



Public Health
England

Protecting and improving the nation's health

Management of infection guidance for primary care for consultation and local adaptation

About Public Health England

Public Health England exists to protect and improve the nation's health and wellbeing, and reduce health inequalities. We do this through world-class science, knowledge and intelligence, advocacy, partnerships and the delivery of specialist public health services. We are an executive agency of the Department of Health, and are a distinct delivery organisation with operational autonomy to advise and support government, local authorities and the NHS in a professionally independent manner.

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Foreword – aims and adaptations

Audience

- primary care prescribers in general practice and out of hours settings including doctors, nurses and pharmacists
- those giving first point of contact for infections
- others giving symptomatic advice on infections - pharmacists and nurses

Aims

- to provide a simple, effective, economical and empirical approach to the treatment of common infections
- to target the use of antibiotics and antifungals in primary care
- to minimise the emergence of bacterial resistance in the community

Implication

- the guidance should lead to more appropriate antibiotic use
- use of this guidance may increase or decrease laboratory workload
- change in laboratory workload may have financial implications for laboratories and primary care commissioners

Production

- the templates have been produced in consultation with GPs and specialists in the field
- they are in agreement with other guidance, including **CKS**, **SIGN** and **NICE**
- the guidance is fully referenced and graded
- the guidance is not all-encompassing, as it is meant to be 'quick reference'
- if more detail is required we suggest referral to the websites and references quoted
- the guidance is updated every three years; or more frequently if there are significant developments or publications in the field

Poster presentation of guidance

- the five summary tables are designed to be printed out as posters to use in the surgery
- the rationale and evidence is designed to be used as an educational tool for you and your colleagues to share with patients as needed

Local adaptation

- major guidance changes are discouraged; Word format allows minor tweaks reflecting local service delivery, antimicrobial resistance and sampling protocols
- create local ownership agreement for the guidance; disseminate in collaboration between primary care clinicians, laboratories and secondary care providers

Summary tables: infections in primary care

Principles of Treatment

1. This guidance is based on the best available evidence but use professional judgement and involve patients in management decisions.
2. It is important to initiate antibiotics as soon as possible in severe infection.
3. Where an empirical therapy has failed or special circumstances exist, microbiological advice can be obtained from ** ☎ **
4. Prescribe an antibiotic only when there is likely to be a clear clinical benefit.
5. Consider a 'No' or 'Back-up/Delayed', antibiotic strategy for acute self-limiting upper respiratory tract infections,^{1A+} and mild UTI symptoms.
6. Limit prescribing over the telephone to exceptional cases.
7. 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 risk of *Clostridium difficile*, MRSA and resistant UTIs.
8. A dose and duration of treatment for adults is usually suggested, but may need modification for age, weight and renal function. In severe or recurrent cases consider a larger dose or longer course.
9. Child doses are provided when appropriate and can be accessed through the ☺ symbol.
10. Please refer to BNF for further dosing and interaction information (e.g. interaction between macrolides and statins) if needed and please check for hypersensitivity.
11. Lower threshold for antibiotics in immunocompromised or those with multiple morbidities; consider culture and seek advice.
12. Avoid widespread use of topical antibiotics (especially those agents also available as systemic preparations, e.g. fusidic acid).
13. In **pregnancy**, take specimens to inform treatment, use this guidance alternative or seek expert advice. **Penicillins, cephalosporins and erythromycin** are not associated with increased risks. If possible, avoid **tetracyclines, quinolones, aminoglycosides, azithromycin, clarithromycin**, high dose **metronidazole** (2g stat) unless the benefits outweigh the risks. 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.
14. This guidance should not be used in isolation; it should be supported with patient information about back-up/delayed antibiotics, infection severity and usual duration, clinical staff education, and audits. Materials are available on the RCGP **TARGET** website.
15. This guidance is developed alongside the **NHS England Antibiotic Quality Premium**. In 2017/19 QP expects: at least a 10% reduction in the number of *E. coli* blood stream infections across the whole health economy; at least a 10% reduction in trimethoprim:nitrofurantoin prescribing ratio for UTI in primary care, and at least a 10% reduction in trimethoprim items in patients ≥ 70 years, based on CCG baseline data from 2015/16; and sustained reduction in antimicrobial items per STAR-PU equal to or below England 2013/14 mean value.

ILLNESS	GOOD PRACTICE POINTS	DRUG	ADULT DOSE Click on ☺ for child doses	DURATION OF TREATMENT
UPPER RESPIRATORY TRACT INFECTIONS¹				
Influenza treatment PHE Influenza For prophylaxis see: NICE Influenza	Annual vaccination is essential for all those at risk of influenza. For otherwise healthy adults antivirals not recommended. Treat 'at risk' patients, when influenza is circulating in the community and ideally within 48 hours of onset (do not wait for lab report) or in a care home where influenza is likely. At risk: pregnant (including up to two weeks post-partum), 65 years or over, chronic respiratory disease (including COPD and asthma), significant cardiovascular disease (not hypertension), immunocompromised, diabetes mellitus, chronic neurological, renal or liver disease, morbid obesity (BMI ≥ 40). Use 5 days treatment with oseltamivir 75mg bd. If resistance to oseltamivir or severe immunosuppression, use zanamivir 10mg BD (2 inhalations by diskhaler for up to 10 days) and seek advice. See PHE Influenza guidance for treatment of patients under 13 years or in severe immunosuppression (and seek advice).			
Acute sore throat CKS FeverPAIN	Avoid antibiotics as 90% resolve in 7 days ^{1A+} without, and pain only reduced by 16 hours. ^{2A+} Use FeverPAIN Score : Fever in last 24h, Purulence, Attend rapidly under 3d, severely Inflamed tonsils, No cough or coryza). ^{3B+,4B+} Score 0-1: 13-18% streptococci, use NO antibiotic strategy; 2-3: 34-40% streptococci, use 3 day back-up antibiotic; 4 or more: 62-65% streptococci, use immediate antibiotic if severe, or 48hr short back-up prescription. ^{5A-} Always share self-care advice & safety net. Antibiotics to prevent Quinsy NNT >4000. ^{4B-} Antibiotics to prevent Otitis media NNT 200. ^{2A+} 10d penicillin lower relapse vs 7d in <18yrs. ⁸	Phenoxymethylpenicillin ^{5B-} <i>Penicillin Allergy:</i> clarithromycin <i>Pregnant & penicillin allergy:</i> erythromycin ^{10A+,12B-}	500mg QDS ☺ or 1G BD ^{6A+} (500mg QDS when severe ^{7D}) 250-500mg BD ☺ 500mg QDS ^{10A+}	10 days ^{8A-} 5 days ^{9A+} 5 days ^{9A+,10D}
Acute Otitis Media (child doses) CKS OM NICE feverish children	Optimise analgesia and target antibiotics ^{2,3B-} AOM resolves in 60% in 24hrs without antibiotics, which only reduce pain at 2 days (NNT15) and does not prevent deafness. ^{4A+} Consider 2 or 3-day delayed ^{1A+} or immediate antibiotics for pain relief if: <2 years AND bilateral AOM (NNT4) or bulging membrane and ≥ 4 marked symptoms. ⁵⁻⁷⁺ All ages with otorrhoea NNT3. ^{8A+} Abx to prevent Mastoiditis NNT >4000. ^{9B-}	Amoxicillin ^{10A+} <i>Penicillin Allergy:</i> erythromycin ^{11D}	Child doses Neonate 7-28 days 30mg/kg TDS 1 month-1 yr: 125mg TDS 1-5 years: 250mg TDS 5-18 years: 500mg TDS <2 years 125mg QDS 2-8 years 250mg QDS 8-18 years 250-500mg QDS	5 days ^{13A+} 5 days ^{13A+}
Acute Otitis Externa CKS OE	First use analgesia. Cure rates similar at 7 days for topical acetic acid or antibiotic +/- steroid. ^{1A+} If cellulitis/disease extending outside ear canal, start oral antibiotics & refer to exclude malignant OE ^{2A+}	<i>First Line:</i> acetic acid 2% <i>Second Line:</i> neomycin sulphate with corticosteroid ^{3A-,4D}	1 spray TDS 3 drops TDS	7 days 7 days min to 14 days max ^{1A+}

ILLNESS	GOOD PRACTICE POINTS	DRUG	ADULT DOSE <small>Click on ☺ for child doses</small>	DURATION OF TREATMENT
Acute Rhinosinusitis ^{5C} CKS RS	Avoid antibiotics as 80% resolve in 14 days without; they only offer marginal benefit after 7 days NNT15. ^{2,3A+} Use adequate analgesia. ^{4B+} Consider 7-day delayed or immediate antibiotic when purulent nasal discharge NNT8. ^{1,2A+} In persistent infection use an agent with anti-anaerobic activity eg. co-amoxiclav. ^{6B+}	Amoxicillin ^{4A+,7A} or doxycycline or phenoxymethylpenicillin ^{8B} <i>For persistent symptoms:</i> co-amoxiclav ^{6B+}	500mg TDS ☺ 1g if severe ^{11D} 200mg stat then 100mg OD 500mg QDS ☺ 625mg TDS	7 days ^{9A+} 7 days 7 days 7 days 7 days
LOWER RESPIRATORY TRACT INFECTIONS				
Note: Low doses of penicillins are more likely to select out resistance ¹ , we recommend 500mg of amoxicillin. Do not use quinolone (ciprofloxacin, ofloxacin) first line due to poor pneumococcal activity. ^{2B-} Reserve all quinolones (including levofloxacin) for proven resistant organisms.				
Acute cough bronchitis CKS ⁶ NICE 69	Antibiotic little benefit if no co-morbidity. ^{1-4A+} Consider 7d delayed antibiotic with advice. ^{1,5A} Symptom resolution can take 3 weeks. Consider immediate antibiotics if > 80yr and ONE of: hospitalisation in past year, oral steroids, diabetic, congestive heart failure OR > 65yrs with 2 of above. Consider CRP test ^{1A,4} if antibiotic being considered. If CRP<20mg/L no antibiotics, 20-100mg/L delayed, CRP >100mg immediate antibiotics.	Amoxicillin or doxycycline	500mg TDS ☺ 200mg stat then 100mg OD	5 days ^{4A+} 5 days ^{4A+}
Acute exacerbation of COPD NICE 12 GOLD	Treat exacerbations promptly with antibiotics if purulent sputum and increased shortness of breath and/or increased sputum volume. ^{1-3B+} Risk factors for antibiotic resistant organisms include co-morbid disease, severe COPD, frequent exacerbations, antibiotics in last 3 months. ²	Amoxicillin or doxycycline or clarithromycin <i>If resistance:</i> co-amoxiclav	500mg TDS 200mg stat/100mg OD 500mg BD 625mg TDS	5 days ^{4C} 5 days ^{4C} 5 days ^{4A} 5 days ^{4A}
Community acquired pneumonia-treatment in the community ^{2,3} BTS 2009 NICE 191	Use CRB65 score to guide mortality risk, place of care & antibiotics ¹ Each CRB65 parameter scores 1: Confusion (AMT<8); Respiratory rate >30/min; BP systolic <90 or diastolic ≤60; Age ≥65; Score 3-4 urgent hospital admission; Score 1-2 intermediate risk consider hospital assessment; Score 0 low risk: consider home based care. Always give safety-net advice and likely duration of symptoms. Mycoplasma infection is rare in >65s. ¹	IF CRB65=0: amoxicillin ^{A+} or clarithromycin ^{A-} or doxycycline ^D IF CRB65=1,2 & AT HOME, clinically assess need for dual therapy for atypicals: amoxicillin ^{A+} AND clarithromycin ^{A-} or doxycycline alone	500mg TDS ☺ 500mg BD ☺ 200mg stat/100mg OD 500mg TDS ☺ 500mg BD ☺ 200mg stat/100mg OD	CRB65=0: use 5 days. Review at 3 days & extend to 7-10 days if poor response. 7-10 days
URINARY TRACT INFECTIONS – refer to PHE UTI guidance for diagnosis information				
Note: As antimicrobial resistance and <i>Escherichia coli</i> bacteraemia is increasing, use nitrofurantoin first line, ^{16B-} always give safety net and self-care advice, and consider risks for resistance. ^{1D} Give TARGET UTI leaflet.				
UTI in adults (lower) PHE URINE SIGN CKS women CKS men RCGP UTI clinical module SAPG UTI	Treat women with severe/or ≥3 symptoms. ^{1A+,3D} All patients first line antibiotic: nitrofurantoin if GFR >45mls/min; if GFR 30-45 ^{22B+,24B+} only use if resistance and no alternative. Women (mild/≤ 2 symptoms): ^{1A+} Pain relief, ^{42A-} and consider back-up/ delayed antibiotic. ^{19A+} If urine not cloudy, 97% NPV of no UTI. ^{4A-} If urine cloudy, use dipstick to guide treatment: nitrite, leucocytes, blood all negative 76% NPV; nitrite plus blood or leucocytes 92% PPV of UTI. ^{4A-} Men: Consider prostatitis and send MSU ^{1A+} OR if symptoms mild/non-specific, use negative dipstick to exclude UTI. >65 years: treat if fever ≥38°C or 1.5°C above base twice in 12h AND dysuria OR ≥2 other symptoms. ⁴⁰ If treatment failure: always perform culture. ^{1A+}	1st line: nitrofurantoin <i>If low risk of resistance:</i> trimethoprim If 1st line options unsuitable: <i>If GFR<45mls/min:</i> pivmecillinam ^{10A+,12A-,30A+} <i>If high risk of resistance:</i> fosfomycin ^{15B-,16B-,17A-} <i>If organism susceptible:</i> amoxicillin ^{30A+}	100mg m/r BD ^{7A-,9D,31D,32B-,33B+,35A-} 200mg BD ^{12A+,30A+} 400mg stat then 200mg TDS ^{12A+,36B+,37A+,38B+} 3g stat in women; men: 2 nd 3g dose 3d later (unlicensed) ^{1A+,15B-,16B-,17A-} 500mg TDS	3 days Men: 7 days
Catheter in situ: antibiotics will not eradicate asymptomatic bacteriuria. Only treat if systemically unwell or pyelonephritis likely; ^{1B+} do not use prophylaxis for catheter change unless history of catheter-change-associated UTI or trauma. ^{2D} Take sample if new onset of delirium, or two or more symptoms of UTI. ^{3B+}				
Acute prostatitis BASHH, CKS	Send MSU for culture and start antibiotics. ^{1C} 4 week course may prevent chronic prostatitis. ^{1C} Quinolones achieve higher prostate levels. ^{2D}	Ciprofloxacin ^{1C} or ofloxacin ^{1C} 2 nd line: trimethoprim ^{1C}	500mg BD 200mg BD 200mg BD	28 days ^{1C} 28 days ^{1C} 28 days ^{1C}
UTI in pregnancy PHE URINE CKS UKtis	Send MSU for culture: start antibiotics in all with significant bacteriuria, even if asymptomatic. ^{1A} Short-term use of nitrofurantoin is unlikely to cause problems to the foetus. ^{2C,3C} Avoid trimethoprim if low folate status or on folate antagonist.	First line: nitrofurantoin IF susceptible, amoxicillin Second line: trimethoprim Give folate if 1st trimester Third line: cefalexin ^{5B-}	100mg m/r BD 500mg TDS 200mg BD (off-label) 500mg BD	All for 7 days ^{7C}
UTI in Children PHE URINE CKS NICE	Child <3 mths: refer urgently for assessment. ^{1C} Child ≥ 3 mths: use positive nitrite to guide. Start antibiotics: ^{1A+} also send pre-treatment MSU. Imaging: only refer if child <6 months, or recurrent or atypical UTI. ^{1C}	Lower UTI: trimethoprim ^{1A} ☺ or nitrofurantoin ^{1A} ☺ IF susceptible, amoxicillin ^{1C} ☺ Second line: cefalexin ^{1C} ☺ Upper UTI: co-amoxiclav ^{1A} Second line: cefixime ^{2A} ☺		Lower UTI 3 days ^{1A+} Upper UTI 7-10 days ^{1A+}

