstrates low cure rates after long treatment times with ciclopiroxolamine. Amorolfine and butenafine regimens may be much more effective than ciclopiroxolamine and tea tree oil, but only a few observations are available. Large randomised controlled trials comparing the effectiveness of topical amorolfine and butenafine are needed to establish an alternative to oral treatments.

6. Primary Care Dermatology Society (PCDS). Tinea manuum (hands), pedis (feet), and unguium (nails). 2015 Oct. Available from: <http://www.pcds.org.uk/clinical-guidance/tinea-pedis-feet-manuum-hands-and-unguium-nails>.

RATIONALE: A PCDS guideline on the diagnosis and management of tinea. For tinea unguium, a patient information leaflet should be provided. Topical treatments have a low cure rate, but may be suitable for treating distal nail infection (as opposed to involvement of the nail matrix), or superficial white infections. Nails should be filed or cut back as much as possible prior to applying the treatment. For adults, oral terbinafine is the most effective systemic treatment, with eradication rates of 69%, compared with 48% for itraconazole. Terbinafine 250mg OD should be given for six weeks for fingernails, and three to four

Management and treatment of common infections-Antibiotic guidance for primary care

months for toenails. If the patient is unable to take terbinafine, or the tinea appears resistant to treatment, then itraconazole can be used as pulse therapy. Treatment success is denoted by the continued growth of new, healthy, proximal nail. Once treatment is complete it can still take a number of months for any previously affected nail to fully grow out. Recurrent episodes may be due to tinea pedis, in which case, once the infection has been eradicated, it is worth considering the application of a topical antifungal cream once to twice a week, including interdigital spaces.

Varicella zoster/chickenpox; herpes zoster/shingles:

1. Public Health England (PHE). Varicella: the green book, chapter 34. 2015 Aug. Available from: <https://www.gov.uk/government/publications/varicella-the-green-book-chapter-34>.
RATIONALE: A PHE guideline stating that pregnant women are at greater risk of varicella pneumonia, and there is a risk to the foetus of congenital varicella syndrome if exposure occurs during the first 20 weeks of pregnancy, and severe disease in the neonate if varicella is contracted a week before delivery. Following infection in the second and third trimesters, herpes zoster may present in otherwise healthy infants. Occasional cases of foetal damage comprising chorioretinal damage, microcephaly, and skin scarring have been reported following maternal varicella infection between 20 and 28 weeks' gestation, but the risk is lower than for the first trimester. Neonates and immunocompromised individuals are at greater risk of disseminated or haemorrhagic varicella. Urgent specialist assessment is needed for all neonates, pregnant women, or immunocompromised individuals with varicella, in order to assess the need for varicella immunoglobulin and antiviral treatment.
2. Klassen TP, Hartling L, Wiebe N, Belseck EM. Acyclovir for treating varicella in otherwise healthy children and adolescents (Review). *Cochrane Database Syst Rev*. 2005 Oct; 19(4):1-24. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002980.pub3/epdf>.
RATIONALE: A systematic review and meta-analysis, pooling data from three studies with participants from two to 18 years of age within 24 hours of rash onset. Findings indicated that aciclovir was associated with a small reduction in the number of days with fever (-1.1; 95% CI -1.3 to -0.9), and in reducing the maximum number of lesions. Results were less supportive of a reduction in the number of days of itching. There were no differences in complication rates between those treated with aciclovir or placebo.
3. Swingler G. Chickenpox. *Clin Evid*. 2005 Dec; 14:875-881. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2943770/>.
RATIONALE: A literature review, identifying one systematic review that cited one randomised controlled trial (n=148), comparing early versus late administration of aciclovir 800mg five times daily with placebo. Findings indicated that aciclovir given within 24 hours of the onset of rash significantly reduced the maximum number of lesions (p<0.01), and the time to full crusting of lesions (p=0.001), compared with placebo. No significant differences were found in time to full crusting of lesions if aciclovir was given 24-72 hours after onset of rash (p>0.2).

Management and treatment of common infections-Antibiotic guidance for primary care

4. Public Health England Expert Panel. In a conversation with the British Infection Association Expert Panel (oral communication, June 2012).
RATIONALE: Expert consensus, recommending that treatment with aciclovir should be considered if it can be started within 24 hours of rash, and if they are at increased risk of complications. This includes those: over 14 years of age; in severe pain; with dense/oral rash; taking steroids; smokers. For shingles, treatment should be considered if patient has Ramsey Hunt syndrome, or eczema, and can be considered up to a week after rash onset if continued vesicle formation or immunocompromised.

5. Mohsen AH, Peck RJ, Mason Z, Mattock L, McKendrick MW. Lung function tests and risk factors for pneumonia in adults with chickenpox. *Thorax*. 2001 Oct; 56(10):796-799. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/11562520>.
RATIONALE: A prospective study, including 38 patients admitted to a university hospital. 19 patients had pneumonia, and 19 did not. Epidemiological data and density of rash were recorded, spirometric tests were performed, and carbon monoxide transfer factor was measured. Results indicated that varicella pneumonia was associated with the presence of respiratory symptoms ($p=0.006$), current smoking ($p=0.003$), and a history of close contact ($p=0.009$). There was also a trend towards patients with pneumonia having a more severe rash. Current smokers had a higher mean number of spots than non-smokers ($p=0.005$).

6. Wood MJ, Kay R, Dworkin RH, Soong SJ, Whitley RY. Oral acyclovir therapy accelerates pain resolution in patients with herpes zoster: a meta-analysis of placebo-controlled trials. *Clin Infect Dis*. 1996 Feb; 22(2):341-347. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8838194>.
RATIONALE: A systematic review and meta-analysis of four randomised controlled trials ($n=691$), which found greatest benefit in those aged over 50 years, in whom pain resolved twice as fast with aciclovir compared with placebo. Statistical significance was only recorded in one study in those comparing all patients, to patients over the age of 50 (HR 2.13; 95% CI 1.42, 3.19; $p<.001$). Oral aciclovir 800mg five times daily for seven to 10 days also reduced the incidence of post-herpetic neuralgia at three (21% with aciclovir; 43% with placebo) and six months (12% with aciclovir; 25% with placebo). The authors conclude that, overall, the reductions of pain duration and prevalence with aciclovir were approximately twofold, in comparison with placebo.

7. Dworkin RH, Johnson RW, Breuer J, Gnann JW, Levin MJ, Backonja M et al. Recommendations for the management of herpes zoster. *Clin Infect Dis*. 2007 Jan; 44(1):1-26. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17143845>.
RATIONALE: A review article stating that the treatment of shingles should be considered for non-truncal involvement, people with moderate or severe pain, or those with moderate or severe rash. Evidence from randomised controlled trials supports treatment for all those over 50 years of age, to prevent the incidence of post-herpetic neuralgia. The results of further trials support the use of aciclovir, brivudin, famciclovir, and valaciclovir as first line antiviral therapy for the treatment of patients with herpes zoster.

Management and treatment of common infections-Antibiotic guidance for primary care

8. Hope-Simpson RE. Postherpetic neuralgia. *J R Coll Gen Pract.* 1975 Aug; 25(157):571-575. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2157719/>.

RATIONALE: A prospective study, showing that the incidence of post-herpetic neuralgia (PHN) in a general practice population increases with age, with a third of cases being among those over 80 (34.4%). Women, especially those between 50 and 69 years old, suffered more zoster than men, and women with zoster suffered more post-herpetic neuralgia. Results indicated that there is a demonstrable change in the rate of post-herpetic neuralgia after the age of 50, with 7.4% of people between the ages of 50 and 59 developing PHN; 21.2% of those between 60 and 69; 28.6% of those between 70 and 79; 34.4% in those over the age of 80. No post-herpetic neuralgia occurred after zoster in those under 30 years of age, and the incidence of neuralgia was not affected by the anatomical location of the zoster. The duration of post-herpetic neuralgia was unrelated to the age of the patient, but cranial neuralgias lasted much longer on average than neuralgia in other sites.