GENITAL TRACT INFECTIONS Contact UKTIS for information on foetal risks if patient is pregnant.

ILLNESS	GOOD PRACTICE POINTS	DRUG	ADULT DOSE <small>Click on ☺ for child doses</small>	DURATION OF TREATMENT
Vaginal Candidiasis BASHH PHE, CKS	All topical and oral azoles give 75% cure. ^{1A+} In pregnancy avoid oral azoles ^{2B-} and use intravaginal treatment for 7 days. ^{3A+, 2, 4B-}	Clotrimazole ^{1A+} or oral fluconazole ^{1A+} <i>Pregnant:</i> clotrimazole ^{3A+} or miconazole 2% cream ^{3A+}	500mg pess or 10% cream 150mg orally 100mg pessary at night 5g intravaginally BD	Stat Stat 6 nights ^{5C} 7 days
Bacterial vaginosis BASHH PHE CKS	Oral metronidazole (MTZ) is as effective as topical treatment ^{1A+} but is cheaper. Less relapse with 7 day than 2g stat at 4 weeks. ^{3A+} Pregnant^{2A+}/breastfeeding: avoid 2g stat. ^{3A+} Treating partners does not reduce relapse. ^{5B+}	Oral metronidazole ^{1,3A+} or MTZ 0.75% vag gel ^{1A+} or clindamycin 2% crm ^{1A+}	400mg BD or 2g stat 5g applicator at night 5g applicator at night	7 days ^{1A+} Stat ^{3A+} 5 nights ^{1A+} 7 nights ^{1A+}
Gonorrhoea	Antibiotic resistance is now very high. ^{1C} Use IM ceftriaxone plus azithromycin and refer to GUM ^{2,3B}	Ceftriaxone ^{2B+, 3B+} PLUS azithromycin ^{2B+, 3B+}	500mg IM 1g	Stat Stat
Trichomoniasis BASHH PHE CKS	Treat partners and refer to GUM service. ^{1B+} In pregnancy or breastfeeding avoid 2g single dose MTZ. Consider clotrimazole for symptom relief (not cure) if MTZ declined. ^{3B+}	Metronidazole (MTZ) ^{4A+} Clotrimazole ^{3B+}	400mg BD or 2g 100mg pessary at night	5-7 days ^{4A+} Stat ^{4A+} 6 nights ^{3B+}
Pelvic Inflammatory Disease BASHH CKS	Refer woman and contacts to GUM service. ^{1, 2B+} Always culture for gonorrhoea and chlamydia. ^{2B+} If gonorrhoea likely (partner has it, sex abroad, severe symptoms), resistance to quinolones is high, use ceftriaxone regimen, ^{3B+} or refer to GUM.	Metronidazole PLUS ofloxacin ^{1, 2, 4, 6B} or doxycycline ^{1, 2, 4B+} <i>If high risk of gonorrhoea</i> ADD ceftriaxone ^{3, 5C}	400mg BD 400mg BD 100mg BD 500mg IM	14 days 14 days Stat
SKIN INFECTIONS – For MRSA infection see PHE Quick Reference Guide				
Impetigo CKS	For extensive, severe, or bullous impetigo, use oral antibiotics. ^{1C} Reserve topical antibiotics for very localised lesions to reduce the risk of resistance. ^{1, 5C, 4B+} Reserve mupirocin for MRSA. ^{1C}	Oral flucloxacillin ^{2C} <i>If penicillin allergic:</i> oral clarithromycin ^{2C} Topical fusidic acid ^{3B+} MRSA only: mupirocin ^{3A+}	500mg QDS ☺ 250-500mg BD ☺ TDS TDS	7 days 7 days 5 days 5 days
Eczema CKS	If no visible signs of infection, use of antibiotics (alone or with steroids) encourages resistance and does not improve healing. ^{1B} In eczema with visible signs of infection, use treatment as in impetigo. ^{2C}			
Cellulitis CKS	Class I: patient afebrile and healthy other than cellulitis, use oral flucloxacillin alone. ^{1, 2, 5C} Class II febrile & ill, or comorbidity, admit for intravenous treatment, or use OPAT (if available). Class III toxic appearance: admit. ¹ If river or sea water exposure, discuss with specialist.	Flucloxacillin ^{1, 2, 3, 5C} <i>If penicillin allergic:</i> clarithromycin ^{1, 2, 3, 5C} <i>If on statins:</i> doxycycline <i>If unresolved:</i> clindamycin ^{1, 2} <i>If facial:</i> co-amoxiclav ^{4C}	500mg QDS ☺ 500mg BD ☺ 200mg stat then 100mg OD 300-450mg QDS 500/125mg TDS ☺	All for 7 days. If slow response continue for a further 7 days ^{1C}
Leg ulcer PHE CKS	Ulcers always colonised. Antibiotics do not improve healing unless active infection. ^{1A+} If active infection, send pre-treatment swab. ^{3C} Review antibiotics after culture results.	Active infection if cellulitis/increased pain/pyrexia/purulent exudate/odour. ^{2C} <i>If active infection:</i> flucloxacillin or clarithromycin	 500mg QDS ☺ 500mg BD ☺	 As for cellulitis
PVL PHE	Panton-Valentine Leukocidin (PVL) is a toxin produced by 4.9% of <i>S. aureus</i> from boils/abscesses. This bacteria can rarely cause severe invasive infections in healthy people; if found suppression therapy should be given. ^{1C} Send swabs if recurrent boils/abscesses. At risk: close contact in communities or sport; poor hygiene. ^{1C}			
Bites Human: CKS Cat or dog:	Thorough irrigation is important. Assess risk of tetanus, rabies, HIV, hepatitis B/C. ¹ Antibiotic prophylaxis is advised. ^{2B-} Give prophylaxis if cat bite/puncture wound, ² bite to hand, foot, face, joint, tendon, ligament; immunocompromised/diabetic/asplenic/cirrhotic/presence of prosthetic valve or prosthetic joint.	<i>Prophylaxis or treatment:</i> co-amoxiclav <i>If penicillin allergic:</i> metronidazole PLUS doxycycline (cat/dog/man) or metronidazole PLUS clarithromycin (human bite) AND review at 24&48hrs ^{6C}	375-625mg TDS ^{3C} ☺ 400mg TDS ☺ 100mg BD ^{4C} 200-400mg TDS 250-500mg BD ^{5C} ☺	All for 7 days ^{3, 4, 5C}
Scabies CKS	Treat whole body from ear/chin downwards and under nails. If under 2/elderly, also face/scalp. ² Treat all home and sexual contacts within 24hrs. ^{1C}	Permethrin ^{3A+} <i>If allergy:</i> malathion ^{3C}	5% cream 0.5% aqueous liquid	2 applications 1 week apart ^{1C}
Dermatophyte infection - skin CKS CKS foot CKS scalp	Terbinafine is fungicidal: ¹ treatment time shorter than with fungistatic imidazoles. If candida possible, use imidazole. ¹ If intractable, send skin scrapings, ^{2C} and if infection confirmed, use <i>oral</i> terbinafine/itraconazole. ^{3B+, 5C} Scalp: discuss, oral therapy indicated.	Topical terbinafine ^{4A+, 5C} or topical imidazole ^{4A+} or (athlete's foot only): topical undecanoates: Mycota	BD BD BD	1-2 weeks ^{4A+} for 1-2 wks after healing (i.e. 4-6wks) ^{4A}
Dermatophyte infection - nail CKS	Take nail clippings: start therapy only if infection is confirmed by laboratory. ^{1C} Oral terbinafine is more effective than oral azole. ⁶ Liver reactions rare with oral antifungals. ^{2A+} If candida or non-dermatophyte infection confirmed, use oral itraconazole. ^{3B+ 4C} For children, seek specialist advice. ^{3C}	<i>First line:</i> terbinafine ^{6A+} <i>Second line:</i> itraconazole ^{6A+} <i>Third line for very superficial as limited evidence of effectiveness:</i> amorolfine 5% nail lacquer ^{5-8B-}	250mg OD fingers toes 200mg BD fingers toes 1-2x/weekly fingers toes	6 – 12 weeks 3 – 6 months 7 days monthly 2 courses 3 courses 6 months 12 months
Varicella zoster/chicken pox CKS Herpes zoster / shingles CKS	Pregnant/immunocompromised/neonate: seek urgent specialist advice. ^{1B+} Chicken pox: IF onset of rash <24hrs & >14 years or severe pain or dense/oral rash or 2 ^o household case or steroids or smoker, consider aciclovir. ²⁻⁴ Shingles: treat if >50 years ^{5A+} and within 72 hrs of rash ^{6B+} (PHN rare if <50 years ^{7B-}); or if active ophthalmic ^{8B+} or Ramsey Hunt ^{9C} or eczema.	<i>If indicated:</i> aciclovir ^{3B+, 5A+} <i>Second line for shingles if compliance a problem, as ten times cost</i> valaciclovir ^{10B+} or famciclovir ^{11B+}	800mg five times a day 1g TDS 500mg TDS or 750mg BD	7 days ^{3B+} 7 days ^{10B+} 7 days ^{11B+}

ILLNESS	GOOD PRACTICE POINTS	DRUG	ADULT DOSE Click on ☺ for child doses	DURATION OF TREATMENT
Cold sores	Cold sores resolve after 7–10d without treatment. Topical antivirals applied prodromally reduce duration by 12-24hrs. ^{1,2,3B+,4}			
EYE INFECTIONS				
Conjunctivitis CKS	Treat if severe, as most viral or self-limiting. Bacterial conjunctivitis is usually unilateral and <u>also</u> self-limiting; ^{2C} it is characterised by red eye with mucopurulent, not watery, discharge; 65% resolve on placebo by day five. ^{1A+} Fusidic acid has less Gram-negative activity. ³	<i>If severe:</i> ^{4,5B+,6B-} chloramphenicol 0.5% drop and 1% ointment <i>Second line:</i> fusidic acid 1% gel	2 hourly for 2 days then 4 hourly (whilst awake) at night Two times a day	All for 48 hours after resolution