9. Wood MJ, Shukla S, Fiddian AP, Crooks RJ. Treatment of acute herpes zoster: effect of early (< 48 h) versus late (48-72 h) therapy with acyclovir and valaciclovir on prolonged pain. *J Infect Dis.* 1998 Nov; 178(1):81-84. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9852981>.

RATIONALE: A systematic review of two databases (n=1,076), which found no difference in time to complete resolution of zoster-associated pain, whether treatment was started within 48 hours, or between 48 and 72 hours after the onset of cutaneous herpes zoster. Median times to complete resolution of zoster-associated pain were 26 and 62 days, respectively, for patients treated with aciclovir and placebo within 48 hours (HR 1.68; 95% CL 1.19, 2.38), and 28 and 58 days, respectively, for those treated later (HR 2.20; 95% CL 1.03, 4.71). In the valaciclovir versus aciclovir study, the corresponding figures were 44 and 51 days for patients treated early (HR 1.28; 95% CL 1.03, 1.60), and 36 and 48 days for those treated later (HR 1.40; 95% CL 1.04, 1.87). The authors conclude that aciclovir significantly shortened the time to complete resolution of zoster-associated pain compared with placebo, even when therapy was delayed up to 72 hours after rash onset.

10. Primary Care Dermatology Society (PCDS). Herpes zoster (syn. shingles). 2016 Jul. Available from: <http://www.pcds.org.uk/clinical-guidance/herpes-zoster>.

RATIONALE: A PCDS guideline, recommending that all patients with ophthalmic zoster, irrespective of age or severity of symptoms, should be prescribed oral antiviral drugs at the first sign of disease. First line oral antiviral treatment for adults should be aciclovir 800mg five times daily for seven days. For children, the condition is often mild and may not require treatment. Patients with a red eye or visual complaints must be referred to an ophthalmologist urgently. Those not needing referral must be reviewed after one week.

11. Kurokawa I, Kumano K, Murakawa K, Hyogo Prefectural PHN Study Group. Clinical correlates of prolonged pain in Japanese patients with acute herpes zoster. *J Int Med Res.* 2002 Feb; 30(1):56-65. Available from: <http://journals.sagepub.com/doi/pdf/10.1177/147323000203000109>.

RATIONALE: A prospective study involving 263 adult patients presenting within ten days of the onset of shingles across 17 institutions in Japan. All patients in whom pain persisted

Management and treatment of common infections-Antibiotic guidance for primary care

for more than three months were over 60 years of age. Decreased pain persistence was observed in patients in whom aciclovir therapy was initiated within 72 hours of the onset of symptoms, in comparison with those in whom therapy was initiated after this time. The difference between the two groups of patients was not, however, statistically significant. Treatment should still be initiated up to one week after rash onset, particularly if the patient is at high risk of complications or severe shingles.

12. Rasi A, Heshmatzade Behzadi A, Rabet M, Hassanloo J, Honarbakhsh Y, Dehghan N et al. The efficacy of time-based short-course acyclovir therapy in treatment of post-herpetic pain. *J Infect Dev Ctries*. 2010 Nov; 4(11):754-760. Available from:

<https://www.ncbi.nlm.nih.gov/pubmed/21252455>.

RATIONALE: A prospective clinical trial involving 152 patients diagnosed with acute herpes zoster, aiming to determine whether short-course aciclovir therapy (800mg five times daily for four days) can alleviate HZ-associated pain and prevent post-herpetic neuralgia. Patients were divided into two groups: group one had a rash with a duration of less than 72 hours; group two had a rash with a duration of more than 72 hours. To assess PHN, that patients categorised and assessed the severity of their symptoms using a four-point verbal rating scale. Results indicated that, by the fourth week, 134 out of 152 patients (88.2%) had complete pain response. Of these, 68 patients (89.5%) were from group one, and 66 patients (86.8%) were from group two. After four weeks, the mean verbal rating scale scores had changed significantly in both groups, compared to the scores at the beginning of the study ($p=0.001$), but there was no statistical difference between the two groups ($0.88 + 0.66$; $0.94 + 0.72$; $p=0.66$). After three months, no differences were observed in the treatment results between the two groups ($0.51 + 0.13$; $0.54 + 0.19$; $p=0.77$).

13. Beutner KR, Friedman DJ, Forszpaniak C, Anderson PL, Wood MJ. Valaciclovir compared with aciclovir for improved therapy for herpes zoster in immunocompetent adults. *Antimicrob Agents Chemother*. 1995 Jul; 39(7):1546-1553. Available from:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC162779/pdf/391546.pdf>.

RATIONALE: A randomised double-blind controlled trial ($n=1,141$) including people aged 50 years and older, within 72 hours of onset of herpes zoster. Findings indicated that valaciclovir 1g three times daily for seven or 14 days reduced the time to resolution of pain, compared with aciclovir 800mg five times daily for seven days. Median time to cessation of pain was 38 days for valaciclovir for seven days, compared with 51 days for aciclovir ($p=0.001$), and was 44 days for valaciclovir for 14 days ($p=0.03$).

14. Chen N, Li Q, Yang J, Zhou M, Zhou D, He L. Antiviral treatment for preventing postherpetic neuralgia. *Cochrane Database Syst Rev*. 2014 Feb; 6(2):1-68. Available from:

<https://www.ncbi.nlm.nih.gov/pubmed/24500927>.

RATIONALE: A systematic review and meta-analysis of six randomised controlled trials ($n=1,211$), aiming to assess the effectiveness of antiviral agents in preventing PHN. The randomised controlled trials included examined antiviral treatment given within 72 hours after the onset of herpes zoster for preventing PHN. Results indicated that there were no significant differences between aciclovir and placebo in the incidence of PHN four months after the onset of acute herpetic rash (RR 0.75; 25% difference; 95% CI 0.51 to 1.11), or

Management and treatment of common infections-Antibiotic guidance for primary care

at six months (RR 1.05; 95% CI 0.87 to 1.27; two trials; n=476). In four of the trials analysed (n=692), there was some evidence for a reduction in the incidence of pain four weeks after the onset of rash. In the trial of famciclovir versus placebo, neither 500mg nor 750mg doses of famciclovir reduced the incidence of herpetic neuralgia significantly. The authors conclude that there is high quality evidence suggesting that oral aciclovir does not reduce the incidence of PHN significantly. However, further well-designed trials are needed to investigate famciclovir and other antiviral treatments in preventing PHN. The authors suggest that further trials should pay more attention to the severity of pain and quality of life of participants, and should be conducted among different groups of people, such as people who are immunocompromised.

15. Shen MC, Lin HH, Lee SS, Chen YS, Chiang PC, Liu YC. Double-blind, randomized, acyclovir-controlled, parallel-group trial comparing the safety and efficacy of famciclovir and acyclovir in patients with uncomplicated herpes zoster. *J Microbiol Immunol Infect.* 2004 Apr; 37(2):75-81. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15181487>.

RATIONALE: A small randomised controlled trial (n=55), in which the efficacy and safety of famciclovir administered at 250mg three times daily and aciclovir 800mg five times daily, both for seven days, for the treatment of acute uncomplicated herpes zoster in immunocompetent adults was compared. Results indicated that both famciclovir and aciclovir were comparable in healing lesions, and in the cessation of acute-phase pain. The authors conclude that famciclovir, administered less frequently and at lower unit doses than aciclovir, is an effective treatment for uncomplicated herpes zoster.