Summary table – dental infections treated in primary care outside dental setting

Derived from the Scottish Dental Clinical Effectiveness Programme 2011 SDCEP Guidelines				
This guidance is not designed to be a definitive guide to oral conditions. It is for GPs for the management of acute oral conditions pending being seen by a dentist or dental specialist. GPs should not routinely be involved in dental treatment and, if possible, advice should be sought from the patient's dentist, who should have an answer-phone message with details of how to access treatment out-of-hours, or telephone 111 (NHS 111 service in England).				
ILLNESS	COMMENTS	DRUG	ADULT DOSE <small>Click on ☺ for child doses</small>	DURATION OF TREATMENT
Mucosal ulceration and inflammation (simple gingivitis)	Temporary pain and swelling relief can be attained with saline mouthwash. ^{1C} Use antiseptic mouthwash if more severe and pain limits oral hygiene to treat or prevent secondary infection. ^{2-8C} The primary cause for mucosal ulceration or inflammation (aphthous ulcers, oral lichen planus, herpes simplex infection, oral cancer) needs to be evaluated and treated.	Simple saline mouthwash ^{1C} Chlorhexidine 0.12-0.2% ^{2-6A+} (<i>do not use within 30 mins of toothpaste</i>) Hydrogen peroxide 6% ^{6-8A-} (<i>spit out after use</i>)	½ tsp salt dissolved in glass warm water Rinse mouth for 1 minute BD with 5 ml diluted with 5-10 ml water. Rinse mouth for 2 mins TDS with 15ml diluted in ½ glass warm water	Always spit out after use. Use until lesions resolve or less pain allows oral hygiene
Acute necrotising ulcerative gingivitis ^C	Commence metronidazole ¹⁻⁷ and refer to dentist for scaling and oral hygiene advice. ^C Use in combination with antiseptic mouthwash if pain limits oral hygiene.	Metronidazole ^{1-7C} Chlorhexidine or hydrogen peroxide	400mg TDS See above dosing in mucosal ulceration	3 days Until oral hygiene possible
Pericoronitis ^{1B}	Refer to dentist for irrigation & debridement. ^{1C} If persistent swelling or systemic symptoms use metronidazole. ^{1-5A} Use antiseptic mouthwash if pain and trismus limit oral hygiene.	Amoxicillin Metronidazole ^{1-7C} Chlorhexidine or hydrogen peroxide	500mg ⁶ TDS 400mg TDS See above dosing in mucosal ulceration	3 days 3 days Until oral hygiene possible
Dental abscess ^B	Regular analgesia should be first option until a dentist can be seen for urgent drainage, as repeated courses of antibiotics for abscess are not appropriate. ¹ Repeated antibiotics alone, without drainage are ineffective in preventing spread of infection. Antibiotics are only recommended if there are signs of severe infection, systemic symptoms or high risk of complications. ^{2,3} Severe odontogenic infections; defined as cellulitis plus signs of sepsis, difficulty in swallowing, impending airway obstruction, Ludwig's angina. Refer urgently for admission to protect airway, achieve surgical drainage and IV antibiotics. The empirical use of cephalosporins, ⁹ co-amoxiclav, clarithromycin, and clindamycin do not offer any advantage for most dental patients and should only be used if no response to first line drugs when referral is the preferred option. ^{6,12C}			
	<i>If pus</i> drain by incision, tooth extraction or via root canal. ^{4-7B} Send pus for microbiology. <i>If spreading infection</i> (lymph node involvement, or systemic signs ie fever or malaise) ADD metronidazole. ^{8-10C} <i>True penicillin allergy</i> : use clarithromycin <i>If severe</i> : refer to hospital. ^C	Amoxicillin ² or phenoxymethylpenicillin ² <i>Spreading infection or allergy</i> : metronidazole ⁸⁻¹⁰ <i>True penicillin allergy</i> : clarithromycin	500mg ² TDS 500mg ² – 1g QDS 400mg TDS 500mg BD	Up to 5 days review at 3 days ¹¹

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 initially developed in 1999 by practitioners in South Devon, as part of the S&W Devon Joint Formulary Initiative, and Cheltenham & Tewkesbury Prescribing Group and 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. It was further modified following comments from Internet users. If you would like to receive a copy of this guidance with the most recent changes highlighted please email the author cliodna.mculty@phe.gov.uk

The guidance has been updated regularly as significant research papers, systematic reviews and guidance have been published. Public Health England (previously Health Protection Agency) 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 back-up / delayed antibiotics, infection severity and usual duration, clinical staff education, and audits. Materials are available on the **RCGP TARGET website**.

GENERAL COMMENTS ON 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. Erythromycin is preferred in pregnancy, as there is some indication that clarithromycin and azithromycin may be associated with increased risk of spontaneous abortion. In children, erythromycin may be preferable as clarithromycin syrup is twice the 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 appropriate. We recommend a higher dose of 500mg amoxicillin and 400mg metronidazole. The rationale for this is when antimicrobials are considered appropriate, it is important to have sufficient concentrations at the site of infection. For β -lactams such as amoxicillin, the killing effect of the antibiotic is time-dependent (i.e. the time period for which concentrations of the antibiotic at the site of infection are above the Minimum Inhibitory Concentration (MIC) that is required 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, so it is the maximum concentration attained above the MIC that is important (Lewis, 2000). Metronidazole has simple first-order kinetics, so doubling the dose doubles the plasma concentrations (Cudmore et al, 2004). Oral metronidazole is well tolerated and the side-effects reported at doses of 400mg TDS are either very rare or unknown (eMC medicine, 2014). Metronidazole distributes well throughout the body with non-significant differences in the concentrations attained in saliva and crevice fluid compared to plasma (Pahkla, 2005). Metronidazole has a volume of distribution of 0.5-1.0l/kg, so increasing body mass will decrease plasma concentrations (Lamp, 1999). $AUC/MIC > 70$ is only attainable against *Bacteroides fragilis* with a 400mg dose, and mouth anaerobes have similar susceptibility to *Bacteroides fragilis* (Wexler, 2015). 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, we recommend metronidazole 400mg three times daily (Poulet et al, 2005).

References – general Infections

Influenza

1. National Institute for Health and Clinical Excellence. Amantadine, oseltamivir and zanamivir for the treatment of influenza. NICE technology appraisal guidance TA 168. 2009.
<http://www.nice.org.uk/guidance/TA168> Accessed 23.09.14.
2. Seasonal influenza: guidance, data and analysis. **Health protection** – collection.
<https://www.gov.uk/government/collections/seasonal-influenza-guidance-data-and-analysis>
RATIONALE: This website hosts all the up to date advice on the prevention and management of influenza.
3. Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modelling for the prevention and treatment of influenza A and B. Health Technology Assessment 2003;7(35):iii-iv, xi-xiii, 1-170.
4. PHE guidance on use of antiviral agents for the treatment and prophylaxis of seasonal influenza (2015-16). Version 6.0: September 2015
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/457735/PHE_guidance_antivirals_influenza_2015_to_2016.pdf

Further reading

1. The Cochrane Library. 2014. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children.
<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008965.pub4/abstract;jsessionid=8B15D92098C5865128E6494B15DC76B4.f04t01>.
2. The Lancet Respiratory Medicine. 2014. 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.
[http://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(14\)70041-4/abstract](http://www.thelancet.com/journals/lanres/article/PIIS2213-2600(14)70041-4/abstract)
3. Emerging Infectious Diseases. 2011. Use of Antiviral Drugs to Reduce Household Transmission of Pandemic (H1N1) 2009, United Kingdom.
http://wwwnc.cdc.gov/eid/article/17/6/10-1161_article.htm

UPPER RESPIRATORY TRACT INFECTIONS

1. NICE 69: National Institute for Health and Clinical Excellence. Prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care. 2008. (Clinical guideline 69).

A no antibiotic prescribing strategy or a delayed antibiotic prescribing strategy should be negotiated for patients with the following conditions: acute otitis media, acute sore throat, common cold, acute rhinosinusitis, acute cough/acute bronchitis. Depending on patient preference and clinical assessment of severity, patients in the following specific subgroups can also be considered for immediate antibiotics in addition to the reasonable options of a no antibiotic strategy or safety netting 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: 4 days;
- acute sore throat/acute pharyngitis/acute tonsillitis: 1 week;
- common cold: 1½ weeks;
- acute rhinosinusitis: 2½ weeks;
- acute cough/acute bronchitis: 3 weeks.

Advice should also be given about managing symptoms, including discomfort caused by fever (particularly analgesics and antipyretics).

When the 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; this can either be given to the patient or left at an agreed location to be collected at a later date
2. The Royal College of General Practitioners (RCGP) has a free two hour training module on **Managing Acute Respiratory Tract Infections** (MARTI) for continued professional development. The MARTI series of training modules enables clinical staff to improve the care provided to patients presenting with acute ear pain, acute sore throat, sinusitis and acute cough. The module equals two hours towards CPD, and can be imported into the RCGP Revalidation portfolio. <http://www.rcgp.org.uk/courses-and-events/online-learning/ole/managing-acute-respiratory-tract-infections.aspx>

Acute sore throat

1. NICE 69: National Institute for Health and Clinical Excellence. Prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care. 2008. (Clinical guideline 69).
RATIONALE: Acute Sore Throat: NICE 69 includes 3 trials that use a delayed-antibiotic strategy for treating Acute Sore Throat. Two USA studies used a 2-day-delayed antibiotic and the UK primary care study used a 3-day-delayed antibiotic.
2. Spinks A, Glasziou PP, Del Mar C. Antibiotics for sore throat. *Cochrane Database of systematic reviews* 2006, Issue 4. Art. No CD000023. DOI:10.1002/14651858.CD000023.pub3. (Review content up to date 24 November 2008).
RATIONALE: This meta-analysis includes 27 RCT's and 2,835 cases of sore throat. Without antibiotics 40% of sore throats resolve in 3 days and 90% in 7 days. Antibiotics do confer a marginal benefit: To resolve one sore throat at 3 days the NNT is 6 and at 7 days the NNT is 21. However, absolute benefits are modest, especially as the Number Needed to Harm for antibiotic use in respiratory infections is about 15.
3. Little P, Moore M, Hobbs FDR, 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 Open*. 2013, doi:10.1136/bmjopen-2013-003943. Available from: <http://bmjopen.bmj.com/content/3/10/e003943.full>.
RATIONALE: This diagnostic cohort study of 606 patients in cohort one and 517 patients

in cohort two in UK general practices focuses on the association between features of acute sore throat and the growth of streptococci from culturing a throat swab in patients aged 5 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 throats are 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.

4. Little P, Hobbs FDR, Moore M. 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). 2013. *BMJ*. Available from:

<http://www.bmj.com/content/347/bmj.f5806>.

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 ≥ 3 with acute sore throat. This study compared three strategies for limiting or targeting antibiotic using a validated FeverPAIN score in 631 patients with sore throat: they compared delayed antibiotic prescribing, the use of a clinical score designed to identify streptococcal infection, and the targeted use of rapid antigen tests according to the 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 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% confidence interval 0.50 to 0.95; $P=0.02$) and in the antigen test group (58/164) was 27% lower (0.73, 0.52 to 0.98; $P=0.03$). There were no significant differences in complications or reconsultations. The authors therefore suggest the use of the following system and this is available on line: With a low FeverPAIN score of 0-1: only 13-18% have streptococcus, close to background carriage and therefore a no antibiotic strategy is appropriate with discussion. With a FeverPAIN score of 2-3: 34-40% have streptococcus, therefore a back-up/delayed antibiotic is appropriate with discussion. With a FeverPAIN score of ≥ 4 : 62-65% have streptococcus, therefore consider immediate antibiotic if symptoms are severe or a short 48 hour delayed antibiotic prescribing strategy may also be appropriate after agreement with the patient and safety netting advice.

5. Centor RM, Whitherspoon JM, Dalton HP, Brody CE, Link K. The diagnosis of strep throat in adults in the emergency room. *Med Decision Making* 1981;1:239-46.

RATIONALE: Some GPs still prefer to use Centor over FeverPAIN. Centor Criteria: History of fever; absence of cough; tender anterior cervical lymphadenopathy and tonsillar exudates. A low Centor score (0-2) has a high negative predictive value (80%) and indicates low chance of Group A Beta Haemolytic Streptococci (GABHS). A Centor score of 3-or-4 suggests the chance of GABHS is 40%. If a patient is unwell with a Centor score of 3-or-4 then the chance of developing Quinsy is 1:60.

6. 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;**335**:982-4.

RATIONALE: This UK retrospective cohort study looked at the extent to which antibiotics prevent serious suppurative complications of 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. Most patients with Quinsy develop the condition rapidly and don't present first with an acute sore throat.

7. Kagan, B. Ampicillin Rash. *Western Journal of Medicine* 1977;126(4):333-335.

RATIONALE: Amoxicillin should be avoided in the treatment of acute sore throat due to the high risk of developing a rash, when the Epstein Barr virus is present (up to 90%). Although this is now quite an old study and EBV infection may now not be as common in acute sore throat.