Eye Infections

Conjunctivitis:

1. The College of Optometrists. Conjunctivitis (bacterial). 2016 Jan. Available from: <https://www.college-optometrists.org/guidance/clinical-management-guidelines/conjunctivitis-bacterial-.html>.

RATIONALE: A college of Optometrists guideline, providing clear step-by-step descriptions of the aetiology, predisposing factors, symptoms, signs, differential diagnoses, and management of conjunctivitis. This guideline states that conjunctivitis often resolves in five to seven days without treatment, and suggests that patients can bathe/clean the eyelids with lint or cotton wool dipped in sterile saline or boiled (cooled) water to remove crusting. The patient should be advised that the condition is contagious, so towels should not be shared. Treatment with topical antibiotics for bacterial cases may improve short-term outcomes, and render the patient less infectious to others.

2. Jefferis J, Perera R, Everitt H, van Weert H, Rietveld R, Glasziou P et al. Acute infective conjunctivitis in primary care: who needs antibiotics? An individual patient data meta-analysis. *Br J Gen Pract.* 2011 Sep; 61(590):542-548. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3162176/pdf/bjgp61-e542.pdf>.

RATIONALE: A systematic review and meta-analysis of three trials and 622 patients with both viral and bacterial acute conjunctivitis. 80% (246/308) of patients who received

Management and treatment of common infections-Antibiotic guidance for primary care

antibiotics, and 74% (233/314) of controls were cured at day seven. Overall, six of 100 experienced clinical benefit (8% difference; 95% CI 1% to 14%) at seven days. Subgroups that showed a significant benefit from antibiotics were patients with purulent discharge, which is more indicative of bacterial infection (RD 0.09; 91% difference; 95% CI 0.01 to 0.17), and patients with mild severity of red eye (RD 0.10; 90% difference; 95% CI 0.02 to 0.18). The authors conclude that acute conjunctivitis seen in primary care can be thought of as a self-limiting condition, with most patients getting better regardless of antibiotic therapy. Patients with purulent discharge or a mild severity of red eye may have a small benefit from antibiotic treatment, such as chloramphenicol 0.5% eye drops, and fusidic acid 1% gel.

3. American Academy of Ophthalmology (AAO). Conjunctivitis PPP – 2013. 2013 Oct. Available from: <http://www.aao.org/preferred-practice-pattern/conjunctivitis-ppp--2013>.

RATIONALE: An AAO guideline outlining the signs and symptoms of both viral and bacterial conjunctivitis, and stating that conjunctivitis infrequently causes permanent visual loss or structural damage. Treatment of conjunctivitis is ideally directed at the root cause. Indiscriminate use of topical antibiotics or corticosteroids should be avoided, as antibiotics can induce toxicity and corticosteroids can potentially prolong adenoviral infections, and worsen herpes simplex virus infections. Most cases of conjunctivitis are viral and will not respond to anti-bacterial agents, and mild bacterial conjunctivitis is likely to be self-limiting.

4. Rose PW, Harnden A, Brueggemann AB, Perera R, Sheikh A, Crook D et al. Chloramphenicol treatment for acute infective conjunctivitis in children in primary care: a randomised double-blind placebo-controlled trial. *Lancet*. 2005 Jul; 366(9479):37-43.

Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15993231>.

RATIONALE: A randomised controlled trial including 326 school children with a clinical diagnosis of conjunctivitis, which found that most children presenting with acute infective conjunctivitis in primary care get better by themselves, and there is no statistically significant difference between using placebo or chloramphenicol (0.5% eye drops every two hours for the first 24 hours, and then four times daily until 48 hours after the infection had resolved). Clinical cure by day seven occurred in 83% of children given placebo, compared to 86% of children given chloramphenicol (RD 3.8%; 95% CI -4.1% to 11%). The authors conclude that most children presenting with acute infective conjunctivitis in primary care will get better by themselves, and do not need treatment with an antibiotic.

5. Sheikh A, Hurwitz B. Antibiotics versus placebo for acute bacterial conjunctivitis (Review). *Cochrane Database Syst Rev*. 2006 Apr; 19(2):1-21. Available from:

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001211.pub2/epdf>.

RATIONALE: A systematic review and meta-analysis of 11 randomised controlled trials (n=3,673), looking specifically at clinical and microbiological remission rates, in patients with acute bacterial conjunctivitis, aged greater than one month. The diagnosis may have been on clinical or microbiological grounds, and acute was defined as symptoms of less than four weeks duration. Findings indicated that topical antibiotics (ciprofloxacin 0.3% one to two drops every two hours whilst awake on the first day, and every four hours whilst awake on day two; fusidic acid gel 1% four times daily over a week; chloramphenicol 0.5% eye drops) were of benefit in improving early (days two to five)

Management and treatment of common infections-Antibiotic guidance for primary care

clinical (RR 1.36; 95% CI 1.15 to 1.61), and microbiological (RR 1.55; 95% CI 1.37 to 1.76) remission rates. At the late time point (days six to 10), antibiotics were found to still confer modest benefits in clinical remission (RR 1.21; 95% CI 1.10 to 1.33), and microbiological cure rates (RR 1.37; 95% CI 1.24 to 1.52). By days six to 10, 41% (95% CI 38 to 43) of cases had resolved in those receiving placebo. No data was found on the cost-effectiveness of antibiotics. No serious outcomes were reported in either the active or placebo arms of these trials, suggesting that important sight-threatening complications are an infrequent occurrence. The authors conclude that, although acute bacterial conjunctivitis is frequently self-limiting, the findings from this review suggest that the use of antibiotic eye drops is associated with modestly improved rates of clinical and microbiological remission, in comparison to the use of placebo. Use of antibiotic eye drops should therefore be considered in order to speed the resolution of infection.

6. Rietveld RP, ter Riet G, Bindels PJE, Bink D, Sloos JH, van Weert HCPM. The treatment of acute infectious conjunctivitis with fusidic acid: a randomised controlled trial. *Br J Gen Pract*. 2005 Dec; 55(521):924-930. Available from:

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1570507/pdf/bjpg55-924.pdf>.

RATIONALE: A randomised controlled trial including 163 patients in the Netherlands, which found no statistically significant difference in clinical cure rates at seven days in people using fusidic acid 1% gel four times daily for seven days (62%), compared with people taking a placebo (59%) (RD 5.3%; 95% CI -11% to 18%). The authors conclude that, at seven days, cure rates in the fusidic acid 1% gel and placebo group were similar, but the confidence interval was too wide to clearly demonstrate their equivalence (ARD 5.3%; 95% CI -11 to 18). These findings do not support the current prescription practices of fusidic acid by general practitioners.

7. Medicines.org. *Fucithalmic/Fusidic Acid 1% Viscous Eye Drops*. Available from:

<http://www.medicines.org.uk/emc/medicine/28430> [Accessed: 22nd September, 2016].

RATIONALE: An EMC webpage stating that fucithalmic/fusidic acid 1% viscous eye drops is active against a wide range of Gram-positive organisms, particularly *Staphylococcus aureus*. Other species against which fucithalmic has been shown to have in vitro activity against include: Streptococcus; Neisseria; Haemophilus; Moraxella; Corynebacteria. This website states that fucithalmic/fusidic acid 1% viscous eye drops can be used as treatment for bacterial conjunctivitis, where the organism is known to be susceptible. One drop should be administered into each eye twice daily, and treatment should be continued for at least 48 hours after the eye returns to normal.

Blepharitis:

1. The College of Optometrists. Blepharitis (inflammation of the lid margins). 2016 Feb.

Available from: <http://www.college-optometrists.org/en/utilities/document-summary.cfm/docid/91502CC4-6126-47D9-A707F0E015D55230>.