8. Lan AJ, Colford JM, Colford JMJ. The impact of dosing frequency on the efficacy of 10 day penicillin or amoxicillin therapy for streptococcal tonsillopharyngitis: A meta-analysis. *Pediatr* 2000;105(2):E19.

RATIONALE: This meta-analysis provides the evidence that BD dosing with phenoxymethylpenicillin is as effective as QDS in treating GABHS. Expert opinion is that phenoxymethylpenicillin should be dosed QDS for severe infections in order to optimise the therapeutic drug concentrations.

9. Schwartz RH, Wientzen RL Jr, Predreira 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 16;246(16):1790-5.

RATIONALE: This RCT demonstrates that a 10 day course of oral phenoxymethylpenicillin is better than 7 days for resolution of symptoms and eradication of GABHS. In total, 210 middle-class paediatric patients (children aged 1-18 years) with positive group A streptococcal sore throat were admitted to the study. Of the remaining 191 patients available for analysis, 96 were randomly assigned to seven days of penicillin therapy and 95 to ten days of treatment with excellent compliance. Symptomatic recurrence was higher with 7 days treatment (23%) than 10 days (12%).

10. Altamimi S, Khali A, Khalaiwa KA, Milner R, Pusic MV, Al Othman MA. Short versus standard duration antibiotic therapy for acute streptococcal pharyngitis in children. *Cochrane Database of systematic reviews* 2009, Issue 1. Art No.: CD004872. DOI: 10/1002/14651858.CD004872.pub2.

RATIONALE: This recent meta-analysis shows short-course (including 5 days Clarithromycin) broad-spectrum antibiotics are as efficacious as 10-day-penicillin for sore throat symptom treatment and GABHS eradication. 10-day-phenoxymethylpenicillin remains the treatment of choice. Evidence suggests the use of broader spectrum antibiotics will drive the emergence of bacterial resistance; increase the risk of developing Clostridium difficile Associated Disease; and are associated with more adverse drug reactions. 5-days-clarithromycin or erythromycin should be reserved for those with true penicillin allergy.

11. Lasseter GM, McNulty CAM, Hobbs FDR, Mant D, Little P on behalf of the PRISM investigators. In vitro analysis of five rapid antigen detection tests for group A beta-haemolytic streptococcal sore throat infections. *Family Practice* 2009 Dec 26(6):437-44.

RATIONALE: A comparative study of 5 rapid antigen detection kits for group A Strep concluded that the IMI test pack Plus Strep A (Inverness Medical, Bedford, UK) was easy to use with clear kit instructions and a high sensitivity (95% at group A streptococcal concentrations of 10×10^6 CFU/mL) and specificity (100%), thus offering best value for money (although is not the cheapest). The authors note that the quality of any throat swab taken will affect the performance of the test so swabbing technique is as important as the choice of test.

12. Flory TM, Sheehy O, Berard A. Use of antibiotics during pregnancy and risk of spontaneous abortion. *CMAJ*. 2017 May; 1(189):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 20th 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, 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 for pregnant women.

Additional references:

1. Howie JGR, Foggo BA. Antibiotics, sore throats and rheumatic fever. *BJGP* 1985;**35**:223-224.
RATIONALE: This Scottish retrospective study confirms the low incidence of Rheumatic Fever in the UK, (0.6 per 100,000 children per year). It would take 12 working GP life times to see one case of Rheumatic Fever. The risk of developing Rheumatic Fever was not reduced in this study by treating sore throats 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. Taylor JL, Howie JGR. Antibiotics, sore throat and acute nephritis. *BJGP* 1983;**33**:783-86.
RATIONALE: This study shows that Glomerulonephritis is a rare condition, (2.1 per 100,000 children per year) and that treating acute sore throat with antibiotics doesn't prevent it occurring.
3. Maholtra-Kumar S, Lammens C, Coenen S, Van Herck K, Goossens H. Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo controlled study. *Lancet* 2007;**369**:482-490.
RATIONALE: This randomised, double blind, placebo controlled study showed both azithromycin and clarithromycin significantly increased the proportion of macrolide-resistant streptococci compared with placebo at all points studied. Peaking at day 8 in the clarithromycin group (mean increase 50.0%, 95% CI 41.7–58.2; $p<0.0001$) and at day 4 in the azithromycin group (53.4%, 43.4–63.5; $p<0.0001$). The proportion of macrolide-resistant streptococci was higher after azithromycin treatment than after clarithromycin use, with the largest difference between the two groups at day 28 (17.4% difference, 9.2–25.6; $p<0.0001$). Use of clarithromycin, but not of azithromycin, selected for the erm (B) gene, which confers high-level macrolide resistance in this study.
4. Shulman TS, Bisno AL, Clegg HW, Gerber MA, Kaplan EL, Lee G, et al. Clinical Practice Guidelines for the Diagnosis and Management of Group A Streptococcal Pharyngitis: 2012
5. Update by the Infectious Diseases Society of America. *CID* 2012; 55: e86.

Acute otitis media

1. NICE 69: National Institute for Health and Clinical Excellence. Prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care. 2008. (Clinical

guideline 69)

RATIONALE: Acute Otitis Media: NICE 69 includes 3 trials that use a delayed-antibiotic strategy for treating AOM. Two USA studies used a 2-day-delayed antibiotic and the UK primary care study used a 3-day-delayed antibiotic.

2. Little P, Gould C, Williamson I, Moore M, Warner G, Dunleavy J. Pragmatic randomised controlled trial of two prescribing strategies for childhood acute otitis media. *BMJ* 2001;322:336-42.

RATIONALE: This RCT makes two important observations: that parents tend to underestimate the amount of analgesia they've administered and that when recommending a no-antibiotic strategy it is all the more important to optimise analgesia.

3. Bertin L, Pons G, d'Athis P, Duhamel JF, Mauelonde C, Lasfargues G, Guillot M, Marsac A, Debregeas B, Olive G. A randomized, doubleblind, multicentre controlled trial of ibuprofen versus acetaminophen and placebo for symptoms of acute otitis media in children. *Fundam Clin Pharmacol* 1996;10(4):387-92.

RATIONALE: This small RCT is probably the best trial evidence we have specifically for analgesia use in AOM. Both Paracetamol and Ibuprofen showed a non-significant trend towards effective analgesia compared with placebo. Note that all children were also treated with an antibiotic.

4. Sanders S, Glasziou PP, Del Mar C, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2004, Issue 1. Art. No: CD000219.DOI:10.1002/14651858.CD00021 9pub2. (Content up to date 08.11.08).

RATIONALE: Most (66%) of children are better in 24 hours and antibiotics have no effect. 80% of children are better in 2-to-7 days and antibiotics have a small effect (symptoms reduced by 16 hours), (RR 0.72; 95% CI 0.62 to 0.83). Antibiotics did not reduce tympanometry (deafness), perforation or recurrence. Vomiting, diarrhoea or rash was more common in children taking antibiotics (RR 1.37; 95% CI 1.09 to 1.76) with a Number Needed to Harm of 16.

5. Rovers MM, Glasziou P, Appleman CL, Burke P, McCormick DP, Damoiseaux RA, Little P, Le Saux N, Hoes AW. 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;119(3):579-85.

RATIONALE: The risk of prolonged illness was 2 times higher for children <2years with bilateral AOM than for children with unilateral AOM. For this sub-group parents should be advised that symptoms may persist for up to 7 days, and they should optimise analgesia use. The protective immunity against infections with encapsulated bacteria, such as the species that cause AOM, depends on the ability to produce specific antibodies against bacterial capsular polysaccharides, which is inadequate until 2 years of age. The anatomic features of the eustachian tubes and the nasopharynx also differ with age. Consequently, children under 2 years of age seem to be more susceptible to AOM.

6. 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. *NEJM* 2011; 364:105-115.

RATIONALE: This study included 291 children 6-23 months with otoscopically confirmed OM and compared co-amoxiclav to placebo. 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 2, 41% by day 4, and 67% by day 7, as compared with 14%, 36%, and 53% with placebo (p=0.04 for the overall comparison). At day 10-12 clinical results were less favourable in children with bilateral AOM (p=0.002), more bulging tympanic membrane compared to less (p<0.001), higher symptom scores at entry, (p=0.004, score ≥8 for fever, tugging ears, crying more, irritability, difficulty sleeping, less playful, eating less, where 0=no symptoms, 1 a little, 2 A lot).

7. Tähtinen PA, Laine MK, Houvinen P, Jalava J, Ruuskanen O, Ruohola A. A placebo-controlled trial of antimicrobial treatment for acute otitis media. *NEJM* 2011;364:116-26.
8. Rovers MM, Glasziou P, Appelman CL, Burke P, McCormick DP, Damoiseaux RA, Gaboury I, Little P, Hoes AW. Antibiotics for acute otitis media: a meta-analysis with individual patient data. *Lancet* 2006;368:1429-1435.
RATIONALE: Note this is sub-analysis of data. In children <2 years old with bilateral AOM, 30% on antibiotics and 55% of controls had pain and/or fever at 3 to 7 days (RD -25%; 95% CI: -36, -14) and the NNT was 4 in children with otorrhoea, 24% on antibiotics and 60% of controls had pain and/or fever at 3 to 7 days (RD-36%; 95% CI: -53, -19) and the NNT was 3.
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;123(2):424-30.
RATIONALE: Antibiotics halved the risk of mastoiditis, but GP's would have to treat 4831 episodes of AOM to prevent one episode of mastoiditis. Although mastoiditis is a serious illness, most children make an uncomplicated recovery after mastoidectomy or IV antibiotics, (Incidence mastoiditis 0.15 per 1000 child years).
10. Takata GI, Chan LS, Shekelle P, et al. Evidence assessment of management of acute otitis media: The role of antibiotics in treatment of uncomplicated acute otitis media. *Pediatrics* 2001;108:239-247.
RATIONALE: Pooled analyses did not show any difference in efficacy between comparisons of penicillin, ampicillin, amoxicillin (2 or 3 times daily; standard or high dose), amoxicillin-clavulanate, cefaclor, cefixime, ceftriaxone, azithromycin and trimethoprim. Macrolides concentrate intracellularly and so are less active against the extracellular H influenzae.
11. Sox CM, Finkelstein JA, Yin R, Kleinman K, Lieu TA. Trends on otitis media treatment failure and relapse. *Pediatrics* 2008;121(4):674-9.
RATIONALE: High-dose amoxicillin treatment did not reduce the risk of individual infections resulting in adverse outcomes.
12. Kozlarsky AL, Hildes Ripstein GF, Longstaffe SE, et al. Short-course antibiotics for acute otitis media. *Cochrane Database Syst Rev* 2000;(2):CD001095.
RATIONALE: This review found that 5 days of antibiotic treatment was as effective as 10 days in otherwise healthy children with uncomplicated AOM.

Acute otitis externa

1. Kaushik V, Malik T, Saeed SR. Interventions for acute otitis externa. *Cochrane Database of Systematic Reviews* 2010, Issue1. Art. No.:CD004740. DOI: 10.1002/14651858.CD004740.pub2.
RATIONALE: The best evidence we have to date. Includes 19 low quality RCT's only two of which are from primary care, and therefore probably included more severe or chronic cases. One big downside for primary care is that over half of the trials involved ear cleaning. The meta-analysis demonstrates topical treatments alone are adequate for treating most cases of AOE. Acetic acid was as effective and comparable to antibiotic/steroid for the first 7 days, but inferior after this point. 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.
2. Thorp MA, Krunker J, Oliver S et al. The antibacterial activity of acetic acid and Burow's solution as topical otological preparations. *Journal of Laryngology and Otology*, Vol 112/10 (925-8). Oct 1998.
RATIONALE: There is little evidence to support the use of one agent over the other. Both 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 1st line treatment for mild otitis externa whilst aluminium is for more resistant cases or extensive swelling, acetic acid's availability compared to aluminium acetate and that an ear wick requires specialist referral for insertion, acetic acid would seem to be a better first-line option. Although there are no trials of acetic acid versus placebo there are trials comparing its use to a topical antibiotic-corticosteroid combination they show equivalence. Only one study was found from a literature search which compared the efficacy between acetic acid and aluminium acetate (also known as Burow's solution). This was a small (n=20) in vitro study which compared 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* and *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 organisms tested.

3. CKS (2007) Acute otitis externa. Clinical Knowledge Summaries. <http://cks.nice.org.uk/otitis-media-acute#azTab> Accessed 24.09.14.

RATIONALE: For acetic acid CKS states that: "Acetic acid alone has not been compared with placebo for treating otitis externa in randomized controlled trials (RCTs). One double blind RCT found no statistically significant difference in efficacy between topical acetic acid and a topical antibiotic-corticosteroid combination at day 7. 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." Whilst for aluminium acetate it states: "Aluminium acetate has not been compared with placebo for the treatment of otitis externa. Two randomized controlled trials (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."

4. Rosenfeld RM, Brown L, Cannon R, Dolor RJ, Ganiats TG, Hannley M, Kokemueller P, Marcy M, Roland PS, Shiffman RN, Stinnett SS, Witsell DL, Singer M, Wasserman JM. Clinical Practice Guideline: Acute Otitis Externa. *Otolaryngology – Head and Neck Surgery* 2006;134(Suppl 4):S4-S23.