RATIONALE: A College of Optometrists guideline, providing clear step-by-step descriptions of the assessment, aetiology, and treatment of blepharitis. This guideline states that blepharitis is typically bilateral, and chronic or relapsing, and is bacterial and usually staphylococcal, caused by: direct infection; reaction to staphylococcal exotoxin;

Management and treatment of common infections-Antibiotic guidance for primary care

allergic response to staphylococcal antigen. This guideline recommends lid hygiene as first line measures for symptom control, including: gentle washing; warm compresses; lid massage; lid scrubs; avoidance of cosmetic products. If infection is still present after two weeks of trying simple measures, antibiotic ointment, such as chloramphenicol, can be placed in the eyes twice daily. If lid hygiene and topical treatment fail, a systemic tetracycline, such as doxycycline or oxytetracycline, can be prescribed as maintenance for several weeks or months.

2. Lindsley K, Matsumura S, Hafez E, Akpek EK. Interventions for chronic blepharitis. *Cochrane Database Syst Rev*. 2014 Dec; 5:1-117. Available from:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4270370/pdf/nihms396402.pdf>.

RATIONALE: A systematic review and meta-analysis of 34 studies, involving 2,169 adults with clinically diagnosed blepharitis. With regard to anterior/mixed staphylococcal and seborrheic blepharitis, the results of treatment interventions are mixed, but these may be due to the fact that most studies included participants with blepharitis from various aetiologies. When only cases of anterior blepharitis and blepharoconjunctivitis were included, there was some suggestion that clinical outcomes were better with topical antibiotics, compared with placebo. Studies measuring microbiological outcomes demonstrated that topical antibiotics (chloramphenicol 0.5% eye drops; norfloxacin 0.3% ophthalmic solution; ciprofloxacin ophthalmic solution) were effective in obtaining negative cultures from the ocular surface, but clinical significance was not clear. There were no significant differences between different kinds of antibiotics when compared directly, or with placebo. Studies that evaluated both topical antibiotics and topical steroids did not show clinically significant improvements from baseline individually, or when compared with one another. Although these studies showed that antibiotic therapy significantly decreases bacteriological cultures compared with steroid therapy, bacteriological improvement was not associated with clinical improvement. Mechanical measures, using lid hygiene and/or detergents, demonstrated improvements of signs and symptoms in the majority of participants, with no side-effects. However, the two studies assessing these measures used different types of detergents and comparison groups. Compliance to lid hygiene and lid scrubs may also be an issue in long-term use. Many therapies were studied for the treatment of posterior blepharitis, but due to the variation in medical and mechanical interventions, most comparisons were evaluated only by a single study. Oral doxycycline was observed to have clinical improvements at high (200mg BD) and low (20mg BD) doses, with adverse events occurring more frequently in the high-dose group. Topical cyclosporine was studied long-term (three months) and showed mixed results for clinical tests, when compared with placebo, or topical antibiotics plus steroids. Castor-oil-containing eyedrops were more efficacious than saline eyedrops, in terms of improving tear function, especially stability. The explanation may be that posterior blepharitis is associated with poor meibum secretion, and adding oily substances may help with improving tear film stability. Finally, heat application showed some benefit in terms of patient symptoms, and some effectiveness regarding tear function.

3. Clinical Knowledge Summaries (CKS). Blepharitis. 2015 Oct. Available from:

<http://cks.nice.org.uk/blepharitis#!topicsummary>.

Management and treatment of common infections-Antibiotic guidance for primary care

RATIONALE: A CKS guideline, which found no significant evidence from randomised placebo-controlled trials on topical or oral antibiotics for the treatment of blepharitis. One systematic review (n=2,169), concluded that, although topical antibiotics were shown to provide some symptomatic relief in anterior blepharitis, there is no strong evidence to support their use. The effectiveness of oral antibiotics was further inconclusive. Although randomised controlled trials to support the effectiveness of chloramphenicol in the treatment of blepharitis are lacking, it is a broad spectrum topical antibiotic which is the drug of choice for superficial eye infections. If chloramphenicol is prescribed, 1% eye ointment should be administered twice daily for a six week trial. Oral antibiotics can be prescribed if lid hygiene and topical antibiotics are ineffective. Oxytetracycline and doxycycline are both licensed for the treatment of acne rosacea, which often accompanies blepharitis, so these tetracyclines can be considered suitable options for treatment. These antibiotics should also be prescribed in the presence of Meibomian gland dysfunction. Oxytetracycline should be prescribed at 500mg twice daily for four weeks, followed by 250mg twice daily for a further eight weeks, if required. Doxycycline should be prescribed at 100mg once a day for the first four weeks, followed by 50mg once a day for a further eight weeks, if required. Eyelid hygiene should be also be maintained.

References and rationale – Suspected dental infections in primary care (outside dental setting)

General references:

1. Scottish Dental Clinical Effectiveness Programme (SDCEP). Drug prescribing for dentistry: Dental clinical guidance. 2016 Jan. Available from: <http://www.sdcep.org.uk/wp-content/uploads/2016/03/SDCEP-Drug-Prescribing-for-Dentistry-3rd-edition.pdf>.

RATIONALE: An SDCEP guideline, stating that antibiotics do not cure toothache or odontogenic pain. Severe throbbing toothache without swelling of the soft tissues or pyrexia is usually caused by pulpitis. As an inflammatory condition, temporary relief of the symptoms of pulpitis is best achieved with regular analgesics, whilst the patient accesses definitive dental treatment (often a root canal treatment, or extraction). Irreversible pulpitis is characterised by throbbing toothache, which keeps the patient awake at night, and the tooth responds to hot and cold temperatures. Untreated, this type of toothache will initially resolve for a few days, weeks, or even months. However, the untreated condition may turn into a dental abscess, the symptoms of which are more dangerous than the initial pulpitis. Patients should be strongly advised to seek definitive dental treatment as soon as possible. Analgesics for the temporary relief of toothache include ibuprofen and/or paracetamol. Opioid analgesics, such as codeine, are relatively ineffective against dental pain. In adults, the dose of ibuprofen can be increased, if necessary, to a maximum dose of 2.4g daily. Avoid use in those with hypersensitivity to aspirin, or any other NSAID, including those in whom attacks of asthma, angioedema, urticaria, or rhinitis have been precipitated by aspirin or any other NSAID. Do not prescribe for patients taking a low dose of aspirin daily. Avoid use in pregnant women, and avoid in those with previous or active

Management and treatment of common infections-Antibiotic guidance for primary care

peptic ulcer disease, unless a proton pump inhibitor is co-prescribed. Use with caution in the elderly, patients with allergic disorders, nursing mothers, those taking oral anticoagulants (such as warfarin), those with coagulation defects, those with an inherited bleeding disorder, and those with renal, cardiac, or hepatic impairment. Restrict ibuprofen use to five days or less in those patients taking antihypertensive drugs.

Mucosal ulceration and inflammation (simple gingivitis):

1. Scottish Dental Clinical Effectiveness Programme (SDCEP). Management of acute dental problems: guidance for healthcare professionals. 2013 Mar. Available from: <http://www.sdcep.org.uk/wp-content/uploads/2013/03/SDCEP+MADP+Guidance+March+2013.pdf>.
RATIONALE: An SDCEP guideline stating that mucosal ulcers are caused by a number of conditions, such as: recurrent aphthous stomatitis; herpes viruses; hand, foot and mouth disease; adverse reactions to drugs; nutritional deficiencies; some gastrointestinal diseases; oral lichen planus; oral cancer. These causes should be evaluated and treated. This guideline recommends that salt solution (half a teaspoon of salt dissolved in warm water) or compound sodium chloride mouthwash (300mL diluted with an equal volume of water) should be used to treat simple gingivitis, if more severe, or if pain limits oral hygiene to treat or prevent secondary infection. Both chlorhexidine 0.2% mouthwash and chlorhexidine oromucosal solution, alcohol-free 0.2% (300mL) are recommended for patients (rinse with 10mL for one minute, twice daily). Patients should spit out mouthwash after use. This guideline recommends leaving a 30-minute interval between using chlorhexidine mouthwash and toothpaste, due to staining of teeth and dilution of chlorhexidine. Mouthwash should be used until lesions resolve, or until less pain allows for good oral hygiene.
2. Lang NP, Hase JC, Grassi M, Hammerle CH, Weigel C, Kely E et al. Plaque formation and gingivitis after supervised mouthrinsing with 0.2% delmopinol hydrochloride, 0.2% chlorhexidine digluconate and placebo for 6 months. *Oral Dis*. 1998 Jun; 4(2):105-113. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9680899>.
RATIONALE: A double-blind, randomised six-month clinical trial of 162 patients with gingivitis, comparing the effects of 0.2% chlorhexidine mouthwash or 0.2% delmopinol mouthwash to placebo, on plaque formation and gingivitis. Both mouthwashes were more effective than placebo; however, chlorhexidine mouthwash was statistically significantly more effective in relation to the clinical outcome parameters measured to quantify gingivitis and plaque formation. Findings also indicated that the long-term use of chlorhexidine mouthwash was less tolerated by subjects.
3. Gunsolley JC. A meta-analysis of six-month studies of antiplaque and antigingivitis agents. *J Am Dent Assoc*. 2006 Dec; 137(12):1649-1657. Available from: <http://www.sciencedirect.com/science/article/pii/S0002817714647942>.
RATIONALE: A meta-analysis of seven studies conducted between 1989 and 2005, looking at chlorhexidine 0.12% mouthwash, and evaluating its efficacy at reducing gingival inflammation. Chlorhexidine had the most consistent results, according to the Modified Gingival Index scoring system (a statistically sensitive scoring system that allows for the non-invasive assessment of the severity and extent of gingival inflammation).

4. Berchier CE, Slot DE, Van der Weijden GA. The efficacy of 0.12% chlorhexidine mouthrinse compared with 0.2% on plaque accumulation and periodontal parameters: a systematic review. *J Clin Periodontol*. 2010 Sep; 37(9):829-839. Available from:

<http://www.ncbi.nlm.nih.gov/pubmed/20618550>.

RATIONALE: A systematic review from the Netherlands, aiming to evaluate the effects of 0.12% chlorhexidine versus 0.2% chlorhexidine in the management of gingival inflammation and plaque control. Medline, PubMed and the Cochrane Database were searched for randomised controlled trials and cohort studies. 409 titles and abstracts identified eight eligible publications. Overall, there was no evidence for the benefit of 0.2% over 0.12% in the reduction of gingivitis; however, there was some evidence in favour of 0.2% chlorhexidine regarding the reduction of plaque.

5. Hasturk H, Nunn M, Warbington M, Van Dyke TE. Efficacy of a fluoridated hydrogen peroxide-based mouthrinse for the treatment of gingivitis: a randomized clinical trial. *J Periodontol*. 2004 Jan; 75(1):57-65. Available from:

<http://www.ncbi.nlm.nih.gov/pubmed/15025217>.

RATIONALE: An American placebo controlled trial of 99 patients, looking at the effects of fluoridated hydrogen peroxide-based mouthrinse for the treatment of gingivitis (over 28 days) and teeth whitening (over five months). There was a statistically significant improvement in gingival inflammation in the mouthrinse group compared with the placebo group (p=0.004).

Acute necrotising ulcerative gingivitis:

1. Clinical Knowledge Summaries (CKS). Gingivitis and periodontitis. 2016 Dec. Available from: <https://cks.nice.org.uk/gingivitis-and-periodontitis#!topicsummary>.

RATIONALE: A CKS guideline, recommending that acute necrotising ulcerative gingivitis should be referred to a dentist for urgent assessment and management. During the acute phase, the person should, if possible, use a soft toothbrush to clean their teeth. Once pain subsides, good oral hygiene should be commenced by brushing teeth for two minutes twice a day (in the morning, and last thing at night), preferably with a powered toothbrush. Paracetamol or ibuprofen can be prescribed for pain relief, or chlorhexidine (0.12% or 0.2%) mouthwash, or hydrogen peroxide 6% mouthwash. Metronidazole 400mg three times a day for three days can be prescribed in the presence of systemic signs or symptoms of infection.

2. Preshaw PM. Antibiotics in the treatment of periodontitis. *Dent Update*. 2004 Oct; 31(8):448-450. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/15554049>.

RATIONALE: A review article recommending root surface instrumentation, chemical plaque control (chlorhexidine mouthwash), and oral hygiene advice as the gold standard treatment for acute necrotising ulcerative gingivitis. This review also states that metronidazole (400mg three times daily, for three days) can be added in acute stages, however systemic antibiotics are not usually indicated in the vast majority of periodontal conditions encountered in general dental practice.

Management and treatment of common infections-Antibiotic guidance for primary care

3. Loesche WJ, Syed SA, Laughon BE, Stoll J. The bacteriology of acute necrotizing ulcerative gingivitis. *J Periodontol*. 1982 Apr; 53(4):223-230. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/6122728>.
RATIONALE: A small longitudinal study, in which a total of eight patients with acute necrotising ulcerative gingivitis were included. Those systemically ill (n=3) were treated with metronidazole (200mg TDS), and those with localised symptoms only received standard periodontal therapy. Those systemically ill initially had more microbiological findings. Metronidazole treatment reduced the number of anaerobes, but at a two to three-month follow-up, these had reverted to pre-treatment levels. This study supports the efficacy of metronidazole on anaerobic pathogens in the treatment of acute necrotising ulcerative gingivitis, and highlights the efficacy of standard periodontal treatment.
4. Kuriyama T, Williams DW, Yanagisawa M, Iwahara K, Shimizu C, Nakagawa K et al. Antimicrobial susceptibility of 800 anaerobic isolates from patients with dentoalveolar infection to 13 oral antibiotics. *Oral Microbiol Immunol*. 2007 Aug; 22(4):285-288. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/17600542>.
RATIONALE: A clinical prospective study, looking at the antimicrobial susceptibility of 800 anaerobic isolates from dentoalveolar infections. *P. intermedia* (a common pathogen found in acute necrotising ulcerative gingivitis) was found to be 100% susceptible to metronidazole, thus supporting the use of metronidazole in this condition. Fusobacterium species was found to have good susceptibility to amoxicillin/clavulanic acid, a wide range of cephalosporins, clindamycin, and metronidazole.
5. Dahlen G. Microbiology and treatment of dental abscesses and periodontal-endodontic lesions. *Periodontol 2000*. 2002 Jan; 28(1):206-239. Available from: <http://onlinelibrary.wiley.com/doi/10.1034/j.1600-0757.2002.280109.x/abstract>.
RATIONALE: A retrospective study suggesting that metronidazole is effective against strict anaerobes (common pathogens seen in acute necrotising ulcerative gingivitis). Four studies demonstrated that Prevotella, Porphyromonas, and Fusobacterium were 100% susceptible to metronidazole. Metronidazole can therefore be used in the face of beta-lactamase-producing anaerobes, and is also suitable for penicillin allergic patients.
6. Scottish Dental Clinical Effectiveness Programme (SDCEP). Management of acute dental problems: guidance for healthcare professionals. 2013 Mar. Available from: <http://www.sdcep.org.uk/wp-content/uploads/2013/03/SDCEP+MADP+Guidance+March+2013.pdf>.
RATIONALE: An SDCEP guideline stating that acute necrotising gingivitis should be treated with a compound sodium chloride mouthwash (300mL diluted with an equal volume of water). Both chlorhexidine 0.2% mouthwash and chlorhexidine oromucosal solution, alcohol-free 0.2% (300mL) are recommended for patients (rinse with 10mL for one minute, twice daily). Patients should spit out mouthwash after use. This guideline recommends leaving a 30-minute interval between using chlorhexidine mouthwash and toothpaste, due to staining of teeth and dilution of chlorhexidine. Mouthwash should be used until lesions resolve, or until less pain allows for good oral hygiene.