RATIONALE: Up to 40% of patients with AOE receive oral antibiotics unnecessarily. The oral antibiotics in the trials were often inactive against *P aeruginosa* (incidence 36%) and *S aureus* (incidence 21%). Topical antibiotics such as neomycin have a broader spectrum of activity. When using topical antibiotics in this situation bacterial resistance is far less of a concern as the high concentration of the drug in the ear canal will generally eradicate all susceptible organisms, plus those with marginal resistance. Malignant Otitis Externa is an aggressive infection that affects the immunocompromised and elderly that requires prompt admission. Facial Nerve paralysis may be an early sign. GPs should refer severe cases, characterised by unremitting pain, cranial nerve deficits, perforated tympanic membrane or history of previous ear surgery.

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. *European Archives of Oto-rhino-laryngology*: 2009;266(1):41-5.

RATIONALE: A hospital outpatient RCT showing superiority of topical steroid-antibiotic therapy. The Cochrane Review 2010 also stated that 'the evidence for steroid-only drops is very limited and as yet not robust enough to allow us to reach a conclusion or provide recommendations.' NEOMYCIN SULPHATE with CORTICOSTEROID is suggested as

topical antibiotic + steroid as it contains an antibiotic that is not used orally, Neomycin is active against *Pseudomonas* and *Staphylococci* the most common bacterial causes, plus there is the choice of four agents: Betnesol-N; Otomize; Otosporin and Predsol-N.

Acute rhinosinusitis

1. NICE 69: National Institute for Health and Clinical Excellence. Prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care. 2008. (Clinical guideline 69).

RATIONALE: Although there are no specific studies looking at delayed antibiotics for acute rhinosinusitis, NICE 69 recommends the same approach as for the other self limiting respiratory tract infections. The 7-day delay is recommended as systematic review shows no benefit of antibiotics in rhinosinusitis within the first 7 days.

2. 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; 371:908-914.

RATIONALE: This meta-analysis included 2,547 patients from 9 Placebo-controlled trials. This primary care meta-analysis showed that 15 people would have to be given antibiotics before an additional patient was cured. The Odds Ratio of treatment effect for antibiotics relative to the 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 a NNT of 8. There was no additional benefit of antibiotics for: older patients; more severe symptoms; or longer duration of symptoms.

3. Ahovuo-Saloranta A, Borisenko OV, Kovanen N, Varonene H, Rautakorpi UM, Williams Jr JW, Makela M. Antibiotics for acute maxillary sinusitis. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No: CD000243. DOI:10.1002/14651858.CD000243.pub2. (Last assessed as up-to-date 28 May 2007).

RATIONALE: This is a big clinical review (57 studies), that contained 6 placebo controlled trials. 5 of these were in primary care and involved 631 patients. There was a slight statistical difference in favour of antibiotics compared with placebo (RR 0.66; 95%CI 0.65 to 0.84). Note cure/improvement rate was high in placebo group (80%) compared with the treatment group (90%). Antibiotics have a small treatment effect in patients with uncomplicated acute rhinosinusitis, in a primary care setting, for more than seven days.

4. Ah-See KW, Evans AS. Sinusitis and its management. *BMJ* 2007;334:358-61.

RATIONALE: Adequate analgesia is becoming recognised as the first-line management for acute rhinosinusitis. Robust evidence for this is limited, as it is for analgesia use in general. This is partly due to the widespread accepted efficacy and tolerability of analgesics, that such research isn't deemed necessary. We have to make do with the consensus expert opinion.

5. Thomas M, Yawn B, Price D, Lund V, Mullol J, Fokkens W. EPOS Primary Care Guidelines: European Position Paper on the Primary Care Diagnosis and Management of Rhinosinusitis and Nasal Polyps 2007 – a summary. *Primary Care Respiratory Journal* 2008;17(2):79-89.

RATIONALE: This primary care guideline states that: 'Acute rhinosinusitis is an inflammatory condition that may be diagnosed on the basis of acute symptoms of nasal blockage, obstruction, congestion with or without facial pain or reduced smell; many episodes are self-limiting, but where symptoms persist or increase after 5 days, topical steroids may be considered to reduce the inflammatory reaction.'

6. Bartlett JG, Gorbach SL. Anaerobic infections of the head and neck. *Otolaryngol Clin North Am* 1976;9:655-78.

RATIONALE: Anaerobes are an unusual finding in acute upper respiratory infections such as acute rhinosinusitis and acute otitis media, but are increasingly found in chronic

disease. Co-amoxiclav is active against many anaerobes as well as *S. pneumoniae* and *H. influenzae*.

7. De Ferranti SD, Lonnidis JPA, Lau J, Anniger WV, Barza M. Are amoxicillin and folate inhibitors as effective as other antibiotics for acute sinusitis? *BMJ* 1998;317:632-7.
RATIONALE: On current evidence, no one class of antibacterial is more likely than another to cure patients with sinusitis.
8. 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. *Scan J Prim Health Care* 2000;18:44-47.
RATIONALE: This primary care study (133 patients) demonstrates that Penicillin V is more effective than placebo in the treatment of acute maxillary sinusitis, but only where there is pronounced pain.
9. Falagas ME, Karageorgopoulos DE, Grammatikos AP, Matthaïou DK. Effectiveness and safety of short vs. long duration of antibiotic therapy for acute bacterial sinusitis: a meta-analysis of randomised trials. *British Journal of Clinical Pharmacology* 2009;67(2):161-71.
RATIONALE: there was no difference in the comparison of short-course (3-7 days) with long-course treatment (6-10 days). The pragmatic interpretation of this meta-analysis is that a 7 day course is optimal. In severe sinusitis a 1g dose may be considered to ensure bactericidal concentrations of amoxicillin in the sinuses. Lower concentrations may encourage the stepwise form of resistance that occurs with pneumococci.

Additional reference:

1. Hansen JG, Hojbjerg T, Rosborg J. Symptoms and signs in culture proven acute maxillary sinusitis in general practice population. *APMIS* 2009;117(10):724-9.
RATIONALE: We don't yet have robust diagnostic criteria for those patients with acute rhinosinusitis that would most benefit from antibiotics. This primary care prospective cohort study of 174 patients shows: Fever >38 degrees; maxillary toothache and raised ESR were associated with *S. pneumoniae* and *H. influenzae* positive rhinosinusitis.

LOWER RESPIRATORY TRACT INFECTIONS

1. Woodhead M, Blasi F, Ewig S, Huchon G, Leven M, Ortqvist A, Schabert T, Torres A, van der Jeijden G, Werheij TJM. Guidelines for the management of adult lower respiratory tract infection. *Eur Respir J* 2005;26:1138-80. <http://www.erj.ersjournals.com/contents-by-date.0.shtml> Accessed 23.09.14.
RATIONALE: Appendices 1, 2 and 3 give a detailed account of the definitions of LRTI, the microbiological aetiologies of LRTI unspecified, community acquired pneumonia, exacerbations of COPD and bronchiectasis and the pharmacodynamic/pharmacokinetic properties of the antibiotics used to treat them. *Strep. pneumoniae* remains the most commonly isolated pathogen in all of the above except in bronchiectasis. The infective agents causing exacerbations of COPD differ according to the severity of the underlying condition suggesting that more broad spectrum antibiotics are indicated in patients with severe COPD (FEV₁< 50%). 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 they exert a post antibiotic effect. Other factors such as bioavailability are also considered.
2. Patel SN, McGeer A, Melano R, Tyrrell GJ, Green K, Pillai DR, Low DE. Susceptibility of *Strep pneumoniae* to fluoroquinolones in Canada. *Antimicrob. Agents Chemother.* 2011, 55(8):3703.
RATIONALE: The article was published by the Canadian Bacterial Surveillance Network looking at isolates of pneumococci received by them 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. NICE Clinical Guideline 69. Respiratory Tract Infections - antibiotic prescribing for self-limiting respiratory tract infections in adults and children in primary care. July 2008.
RATIONALE: Describes strategies for limiting antibiotic prescribing in self-limiting infections and advises in which circumstances antibiotics should be considered. A no antibiotic or a delayed antibiotic prescribing strategy should be agreed for patients with acute cough/chronic bronchitis. In the 2 RCTs included in the review, the delay was 7-14 days from symptom onset and antibiotic therapy. Patients should be advised that resolution of symptoms can take up to 3 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 a clinical review if condition worsens or becomes prolonged. The evidence behind these statements is primarily from the studies referred to below. There has been no systematic review of the evidence of length of antibiotic treatment for acute cough or bronchitis when antibiotics are prescribed. However the NICE pneumonia guidance group found evidence for the efficacy of 5 days' antibiotic to treat pneumonia; therefore it is reasonable to consider that 5 days would also be effective in bronchitis.
2. Fahey T, Smucny J, Becker L, Glazier R. Antibiotics for acute bronchitis. In: The Cochrane Library, 2006, Issue 4. Chichester, UK: John Wiley & Sons, Ltd
http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD000245/pdf_fs.html
Accessed 23.09.14.
RATIONALE: Systematic review of nine studies (4 in primary care). Studies in primary care showed antibiotics reduced symptoms of cough and feeling ill by less than one day in an illness lasting several weeks in total.
3. Chronic cough due to acute bronchitis. Chest. 2006;129:95S-103S.
RATIONALE: Clinical guidelines on managing cough associated with acute bronchitis. Large body of evidence including meta-analyses and systematic reviews does not support routine antibiotic use.
4. Wark P. Bronchitis (acute). In: Clinical Evidence. London. BMJ Publishing Group. 2008;07:1508-1534.
RATIONALE: Discusses the evidence to support self care and limiting antibiotic prescriptions. Systematic review of 13 RCTs found that antibiotics only modestly improved outcomes compared with placebo.
5. Francis N et al. 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;339:2885.
RATIONALE: Utilising an information booklet during primary care consultations for children with RTIs significantly decreased antibiotic use (absolute risk reduction 21.3% (95%CI, 13.7-28.9 p<0.001). Reconsultation occurred in 12.9% of children in intervention group and 16.2% in control group (absolute risk reduction 3.3%, no statistical difference). There was no detriment noted to patient satisfaction in the intervention group.
6. Treatment of acute bronchitis available in Clinical Knowledge Summaries website:
<http://cks.nice.org.uk/chest-infections-adult> Accessed 23.09.14.

Acute exacerbation of COPD

1. Anthonisen MD, Manfreda J, Warren CPW, Hershfield ES, Harding GKM, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Int Med* 1987;106:196-204.
RATIONALE: Describes the cardinal signs of an infective exacerbation of COPD and the evidence for commencing antibiotics. Randomised double blinded cross-over trial showed a significant benefit from using antibiotics. Success rate with antibiotic therapy 68% vs 55% with placebo.
2. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for Diagnosis, Management, and Prevention of COPD. Management of exacerbations. December 2009.
RATIONALE: Discusses the aetiology, pathophysiology and evidence based therapeutic management of COPD. Antibiotic therapy is stratified according to severity of disease. *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* remain the predominant pathogens in mild disease.
3. Chronic obstructive pulmonary disease. Management of COPD in adults in primary and secondary care. NICE Clinical Guideline 12 February 2004.
<http://guidance.nice.org.uk/CG101> Accessed 23.09.14.
RATIONALE: A meta-analysis of nine trials found a small but statistically significant effect favouring antibiotics over placebo in patients with exacerbations of COPD. Effect size 0.22 (95% CI, 0.1 to 0.34). Four studies assessed whether there was a relationship between severity of exacerbation and the effectiveness of antibiotic use. Three of these studies suggest that the worse the COPD severity of exacerbation (lung function impairment (FEV1, PEFR), purulence of sputum) then the greater the degree of benefit from antibiotics.
4. El Moussaoui R, Roede BM, Speelman P, Bresser P, Prins JM, Bossuyt PMM. Short-course antibiotic treatment in acute exacerbations of chronic bronchitis and COPD: a meta-analysis of double-blind studies. *Thorax* 2008;63:415-22.
RATIONALE: In this meta-analysis they 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. The meta-analysis included 21 double-blind randomised clinical trials with 10,698 adults with exacerbation of COPD or chronic bronchitis, no antimicrobial therapy at the time of diagnosis and random assignment to antibiotic treatment for less than or equal to 5 days versus more than 5 days. At early follow-up (<25 days), the summary odds ratio (OR) for clinical cure with short treatment versus conventional treatment was 0.99 (95% CI 0.90 to 1.08). At late follow-up the summary OR was 1.0 (95% CI 0.91 to 1.10). No trials of amoxicillin or doxycycline were included in the meta-analysis; however there is no microbiological reason that a 5 day course of these agents would be inferior to a 5 day course of clarithromycin in acute exacerbations of COPD.

Community-acquired pneumonia

1. NICE clinical guideline 191. Diagnosis and management of community- and hospital-acquired pneumonia in adults. Issued: December 2014.
<https://www.nice.org.uk/guidance/cg191> Accessed 05.01.15.
RATIONALE:
a) 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 20mg/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 20mg/litre and 100mg/litre.
- Offer antibiotic therapy if the C-reactive protein concentration is greater than 100mg/litre.

Updated guideline on the management of CAP – includes diagnosis, severity assessment, microbiological profile and therapeutic management in both the community and hospital. 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, 1-10%; scores 3-4, more than 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 or more. Patients with moderately severe CAP (score 1-2) should receive antibiotics which also cover atypical organisms. BTS guidelines state that for patients treated at home 5 days is appropriate with safety netting guidance to return for urgent review if they are worsening, or at 3 days if they are not improving. With moderate to severe pneumonia 7-10 days should be considered based on severity and response.

NICE advises that glucocorticosteroids should not be given unless indicated for another condition.

Patient information:

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, and most people can expect that by:

1 week: fever should have resolved

4 weeks: chest pain and sputum production should have substantially reduced

6 weeks: cough and breathlessness should have substantially reduced

3 months: most symptoms should have resolved but fatigue may still be present

6 months: most people will feel back to normal

2. Loeb M. Community-acquired pneumonia. In: Clinical Evidence. London BMJ Publishing Group. 2008;07:1503-1516. Accessed 06.01.2010.

RATIONALE: While there is no direct information about the benefits of antibiotics in the treatment of CAP in the community, there is consensus they are beneficial. No one regime has shown superiority over another.

3. van der Poll T, Opal S. Pathogenesis, treatment and prevention of pneumococcal pneumonia. *Lancet*. 2009;374:1543-1556.

RATIONALE: Detailed review of pneumococcal pneumonia, the most common cause of CAP. Includes discussion of clinical features, risk factors and rationale for high dose penicillins to overcome resistance.

4. Cals JWL, Marjolein JC, Schot Sanne AM, et al. Point-of-Care C-Reactive Protein Testing and Antibiotic Prescribing for Respiratory Tract Infections: A Randomized Controlled Trial. *Ann Fam Med* 2010;8:124-33.

RATIONALE: This, and related articles by the same authors, indicate that the use of point of care CRP tests in general practice can assist diagnosis resulting in improved patient satisfaction as well as reduced overall antibiotic use due to reduced use of unnecessary antibiotics. An economic evaluation (Cals et al, *J Eval Clin Pract* 2011 Dec 17(6): 1059-69) showed that the use of CRP tests as well as communication skills training are cost effective interventions to reduce antibiotic prescribing for LRTI.

MENINGITIS

1. NICE. Bacterial meningitis and meningococcal septicaemia. *National Collaborating Centre for Women's and Children's health* 2009. <http://guidance.nice.org.uk/CG102/Guidance> Accessed 23.09.14.
2. Saeed, K., 2011. 'One for all' concerns regarding NICE antibiotic guidelines on suspected bacterial meningitis! [letter] *Brit J Gen Pract* 2011;61:606.
RATIONALE: Expert opinion is that in children or young people with suspected bacterial meningitis or meningococcal septicaemia, transfer to hospital is the priority, and that intravenous benzylpenicillin should be given at the earliest opportunity if a non-blanching rash is present, either in primary or secondary care. The NICE guideline development group recommended benzylpenicillin because they are aiming to cover only meningococcal septicaemia, which causes highest mortality, and it is the most frequently used antibiotic in primary care and they found no evidence to recommend an alternative antibiotic. Following prompt admission evaluation a more definitive choice of antimicrobials can be made. Although the scope of the NICE guideline is for children, it seems reasonable to extrapolate the advice to older age groups.
3. SIGN. Management of invasive meningococcal disease in children and young people. *Scottish Intercollegiate Guidelines Network*. 2008
<http://www.sign.ac.uk/guidelines/fulltext/102/index.html> Accessed 23.09.14.
RATIONALE: Expert opinion is that parenteral antibiotics (either benzylpenicillin or cefotaxime) should be administered in children as soon as invasive meningococcal disease is suspected, and not delayed pending investigations.

URINARY TRACT INFECTIONS

The Royal College of General Practitioners (RCGP) has a free two hour training module on Managing Urinary Tract Infections (MUTs) for continued professional development. Urinary tract infections are frequently seen in primary care. What may seem initially a simple diagnosis, on closer inspection and reflection can be quite complex. The RCGP course explains the importance and appropriateness of diagnostics and offers advice on how to assess and treat patients with a range of urinary symptoms. It encourages reflection on how to minimise antibiotic resistance and offers 'real-life' cases. This course has been developed in partnership with Public Health England's Primary Care Unit. It was funded by an educational grant from **Public Health England**. Access to this course is FREE to all primary healthcare professionals in the UK. The module equals two hours towards CPD, and can be imported into the RCGP Revalidation portfolio.

1. ARHAI *E. coli* subgroup final report. 2014.
RATIONALE: Mandatory *E. coli* bacteraemia surveillance over the past 10 years has demonstrated a sustained increase in *E. coli* bacteraemia that is unexplained by improved ascertainment. Analysis of these data by the sub-group has demonstrated that only a small proportion of infections are related to urinary catheterisation and that other factors such as repeated urinary tract infections treated by sub-optimal antibiotic prescribing and dehydration as a risk factors for urinary tract infection have a significant impact. The subgroup recommended: **1:** All organisations providing care to patients with 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 this. **2:** To help prevent UTI maintenance of hydration status must be a priority for those at risk of dehydration, particularly in hospitals, and long-term care facilities. **3:** Significant numbers of *E. coli* bacteraemias occur in patients with a history of repeated urinary tract infections. 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.

UTI

1. SIGN. Management of suspected bacterial urinary tract infection in adults: a national clinical guideline. *Scottish Intercollegiate Guidelines Network*. 2006

<http://www.sign.ac.uk/guidelines/fulltext/88/index.html> Accessed 23.09.14.

RATIONALE: Diagnosis in women: expert consensus is that it is reasonable to start empirical antibiotics in women with symptoms of UTI without urine dipstick or urine culture. Diagnosis in men: a urine sample is recommended because UTI in men is generally regarded as complicated (it results from an anatomic or functional abnormality) and there are no studies on the predictive values of dipstick testing in men. Duration of treatment for men: there is no evidence to guide duration of treatment; expert consensus is that 7 days of antibiotics should be used because men are likely to have a complicating factor. Second line treatment: resistance is increasing to all antibiotics used to treat UTI, if possible antibiotic choice should be based on microbiology results. Safety net advice includes: blood in the urine (haematuria); severe pain in the back or side below the ribs; signs of systemic infection (fever or chills; nausea or vomiting).

2. Lutters M, Vogt-Ferrier NB. Antibiotic duration for treating uncomplicated, symptomatic lower urinary tract infections in elderly women. *Cochrane Database of Systematic Reviews*. 2002(3):CD001535.

RATIONALE: In this Cochrane Review Lutters and Vogt-Ferrier examined 4 studies comparing 3 days to 7 days treatment of ciprofloxacin or norfloxacin and 1 study comparing 3 days to 5 days treatment of trimethoprim in uncomplicated UTI in elderly women (age 60 or more). There was no significant difference in persistent UTI, clinical failure or re-infection rates but side-effects were higher in those given 7 days treatment. This review also included a study by Bitsch et al 1984 which involved 193 patients with lower UTI treated with pivmecillinam 400mg TDS for 3 days. Bacteriological cure was 81% 10 weeks after treatment. (Bitsch M et al Treatment of Acute Cystitis – A comparison of a three day course of pivmecillinam (Selexid) and a six day course of sulphamethiazole. *Journal for Drug Therapy and Research* 1984; 9(1): 26-28)

3. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin no. 91: Treatment of urinary tract infections in non-pregnant women. *Obstetrics and Gynecology* 2008;111(3):785-794.

RATIONALE: Diagnosis in women: expert consensus is that it is reasonable to start empirical antibiotics in women with symptoms of UTI without urine culture.

4. Little P, Turner S, Rumsby K., Warner G, Moore M, Lowes JA, Smith H, Hawke C, Turner D, Leydon GM, Arscott A, Mullee M. Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort and qualitative study. *Health Technology Assessment* 2009;13(19):1-96.

RATIONALE: In women with uncomplicated UTI, the negative predictive value when nitrite, leucocytes, and blood are ALL negative was 76%. The positive predictive value for having nitrite and EITHER blood or leucocytes was 92%.

5. Grabe M, Bishop MC, Bjerkland-Johansen TE, Botto H, Cek M, Lobel B, Naber KG, Palou, J, Tenke, P, Wagenlehner F. Guidelines on Urological Infections. *European Association of Urology* 2009: 1-110.

RATIONALE: Diagnosis in men: a urine sample is recommended because UTI in men is generally regarded as complicated (it results from an anatomic or functional abnormality) and there are no studies on the predictive values of dipstick testing in men. Duration of treatment for men: there is no evidence to guide duration of treatment; expert consensus is that 7 days of antibiotics should be used because men are likely to have a

complicating factor. Although 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 only mild symptoms of UTI as contamination is likely to be lower.

6. Gossius G and Vorland L. The treatment of acute dysuria-frequency syndrome in adult women: Double-blind, randomized comparison of three-day vs ten-day trimethoprim therapy. *Current Therapeutic Research, Clinical & Experimental* 1985;37: 34-42.
 RATIONALE: Two-weeks after completion of treatment, 94% of women using a 3-day course of trimethoprim achieved bacteriological cure compared with 97% of those using a 10-day course of trimethoprim (n=135).
7. Christiaens TCM, De Meyere M, Verschragen 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. *Brit J Gen Pract* 2002;52:729-34.
 RATIONALE: This small (n=78) double-blind RCT found that nitrofurantoin 100mg qds for 3 days was more effective than placebo at attaining symptomatic cure in bacteriologically proven UTI (nitrofurantoin 80% and 88% at three and seven days respectively; placebo 54%, and 51% respectively) (NNT = 4.4, 95% CI 2.3 to 79). And attained bacteriological cure (<10⁵ CFU/ml) of 81% at three days, and 74% at seven days post treatment .
8. Public Health England and the British Infection Association.
 RATIONALE: We recommend nitrofurantoin as first-line empirical treatment (and trimethoprim or pivmecillinam as alternatives if GFR is under 45mL/min) for uncomplicated UTI in women and men because they are narrow-spectrum antibiotics that cover the most prevalent pathogens. Broad spectrum antibiotics (e.g. co-amoxiclav, quinolones and cephalosporins) should be avoided when narrow spectrum antibiotics remain effective, as they increase risk of *Clostridium difficile*, MRSA and resistant UTIs. The choice of nitrofurantoin, trimethoprim or pivmecillinam as first line varies by locality and is dependent on resistance rates to the three agents. Resistance to nitrofurantoin is generally lower however nitrofurantoin should not routinely be used if upper UTI suspected or in patients with eGFR less than 45mL/minute/1.73m². Several guidelines recommend that nitrofurantoin should not be used to treat UTI in men. This is on the grounds that it can be difficult to exclude the possibility of prostatitis, and that nitrofurantoin is not present in therapeutic concentrations in prostatic secretions. However, these recommendations refer to UTI with fever or other signs of acute prostatitis, and neither guideline expressed concern that acute prostatitis would be likely in men with symptoms of lower UTI and without fever and other symptoms of prostatitis.
 There has been a recent systematic review suggesting that five days nitrofurantoin may be more effective than three days. However the review does not include any prospective studies that directly compare three and five days nitrofurantoin. The strongest evidence for five days comes from one retrospective cohort study in the Netherlands, however recent evidence again from a retrospective study in Scotland including 17,046 individuals treated with nitrofurantoin indicate that a second course of antibiotic treatment was given to a similar percentage of patients given three days (17.1%), five days (16.8%) and seven days (17.3%) treatment. Therefore PHE will continue to advise three days treatment until any stronger evidence refutes the recommendation.
9. MeReC Bulletin. Modified-release preparations. 2000;11(4).
 RATIONALE: Modified-release preparations can be used to reduce dosing frequency. Reduced dosing frequency (e.g. from four times a day to twice a day) improves compliance.
10. 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;33(Suppl A):121-9.

RATIONALE: This non-blinded RCT (n=538) found that 7 days nitrofurantoin MR had equivalent clinical cure rates to co-trimoxazole, and trimethoprim. The rate of gastrointestinal adverse effects was similar between groups (7-8%). This study used 7 days of treatment with each antibiotic; no shorter durations were trialled.

11. Flagas, M.E., Kotsantis I.K., Vouloumanou, E.K. and Rafailidis, P.I. Antibiotics versus placebo in the treatment of women with uncomplicated cystitis: a meta-analysis of randomized controlled trials. *Journal of infection*. 2009; 58(2):91-102.

RATIONALE: Clinical cure for antibiotics compared with placebo: OR 4.67 (95% CI 2.34 to 9.35; four RCTs, n=1062).

12. Milo G, Katchman EA, Paul M, Christiaens T, Baerheim A, Leibovici L. Duration of antibacterial treatment for uncomplicated urinary tract infection in women. Cochrane Database Review. *The Cochrane Library* 2006, Issue 2.

http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD004682/pdf_fs.html

Accessed 23.09.14.