Pericoronitis:

Management and treatment of common infections-Antibiotic guidance for primary care

1. Scottish Dental Clinical Effectiveness Programme (SDCEP). Management of acute dental problems: guidance for healthcare professionals. 2013 Mar. Available from: <http://www.sdcep.org.uk/wp-content/uploads/2013/03/SDCEP+MADP+Guidance+March+2013.pdf>.
RATIONALE: An SDCEP guideline, stating that pericoronitis is the inflammation and infection of perimolar soft tissue, often provoked by emerging molar teeth. This condition should be managed by referral to a dentist for local surgical treatment, primarily with irrigation or incision and debridement of the lesion. If pain or trismus limit good oral hygiene, treatment with analgesia and either 0.2% chlorhexidine mouthwash (rinse with 10mL for one minute, twice daily) or hydrogen peroxide 6% mouthwash should be recommended. Mouthwash should be used until lesions resolve, or until less pain allows for good oral hygiene. Antibiotics can be added where there is systemic involvement or ongoing symptoms, including metronidazole 400mg three times daily, for three days, or amoxicillin 500mg three times daily, for three days.
2. Ellison SJ. The role of phenoxymethylpenicillin, amoxicillin, metronidazole and clindamycin in the management of acute dentoalveolar abscesses – a review. *Br Dent J*. 2009 Apr; 206(7):357-362. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/19357666>.
RATIONALE: A literature search of over 5,000 references worldwide, recommending the use of metronidazole 200mg three times daily, for three days, as first line treatment in pericoronitis. The author concludes that, given the current climate of evidence-based research, the need to keep antibiotic prescribing to an acceptable minimum, increasing levels of resistance of microorganisms, and widespread hospital infections with 'superbugs', there is a distinct need for appropriate antibiotic prescribing guidelines.
3. Sixou JL, Magaud C, Jolivet-Gougeon A, Cormier M, Bonnaure-Mallet M. Evaluation of the mandibular third molar pericoronitis flora and its susceptibility to different antibiotics prescribed in France. *J Clin Microbiol*. 2003 Dec; 41(12):5794-5797. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC308963/pdf/0390.pdf>.
RATIONALE: A French prospective study, looking at the microbial flora isolated from samples taken from 35 patients with pericoronitis, and evaluating their susceptibility to amoxicillin, pristinamycin (a macrolide), and metronidazole (alone, or in combination with spiramycin). Obligate anaerobes were isolated in 91% of cases, and resistance to metronidazole was not evident in any species. Amoxicillin was highly active against 91.5% of aerobes and anaerobes isolated, and therefore, in severe infections, amoxicillin can be added to treatment with metronidazole.

Dental abscess:

1. Matthews DC, Sutherland S, Basrani B. Emergency management of acute apical abscesses in the permanent dentition: a systematic review of the literature. *J Can Dent Assoc*. 2003 Nov; 69(10):660. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/14611715>.
RATIONALE: A systematic review of the literature, suggesting that in the management of localised acute apical abscess in the permanent dentition, regular analgesia should be used before the abscess can be drained through a pulpectomy, or incision and drainage. Pus should be sent for investigation, where possible. This review indicated that antibiotics are of no additional benefit in the treatment of dental abscess. In the event of systemic

Management and treatment of common infections-Antibiotic guidance for primary care

complications (eg fever, lymphadenopathy, or cellulitis), or for an immunocompromised patient, antibiotics may be prescribed in addition to drainage of the tooth.

2. Dahlen G. Microbiology and treatment of dental abscesses and periodontal-endodontic lesions. *Periodontol* 2000. 2002 Jan; 28(1):206-239. Available from: <http://onlinelibrary.wiley.com/doi/10.1034/j.1600-0757.2002.280109.x/abstract>.
RATIONALE: A retrospective study, recommending that definitive surgical treatment to drain the abscess (through incision, extraction, or removal of necrotic pulp) by a dentist is the primary management of a dentoalveolar abscess. The use of antibiotic treatment is required only in cases where there is evidence of systemic illness, or in the severely immunocompromised. Antibiotic treatment is only used when it is aimed at limiting spread of infection, and in preventing serious complications.
3. Robertson D, Smith AJ. The microbiology of the acute dental abscess. *J Med Microbiol*. 2009 Feb; 58(2):155-162. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/19141730>.
RATIONALE: A review article stating that, despite few well controlled trials, the literature available supports the use of urgent surgical management of the dental abscess, by incision, tooth extraction, or via root canal, in combination with antimicrobial agents, where there is evidence of cellulitis or sepsis.
4. Ellison SJ. The role of phenoxymethylpenicillin, amoxicillin, metronidazole and clindamycin in the management of acute dentoalveolar abscesses – a review. *Br Dent J*. 2009 Apr; 206(7):357-362. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/19357666>.
RATIONALE: A literature search of over 5,000 references worldwide, concluding that there is little evidence-based antibiotic prescribing in the case of dental infections, and to help control the increase of antimicrobial resistance, it is important to only prescribe antimicrobials if indicated. Antimicrobials should be prescribed if there are systemic signs of acute dental abscess, including: pyrexia; trismus; lymphadenopathy; gross facial or ocular oedema; dysphagia; tachycardia; malaise; rigors.
5. Kuriyama T, Absi EG, Williams DW, Lewis MA. An outcome audit of the treatment of acute dentoalveolar infection: impact of penicillin resistance. *Br Dent J*. 2005 Jun; 198(12):759-763. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/15980845>.
RATIONALE: An audit of 112 patients with dentoalveolar infection who underwent incisional or dental pulp chamber drainage, and were then assigned to one of six different antibiotic regimes. No significant differences in outcome were found with any regime, and the presence of penicillin-resistant strains did not influence the outcome where surgical management was already established, questioning the indication for antibiotics at all. This study did not look at cases where antibiotics were not prescribed in cases where adequate drainage had not been achieved, and reinforced that it would be unethical to undertake such a study where systemic signs of infection were evident.
6. Scottish Dental Clinical Effectiveness Programme (SDCEP). Management of acute dental problems: guidance for healthcare professionals. 2013 Mar. Available from: <http://www.sdcep.org.uk/wp-content/uploads/2013/03/SDCEP+MADP+Guidance+March+2013.pdf>.