RATIONALE: No difference in outcome between 3 day, 5 day or 10 day antibiotic treatment course for uncomplicated UTI in women (RR 1.06; 95% CI 0.88 to 1.28; 32 trials, n=9605). In this systematic review there are several trials of pivmecillinam used at 200mg three times daily for 3 days, which showed similar efficacy to: pivmecillinam 200mg for 10 days (Gordin, 1987) cephalexin 250 mg for 7 days (Menday, 2000); or cotrimoxazole used for 7 days (Bitsch 1985). One trial showed that pivmecillinam 400mg TDS for 3 days had similar efficacy to 200mg TDS for 7 days (Pitkajarvi 1990) or 10 days (Hansen 1981), another study showed that pivmecillinam 400mg BD for 3 days had similar efficacy as 7 days (Richards 1984). In 2016 the MHRA therefore stated that there was insufficient evidence to recommend the 400mg dose of pivmecillinam dose over the 200mg dose for acute uncomplicated UTI. However PHE expert opinion indicates that if there is a risk of resistance then a higher dose of 400mg should be used as a stat dose, then 200mg three times daily, so that higher concentrations are attained in the urine lowering the risk for selecting out resistant mutants.

13. Newell A, Bunting P, Anson K, Fox E. Multicentre audit of the treatment of uncomplicated urinary tract infection in South Thames. *International Journal of STD & AIDS* 2005;16:74-77.

RATIONALE: This audit of urine samples taken at presentation found that 43.3% of isolates were resistant to amoxicillin, 22.6% were resistant to trimethoprim, and 10.3% were resistant to nitrofurantoin.

14. DTB. Risks of extended-spectrum beta-lactamases. *Drug and Therapeutics Bulletin* 2008;46(3):21-24.

RATIONALE: Extended spectrum beta-lactamases (ESBLs) 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 all cephalosporins. Many ESBL-producing *E. coli* are sensitive to nitrofurantoin.

15. 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. *European Urology* 2008;54:1164-1175.

RATIONALE: In all countries, susceptibility rate to *E. coli* above 90% (p < 0.0001) was found only for fosfomycin, mecillinam, and nitrofurantoin.

16. 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;10:43-50.

RATIONALE: Ninety seven per cent of ESBL-producing *E. coli* isolates and 81% of *Klebsiella pneumoniae* ESBL-producing isolates were susceptible to fosfomycin.

Fosfomycin is now available commercially as an intravenous licensed product in the UK.

Nutritional interactions: Food intake can slow down the absorption of fosfomycin with, as a result, lower concentrations in the urine. Fosfomycin should, therefore, be administered while fasting or 2 or 3 hours before meals.

17. Martindale 30th (The Extra Pharmacopeia) and 36th Editions (The Complete Drug Reference).

RATIONALE: Concentrations of fosfomycin are maintained in the urine for 2 days. A single dose is therefore sufficient in uncomplicated UTI in women. A second dose is required at 3 days in men to maintain inhibitory concentrations to ESBLs in the urine for the 6-7 days recommended for treatment of UTI in men.

18. Ben-Ami R, Rodriguez-Bano J, Arslan H, Pitout JD, Quentin C, Calbo ES, Azap OK, Arpin C, Pascual A, Livermore DM, Carau J, Carmeli Y. A multinational survey of risk factors for infection with extended-spectrum beta-lactamase-producing enterobacteriaceae in nonhospitalized patients. *Clin Infect Dis*. 2009 Sep 1;49(5):682-90.

19. Scottish Antimicrobial Prescribing Group, SAPG 2014. Alternative management of lower urinary tract infection in non-pregnant women.

http://www.scottishmedicines.org.uk/files/sapg/Alternative_management_of_lower_UTI_in_non-pregnant_women.pdf Accessed 23.09.14.

RATIONALE: This evidence based guidance has reviewed, and now recommends that clinicians consider the use of delayed / back-up antibiotics for the management of women with less severe or limited urinary symptoms. The guidance is based on two randomised controlled trials in English and Dutch general practice. 51 of 137 (37%) of Dutch women were willing to delay their antibiotics, 55% (28/51) did not use the antibiotics and 71% of these patients (20/28) reported clinical cure.

20. Thomas K, Weinbren MJ, Warner M, Woodford N, Livermore D. Activity of mecillinam against ESBL producers in vitro. *J Antimicrob Chemother*. 2006 Feb;57(2):367-8.

RATIONALE: This laboratory work indicates that mecillinam is active against the majority of enterobacteriaceae causing UTI, including many ESBL: producing organisms.

21. Damsgaard T, Jacobsen J, Korner B, Tybring L. Pivmecillinam and trimethoprim/sulfamethoxazole in the treatment of bacteriuria. A bacteriological and pharmacokinetic study. *J Antimicrob Chemother* 1979 May;5(3):267-74.

RATIONALE: In this study pivmecillinam 600 mg BD was used for lower urinary tract infection, where it had similar short term symptomatic efficacy to co-trimoxazole (80 + 400mg BD); both were given for 6 days.

22. Titelman E, Iversen A, Kalin M, Giske CG. Efficacy of pivmecillinam for treatment of lower urinary tract infection caused by extended-spectrum β -lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*. *Microb Drug Resist*. 2012 Apr;18(2):189-92.

23. Oplinger M, Andrews CO. Nitrofurantoin Contraindication in Patients with a Creatinine Clearance Below 60 mL/min: Looking for the Evidence. *Ann Pharmacother* 2013;47:106-11. Published Online, 22 Jan 2013, *theannals.com*, doi: 10.1345/aph.1R352 MHRA – advice August 2014

24. Bains A, Buna D, Hoag NA (2009). "A retrospective review assessing the efficacy and safety of nitrofurantoin in renal impairment". *Canadian Pharmacists Journal* 142 (5): 248–252. doi:10.3821/1913-701X-142.5.248.

RATIONALE: These recent reviews of the literature, ^{Oplinger} considered patients with reduced renal function, and suggested that nitrofurantoin could be used down to a eGFR of 40mL.min.^{Bains} The MHRA has reviewed this literature and 2014 recommendations from the MHRA will advise that nitrofurantoin may be used down to a GFR of 45mL/min, and can be used for short courses when the GFR is 30 to 45 mL/min in cases where benefits outweigh the risks because resistance testing indicates there is no other

practical antibiotic alternative.

25. Livermore DM, Mushtaq S, Nguyen T, Warner M. Strategies to overcome extended-spectrum β -lactamases (ESBLs) and AmpC β -lactamases in shigellae. *Int J Antimicrob Agents*. 2011; 37:405-9. doi: 10.1016/j.ijantimicag.2010.11.028. Epub 2011 Jan 26.

RATIONALE: Mecillinam is a β -lactam antibiotic that resists hydrolysis by many common β lactamases. However, innate resistance occurs in proteus and some other enterobacteriaceae including some ESBL producing organisms. Co-amoxiclav can be added to prevent hydrolysis by those ESBLs that can attack the molecule. Pivmecillinam is the oral preparation of mecillinam.

26. Baines SD, O'Connor R, Huscroft G et al. Mecillinam: a low-risk antimicrobial agent for induction of *Clostridium difficile* infection in an in vitro human gut model. *J Antimicrob Chemother* 2009; 63: 838–9.

RATIONALE: 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 thus there is a lower rate of *Clostridium difficile*.

27. Dewar S, Lee C, 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* 2013 doi:10.1093/jac/dkt368.

RATIONALE: Pivmecillinam is an oral drug with minimal effect on the normal intestinal or vaginal microflora and is associated with a lower rate of *Clostridium difficile* infection and vaginal candidiasis.

28. Søråas A, Sundsfjord A, Jørgensen SB, Liestøl K, Jenum PA. High rate of per oral mecillinam treatment failure in community-acquired urinary tract infections caused by ESBL-producing *Escherichia coli*. *PLoS One*. 2014 Jan 15;9(1):e85889. doi: 10.1371/journal.pone.0085889. eCollection 2014.

RATIONALE: In this Norwegian study treatment failure with mecillinam was attributed to the 200mg dose used in Norway. The authors showed evidence that the 200mg dose will only achieve a serum concentration above MIC for 40% of the time even if the MIC is less than 0.25mg/L. Thus we advise treatment with the 400mg dose.

29. Jansåker F1, Frimodt-Møller N, Sjögren 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):769-72. doi: 10.1093/jac/dkt404. Epub 2013 Oct 9.

RATIONALE: This prospective GP and hospital based study in Denmark, Holland and Sweden followed 39 patients diagnosed with UTI caused by ESBL-producing enterobacteriaceae, susceptible to and treated with pivmecillinam. The bacteriological cure for 400 and 200mg three times a day 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 who received 200mg and one who received 400mg three times daily, with bacteriological cure, still had a positive urine sample (ie $\geq 10^3$ cfu/mL), but with a significant reduction (ie pre treatment urine of $\geq 10^5$ cfu/mL).

30. 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 by Hooten et al, which compared three day regimens of high-dose nitrofurantoin (100mg four times daily),

trimethoprim/sulfamethoxazole, cefadroxil, and amoxicillin, which showed that at six weeks post-therapy, nitrofurantoin's clinical efficacy was only 61%. Another trial by Christiaens et al found that three days treatment with nitrofurantoin had a clinical efficacy of 70% seven days after the start of therapy. In comparison, nine studies included in the meta-analysis demonstrated that treatment with nitrofurantoin for five or seven days gave microbiological cure rates of between 79% and 92%, suggesting that five or seven days treatment may be more effective. 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. The authors conclude that it is important to note that treatment durations of at least five days of any antibiotic do appear to optimise efficacy. However there were no studies directly comparing three and five days nitrofurantoin.

31. Gupta K, Hooten 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: This primary care study showed that five days of nitrofurantoin had similar efficacy to three days trimethoprim sulfamethoxazole. In this randomised, open-label trial, involving 338 women aged between 18 and 45 years 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%-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). This study cites other research that compares seven days nitrofurantoin for treatment for uncomplicated cystitis, and notes an average microbiological cure rate of 84%, demonstrating similar results for five and seven days treatment. 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 in uncomplicated cystitis. However, it is also noted that at three days, 98% of women had achieved microbiological cure, but three days treatment cannot be recommended until a well-powered randomised trial is conducted measuring its efficacy.

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/>.

RATIONALE: In this study three day courses of nitrofurantoin and trimethoprim were less effective than five and seven day courses in the treatment of uncomplicated urinary tract infections in women. This was 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 of 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 five days (RR 0.67; 95% CI 0.57-0.82; RR 0.82; 95% CI 0.73-0.91, respectively), and seven days (RR 0.64; 95% CI 0.53-0.77; RR 0.85; 95%

CI 0.71-1.02, respectively) trimethoprim and nitrofurantoin treatment appeared to be more effective than three day 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.

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: This study found that three days of trimethoprim-sulfamethoxazole is more effective in treating uncomplicated urinary tract infections, than three days nitrofurantoin m/r, cefadroxil, or amoxicillin. This prospective randomised trial of 149 female students included four different treatment arms for acute cystitis, showing that three days nitrofurantoin 100mg m/r four times daily in 38 patients was not as effective as three days trimethoprim sulfamethoxazole 160mg/800mg twice daily 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%-41%), 66% in the cefadroxil treatment arm ($p=0.11$; 95% CI -4%-37%), and 67% in the amoxicillin treatment arm ($p=0.11$; 95% CI -3%-34%).

34. 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://fis-his2016-abstracts.elsevierdigitaledition.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%) of nitrofurantoin. Taking this evidence into consideration, PHE have decided to continue prescribing nitrofurantoin for three days, until further evidence that suggests that five days is more efficacious is presented.

35. Ernst EJ, Ernst ME, Hoehns JD, Bergus GR. Women's quality of life is decreased by acute cystitis and antibiotic adverse effects associated with treatment. *Health Qual Life Outcomes*. 2005 Jul; 3(45):1-7. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1183236/>.

RATIONALE: A randomised, open-label, multicenter treatment study of 157 women with clinical signs and symptoms of acute uncomplicated cystitis, aiming to evaluate quality of life in women treated for acute cystitis, and the clinical outcome of treatment interventions. 52 patients received trimethoprim/sulfamethoxazole one double-strength tablet twice daily for three days; 54 patients received ciprofloxacin 250mg twice daily for three days; 51 patients received nitrofurantoin 100mg twice daily for seven days. Clinical cure rates did not differ by treatment with 88%, 82% and 87% of patients treated with three days TMP/SMX, three days ciprofloxacin, and seven days nitrofurantoin,

respectively ($p=0.7$). The authors conclude that patients have a greater improvement in quality of life if experienced clinical cure for cystitis, compared to patients who do not.

36. 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: <https://www.ncbi.nlm.nih.gov/pubmed/6245976>.

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 infections. 67 women received a 7-day course, and 58 were given a 3-day course of treatment. 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.

37. 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%-10.3%). Another clinical trial compared pivmecillinam 20mg 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 days 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 urinary tract infections, particularly premenopausal women.