Management and treatment of common infections-Antibiotic guidance for primary care

RATIONALE: An SDCEP guideline, stating that, in dental abscess, if the airway is compromised or the patient is having trouble swallowing their own saliva, or are unable to push their tongue forward out of their mouth, the patient should be admitted urgently to emergency care. This guideline recommends that 400mg metronidazole, three times daily, or 500mg amoxicillin, three times daily, can be prescribed for the treatment of severe dental abscess. Concentrations can be increased at the site of infection above the minimum inhibitory concentration needed to eradicate the infecting bacteria, especially for more resistant bacteroides species. In the case of severe infection, the dose of amoxicillin can be doubled (from 500mg to 1g three times daily), as can the dose of phenoxymethylpenicillin (from 500mg to 1g four times daily). Clindamycin, clarithromycin, cephalosporins, and amoxicillin/clavulanate should be avoided as first line agents, as there is no advantage over amoxicillin, phenoxymethylpenicillin, metronidazole, or erythromycin. Clindamycin and amoxicillin/clavulanate can be used as second line agents where infection has not resolved; however, there is an increased risk of *Clostridium difficile*. An alternative diagnosis should be sought if the abscess is not resolving with local measures, in combination with first line antimicrobials. Clarithromycin can be used in true penicillin allergy, at a dose of 500mg, twice daily, for up to five days.

7. Eick S, Pfister W, Straube E. Antimicrobial susceptibility of anaerobic and capnophilic bacteria isolated from odontogenic abscesses and rapidly progressive periodontitis. *Int J Antimicrob Agents*. 1999 Jun; 12(1):41-46. Available from:

<https://www.ncbi.nlm.nih.gov/pubmed/10389646>.

RATIONALE: A German prospective study, looking at the susceptibility of microbiological samples taken from 140 patients with dentoalveolar disease (periodontitis or odontogenic abscess). Findings indicated that the isolates consisted mainly of Gram-negative anaerobes, which were highly susceptible to metronidazole and clindamycin. 6% of the periodontal isolates (plaque), and 22% of the abscess isolates (pus) were resistant to penicillin, but were highly susceptible to clindamycin and metronidazole. The authors conclude that both clindamycin and metronidazole could be useful antibiotics and could be recommended for empirical antimicrobial treatment.

8. Kuriyama T, Absi EG, Williams DW, Lewis MA. An outcome audit of the treatment of acute dentoalveolar infection: impact of penicillin resistance. *Br Dent J*. 2005 Jun; 198(12):759-763. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/15980845>.

RATIONALE: A prospective study looking at the antimicrobial susceptibility of 800 anaerobic isolates from dentoalveolar infection in Japan. The authors conclude that amoxicillin is still advocated as a first line agent, as it exhibits a high level of activity against the majority of organisms responsible for dentoalveolar infections. Resistance was, however, seen in beta-lactamase-producing *Prevotella* species, and therefore, in more severe infections, these organisms need to be covered. Amoxicillin/clavulanate, clindamycin, and metronidazole have excellent activity against *Prevotella* species and other anaerobes found in dentoalveolar infections. Susceptibility and resistance profiles of cephalosporins were found to be similar to amoxicillin, and therefore, have no advantage over amoxicillin, and are associated with greater side-effects and resistance.

Management and treatment of common infections-Antibiotic guidance for primary care

9. Ellison SJ. An outcome audit of three day antimicrobial prescribing for the acute dentoalveolar abscess. *Br Dent J*. 2011 Dec; 211(12):591-594. Available from:

<https://www.ncbi.nlm.nih.gov/pubmed/22193484>.

RATIONALE: An audit of 6,586 patients in pain attending the Primary Care Department at Bristol Dental Hospital, between 2005 and 2007. Following drainage and removal of the cause of infection, only the 2.9% (n=188) with systemic involvement were given three days amoxicillin 250mg, three times daily (first line), or three days metronidazole 200mg, three times daily (second line). The combination of drainage and a three day antibiotic regimen in these patients was effective in 100% of cases, where review was obtained.

10. Martin MV, Longman LP, Hill JB, Hardy P. Acute dentoalveolar infections: an investigation of the duration of antibiotic therapy. *Br Dent J*. 1997 Aug; 183(4):135-137. Available from:

<https://www.ncbi.nlm.nih.gov/pubmed/9293130>.

RATIONALE: A prospective study, looking at 759 patients with acute dental abscess (and associated systemic features), managed with either abscess drainage or tooth extraction, in combination with amoxicillin, clindamycin, or erythromycin. The outcome measured was the resolution of systemic symptoms (swelling and temperature) after two to three days, and then again at 10 days. Findings indicated that 98.6% of cases had resolution of symptoms at the first review when antibiotics were discontinued, and these patients did not need an additional course of antibiotics at a later stage. The authors conclude that, if drainage has been established, antibiotics may not be needed beyond two to three days. Clinical review should be conducted at three days, where possible. Antibiotics may be stopped if symptoms have resolved, or can be continued to five days duration.

11. Kulik EM, Lenkeit K, Chenux S, Meyer J. Antimicrobial susceptibility of periodontopathogenic bacteria. *J Antimicrob Chemother*. 2008 May; 61(5):1087-1091.

Available from: <https://www.ncbi.nlm.nih.gov/pubmed/18326855>.

RATIONALE: A retrospective, laboratory-based microbiological study based in Switzerland, looking at the resistance profiles of three predominant periodontopathogenic bacteria isolated from dental abscesses over a 14-year period. Findings indicated that there was limited antibiotic resistance to phenoxymethylpenicillin, amoxicillin/clavulanic acid, clindamycin, tetracycline, and metronidazole. The study reiterated the polymicrobial nature of periodontal infections and that, while resistance may well be present amongst commensal flora, resistance to individual species implicated in dental abscesses is not currently an issue.

Management and treatment of common infections-Antibiotic guidance for primary care

General Comments on Selected Antibiotics and Doses Recommended

- Lewis RE, Klepser ME, Ernst EJ, Snabes MA, Jones RN. Comparison of oral immediate-release (IR) and extended-release (ER) metronidazole bactericidal activity against *Bacteroides* spp. using an in vitro model of infection. *Diagn Microbiol Infect Dis*. 2000 May; 37(1):51-55. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10794941>.

RATIONALE: A prospective study using an in vitro infection model inside of an anaerobic chamber, simulating the human serum pharmacokinetic profile of oral metronidazole regimens. Findings indicated that the rapid bactericidal activity in vitro of metronidazole administered as a simulated extended-release formulation at 750-1,500mg/day to be equivalent to metronidazole 500mg three times daily. This confirms that metronidazole exhibits rapid, concentration-dependent bactericidal activity over a broad range of clinically achieved concentrations against *Bacteroides* species, and demonstrates a prolonged post-antibiotic effect (>3 hours). This supports the 400mg three times daily dosing regimen over 200mg, as 400mg will attain about twice the tissue concentrations, and as killing rate is concentration-dependent, this will be improved.
- Cudmore SL, Delgaty KL, Hayward-McClelland SF, Petrin DP, Garber GE. Treatment of infections caused by metronidazole-resistant *Trichomonas vaginalis*. *Clin Microbiol Rev*. 2004 Oct; 17(4):783-793. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC523556/>.

RATIONALE: A review article discussing different dosing regimens (250mg three times daily; 500mg twice daily; 2g single dose) of oral metronidazole. This article states that the concentration of metronidazole in serum, specifically peak concentration in plasma and minimum lethal concentration, are dependent on dosage. All three of the oral dose regimens achieve peak concentrations in plasma in one to two hours, and the height of the peak is proportional to the dose. Therefore, doubling the dose will double the height of the peak above the minimum lethal concentration, before slow, steady elimination.
- Medicines.org. *Flagyl 400mg Tablets*. Available from: <https://www.medicines.org.uk/emc/medicine/21216> [Accessed: 23rd September, 2016].

RATIONALE: An EMC webpage outlining the therapeutic indications and side-effects of 400mg metronidazole tablets. This webpage states that the frequency of adverse events are either rare, very rare, or not known. Serious adverse reactions occur rarely with standard recommended regimens.
- Pahkla ER, Koppel T, Saag M, Pahkla R. Metronidazole concentrations in plasma, saliva and periodontal pockets in patients with periodontitis. *J Clin Periodontol*. 2005 Feb; 32(2):163-166. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15691346>.

RATIONALE: A prospective study aiming to compare the concentrations of metronidazole in plasma, saliva, and gingival crevice fluid in patients with periodontitis, after multiple administration. 11 patients with severe generalised adult periodontitis participated in the study, and metronidazole concentrations in all fluids were measured two hours after the last dose. The authors conclude that metronidazole penetrates well into gingival crevice fluid and saliva. General pharmacokinetic data of metronidazole can be applied in the

Management and treatment of common infections-Antibiotic guidance for primary care

treatment of periodontal disease, and in the design of respective treatment regimens.

5. Lamp KC, Freeman CD, Klutman NE, Lacy MK. Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials. *Clin Pharmacokinet.* 1999 May; 36(5):353-373. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10384859>.

RATIONALE: A review article covering the pharmacokinetics of metronidazole, and highlighting that the volume of distribution at steady state in adults is 0.51 to 1.1L/kg. This means that, as body mass increases, the tissue concentrations decrease. Metronidazole reaches 60-100% of plasma concentrations in most tissues studied. As the BMI of the general population is increasing, it is likely that higher doses of metronidazole will be needed to attain similar concentrations attained in patients in trials undertaken more than 10 years ago.

6. Wexler H. Metronidazole resistance in *Bacteroides fragilis*: an integrated approach. National Institutes of Health. 2015 Nov. Available from: <http://grantome.com/grant/NIH/R21-AI109545-02>.

RATIONALE: A large prospective laboratory study seeking to identify mechanisms that confer metronidazole resistance in *Bacteroides fragilis*, using an integrated approach combining classical genetics, Next Generation Sequencing technology, and molecular manipulation to relate function to specific genes. This study determined susceptibility of 579 different anaerobes, and found that the minimum inhibitory concentration levels were similar in oral bacteria to other anaerobes. The authors conclude that the same antibiotics used for *Bacteroides fragilis* throughout the body can also be used for dental infections.

7. Poulet PP, Duffaut D, Barthet P, Brumpt I. Concentrations and in vivo antibacterial activity of spiramycin and metronidazole in patients with periodontitis treated with high-dose metronidazole and the spiramycin/metronidazole combination. *J Antimicrob Chemother.* 2005 Mar; 55(3):347-351. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15695539>.

RATIONALE: A prospective, parallel-group, small but detailed randomised controlled trial, demonstrating that metronidazole 500mg three times daily alone, or in combination with spiramycin (1,500,000 units, plus 250mg metronidazole) are effective treatments for active periodontitis. The metronidazole at 250mg and 500mg three times daily consistently exceeds the MICs for the pathogens isolated in the corresponding sites. Most of the bacterial species were eradicated during treatment and at follow-up. The authors conclude that the currently used metronidazole dose of 250mg three times daily could be sufficient for the treatment of active periodontitis. However, as killing by metronidazole is time dependent, and it is therefore better to attain crevice fluid concentrations several times that of the measured MICs, 400mg three times daily can be recommended.

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Abbreviations

°C = Degrees centigrade

ABRS = Acute bacterial sinusitis

AIDS = Acquired immune deficiency syndrome

AKI = Acute kidney infection

AmB = Amphotericin B deoxycholate

AMT = Abbreviated mental test

AOM = Acute otitis media

AOM-SOS = Acute Otitis Media Severity of Symptoms Scale

AOR = Adjusted odds ratio

ARD = Adjusted risk difference

ARR = Adjusted risk ratio

ASB = Asymptomatic bacteriuria

ASD = Autism spectrum disorder

AUC = Area under the curve

BD = Twice daily

B-haemolytic = Beta-haemolytic

BMI = Body mass index

BP = Blood pressure

CAP = Community-acquired pneumonia

C. difficile = *Clostridium difficile*

CDAD = *Clostridium difficile*-associated disease

CFU = Colony-forming unit

CI = Confidence interval

COPD = Chronic obstructive pulmonary disease

COX2 = Cyclooxygenase-2

CPD = Continued professional development

CRB65 = Confusion; Respiratory rate; BP systolic; Age >65

CrCl = Creatinine clearance

CRP = C-reactive protein

d = Day

Management and treatment of common infections-Antibiotic guidance for primary care

DU = Duodenal ulcer

E. coli = *Escherichia coli*

eGFR = Estimated glomerular filtration rate

ESBL(s) = Extended-spectrum beta-lactamase(s)

FEV1 = FEV1/FVC ratio

FeverPAIN = Fever; Purulence; Attend rapidly; Inflamed tonsils; No cough or coryza

g = Gram(s)

GABHS = Group A Beta-haemolytic Streptococci

GAS = Group A Streptococci

GC = Gonorrhoea

GFR = Glomerular filtration rate

GORD = Gastro-oesophageal reflux disease

GP(s) = General practitioner(s)

GU = Gastric ulcer

GUM = Genitourinary medicine

H. influenzae = *Haemophilus influenzae*

HIV = Human immunodeficiency virus

H. pylori = *Helicobacter pylori*

HR = Hazard ratio

i/r = Immediate release

iGAS = Invasive Group A Streptococci

IM = Intramuscular

IV = Intravenous

kg = Kilogram(s)

K. pneumoniae = *Klebsiella pneumoniae*

l = Litre(s)

m/r = Modified release

MALToma = Mucosa-associated lymphoid tissue lymphoma

mcg = Microgram(s)

MD = Mean difference

MDRD = Modification of Diet in Renal Disease

MDREB = Multi-drug resistant Enterobacteriaceae

Management and treatment of common infections-Antibiotic guidance for primary care

mg = Milligram(s)

MIC(s) = Minimum inhibitory concentration(s)

ml = Millilitre(s)

M. pneumoniae = *Mycoplasma pneumoniae*

MRC = Medical Research Council dyspnoea (breathlessness) scale

MRSA = Methicillin-resistant *Staphylococcus aureus*

MSM = Men who have sex with men

MSU = Midstream urine

n = Number

NI(s) = Neuraminidase inhibitor(s)

NNT = Number needed to treat

NNTB = Number needed to benefit

NNTH = Number needed to harm

NPV = Negative predictive value

NSAID(s) = Non-steroidal anti-inflammatory drug(s)

OD = Once daily

OPAT = Outpatient parenteral antibiotic therapy

OR(s) = Odds ratio(s)

PHN = Post-herpetic neuralgia

PID = Pelvic inflammatory disease

P. intermedia = *Prevotella intermedia*

PNS *S. pneumoniae* = Penicillin-nonsusceptible *Streptococcus pneumoniae*

PP = Per-protocol

PPI = Proton pump inhibitor

PPV = Positive predictive value

PVL = Panton-Valentine Leukocidin

QDS = Four times daily

RCT(s) = Randomised controlled trial(s)

RD = Risk difference

RR = Relative risk

RTI(s) = Respiratory tract infection(s)

SAT = Stool antigen test

Management and treatment of common infections-Antibiotic guidance for primary care

S. aureus = *Staphylococcus aureus*

S. pneumoniae = *Streptococcus pneumoniae*

SLCI = Symptomatic laboratory-confirmed influenza

STI(s) = Sexually transmitted infection(s)

T = Temperature

TARGET = Treat Antibiotics Responsibly: Guidance, Education, Tools

TDS = Three times daily

TMP-SMX = Trimethoprim sulfamethoxazole

TSS = Toxic shock syndrome

U = Units

UBT = Urea breath test

UHD(s) = Ulcer healing drug(s)

UK = United Kingdom

USA = United States of America

UTI(s) = Urinary tract infection(s)

WCC = White cell count