38. 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

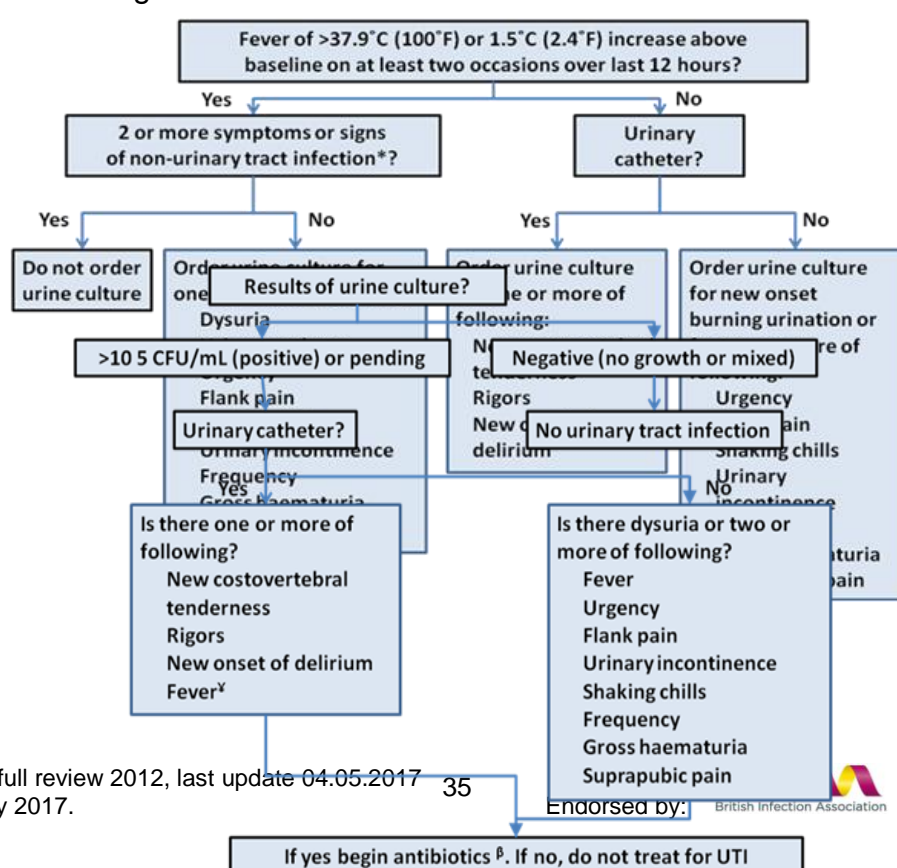
three day treatment group, and nine (17%) patients in the five day treatment group. The authors conclude that a three day course of pivmecillinam is as effective as a five day course of treatment.

39. Abrutyn E, Mossey J, Berlin JA, Boscia J, Levison M, Pitsakis P, Kaye D. Does asymptomatic bacteriuria predict mortality and does antimicrobial treatment reduce mortality in elderly ambulatory women? *Ann Int Med* 1994;120(10):827-33.

RATIONALE: A cohort study and a controlled trial found that bacteriuria was not an independent risk factor for mortality in elderly women without catheters, and that its treatment did not lower the mortality rate.

40. 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/>.

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 (see diagram below), 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. The algorithm indicates that antibiotics should only be prescribed on a positive or pending culture ($>10^5$ CFU/mL), or in cases of systemic symptoms of infection with an in situ catheter. Results indicated that 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). The authors conclude that a multifaceted intervention using algorithms can reduce the number of antimicrobial prescriptions for suspected urinary tract infections in residents of nursing homes.



41. 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 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.

42. 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 and 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 17/33 (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 non-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.

43. 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:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4688879/>.

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 without any antibiotics. Recurrent urinary tract infections were more common in the fosfomycin group, suggesting that antimicrobial treatment might 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.

UTI in patients with catheters

1. Grabe M, Bishop MC, Bjerkland-Johansen TE, Botto H, Cek M, Lobel B, Naber KG, Palou, J, Tenke, P, Wagenlehner F. Guidelines on Urological Infections. *European Association of Urology* 2009: 1-110.

RATIONALE: Asymptomatic bacteriuria is seldom associated with adverse outcomes in people with indwelling catheters. Treatment of bacteriuria causes harms: increased short-term frequency of symptomatic infection, and re-infection with organisms of increased antimicrobial resistance.

2. NICE. Infection control. Prevention of healthcare-associated infections in primary and community care. *The National Collaborating Centre for Nursing and Supportive Care and the Thames Valley University*. 2003 <http://guidance.nice.org.uk/CG139/Guidance> Accessed 23.09.14.

RATIONALE: This guideline originally stated that prophylactic antibiotics were also indicated for people with heart valve lesions, septal defects, patent ductus, or prosthetic valves. However, NICE state that this recommendation has been superseded by their 2008 guideline on prophylaxis of endocarditis, which states that prophylactic antibiotics are no longer required for people with those conditions requiring a catheter change.

3. 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/>.

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 urinary catheter in situ if there is: new costovertebral tenderness; rigors; new onset of delirium, or new onset burning urination, or two or more of: urgency; flank pain; shaking chills; urinary incontinence; frequency; gross haematuria; suprapubic pain. The algorithm indicates that antibiotics should only be prescribed in cases of systemic symptoms of infection with an in situ catheter. Results indicated that 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). The authors conclude that a multifaceted intervention using algorithms can reduce the number of antimicrobial prescriptions for suspected urinary tract infections in residents of nursing homes.

Acute prostatitis

1. BASHH. UK National Guidelines for the Management of Prostatitis. *British Association for Sexual Health and HIV*. 2008.

RATIONALE: MSU for all men: acute prostatitis is a severe illness. It is important that an MSU is sent for culture and sensitivities to ensure that an appropriate antibiotic is used. Treatment regimens: there are no randomized controlled trials of quinolones or trimethoprim for the treatment of prostatitis. Expert opinion is that, for men with acute prostatitis who are suitable for oral antibiotic treatment, ciprofloxacin 500mg BD for 28 days or ofloxacin 200mg BD for 28 days will provide sufficient levels within the prostate gland. Expert opinion is that trimethoprim 200mg BD for 28 days is a suitable alternative for men who are intolerant or allergic to quinolones. Duration of treatment: the optimum duration of treatment is unknown. Expert opinion is that a 4-week course of antibiotics is required to reduce the risk of developing chronic bacterial prostatitis.

2. Micromedex. Drugdex drug evaluations. *Thompson Healthcare*. 2009.

RATIONALE: Trimethoprim reaches good concentrations in prostatic tissue (peak prostate concentration was reported to be 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 concentrations in prostatic fluid, often exceeding serum levels (at 2 to 4 hours following oral administration, prostatic fluid levels ranged from 0.02 to 5.5 mcg/mL compared with serum levels of 1 to 2.5mcg/mL. Ofloxacin also reaches high concentrations in prostatic fluid (at 1 to 4 hours following oral administration prostatic guide levels ranged from 3.22 to 4.25 mcg/g).

UTI in pregnancy

1. SIGN. Management of suspected bacterial urinary tract infection in adults: a national clinical guideline. *Scottish Intercollegiate Guidelines Network*. 2012

<http://www.sign.ac.uk/guidelines/fulltext/88/index.html> SIGN Flow diagram for pregnant women. Accessed 23.09.14.

RATIONALE: MSU should be performed routinely 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. Treatment should also be started in women with asymptomatic bacteriuria.

2. UKTIS. Use of nitrofurantoin in pregnancy. 2015 Nov. Version 3. Available from: <http://111.medicinesinpregnancy.org/bumps/monographs/US-OF-NITROFURANTOIN-IN-PREGNANCY/>.

RATIONALE: There is no strong evidence of an association between in utero nitrofurantoin exposure and an overall increased risk of congenital malformations or of any specific type of malformation. Individual studies have suggested a possible increased risk of hypoplastic left heart, talipes, hypospadias, an/microphthalmia, ASD, and cleft lip/palate; however these findings have not been confirmed in other studies and the increase in risk (if any) of congenital malformations following exposure to nitrofurantoin is likely to be small, especially given that systemic absorption and transfer

to the fetus is low. 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. No studies have investigated the risk of adverse neurodevelopmental outcomes. Nitrofurantoin in the non-pregnant patient can, in rare cases, cause serious adverse reactions including peripheral neuropathy, pulmonary toxicity, and fatal hepatic injury. It has also been associated with haemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Nitrofurantoin use is generally avoided in pregnant patients during labour and delivery because of the theoretical possibility of haemolytic anaemia in the foetus, or in the neonate due to immature erythrocyte enzyme systems. Where possible, antibiotic choice should be informed by culture and sensitivity tests, however if treatment is required urgently or before test results become available, then nitrofurantoin may be considered where clinically appropriate. Any risks to the foetus from the drugs used to treat maternal UTI should be weighed against the potential adverse effects for the mother and foetus from an untreated infection. The decision as to which drug is chosen should be based on the clinical condition of the pregnant woman and local prescribing guidelines. Exposure to nitrofurantoin 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 outcome. Clinicians are reminded of the importance of consideration of such factors when performing case-specific risk assessments.

3. UKTIS. **The treatment of infections in pregnancy.** *The UK Teratology Information Service.* 2008. (Tel: 0844 892 0909, <http://www.uktis.org/docs/Antibiotics.pdf>) Accessed 23.09.14.

RATIONALE: It is important to ensure adequate treatment of maternal infections in pregnancy as failure to treat may lead to adverse maternal and fetal effects as a consequence of uncontrolled infection or fever. When considering treatment with antibacterial agents during pregnancy, the following factors should be considered: the severity of the maternal infection, the effects of any fever present on the pregnancy, the effects of failing to treat the mother, and the potential fetotoxicity of the drugs to be used. Where possible, the results of culture and sensitivity tests should be available before making a treatment choice.

Penicillins, along with cephalosporins, may be used in pregnancy if considered clinically appropriate. Exposure to penicillins at any stage of pregnancy would not usually be regarded as medical grounds for termination of pregnancy.

Penicillins – may be used at any stage in pregnancy if considered clinically appropriate.

Cephalosporins – may be used at any stage in pregnancy if considered clinically appropriate.

Gentamicin – limited data; systemic use may be considered if the clinical indication is strong. Topical use is not expected to be associated with an increased risk to the fetus.

Trimethoprim – risk of neural tube defects due to folate deficiency; folate supplementation is required if trimethoprim is prescribed in pregnancy.

Metronidazole – limited safety data; use may be considered if the clinical indication is strong.

Quinolones – limited safety data; use may be considered if the clinical indication is strong. If a quinolone is required, ciprofloxacin is the agent of choice in the class.

Nitrofurantoin – limited safety data; rare but severe adverse effects have been reported. Treatment with any antibiotic drug listed in this summary at any stage in pregnancy would not usually be regarded as medical grounds for termination of pregnancy. For advice on specific antibiotics in pregnancy please see the individual monographs.

If you are pregnant and require advice regarding exposure to antibiotics please contact your health care professional who can contact UKTIS on your behalf. If you have a patient with exposure to antibiotics and require assistance in making a patient-specific risk assessment, please telephone UKTIS on 0844 892 0909 to discuss the case with a

teratology specialist.

4. Ruxton CHS and Derbyshire E. Women's diet quality in the UK. *Nutrition Bulletin* 2010;35:126-137.
RATIONALE: Data from the National Diet and Nutrition Surveys show that women's dietary intake of iron, vitamin D, calcium and folate remain below recommended levels.
5. Public Health England and the British Society for Antimicrobial Chemotherapy.
RATIONALE: We recommend that cefalexin is reserved for third-line use for the treatment of a UTI in a pregnant woman. Cefalexin has a good safety record in pregnancy. However, because it is a broad-spectrum antibiotic, it increases the risk of *Clostridium difficile*, and there have been reports of *C. difficile* in pregnant women.
6. Roupahel NG, O'Donnell JA, Bhatnagar J, Lewis F, Polgreen PM, Beekman S, Guarner J, Killgore GE, Koffman B, Campbell J, Zaki SR, McDonald LC *Clostridium difficile*-associated diarrhoea: an emerging threat to pregnant women. *Am J Obs Gynaecol* 2008;198:e1-635.e6
RATIONALE: In this series of 10 cases, most were associated with antibiotic use. Seven of the women were admitted to intensive care. Three infants were stillborn and 3 women died.
7. Grabe M, Bishop MC, Bjerkland-Johansen TE, Botto H, Cek M, Lobel B, Naber KG, Palou, J, Tenke, P, Wagenlehner F. Guidelines on Urological Infections. *European Association of Urology* 2009: 1-110.
RATIONALE: Expert consensus is that 7 days of antibiotics should be used to treat urinary tract infections during pregnancy.

Children

1. National collaborating centre for women's and children's health. NICE clinical guideline. *Urinary tract infection in children. Diagnosis, treatment and long-term management*.
<http://www.nice.org.uk/nicemedia/pdf/CG54fullguideline.pdf> Accessed 23.09.14.
RATIONALE: Diagnosis and referral: expert opinion is that children under the age of 3 months with suspected UTI should be admitted; that imaging during the acute episode is only needed for atypical UTI or for children under the age of 6 months with UTI. The guidance differentiates between lower UTI and upper UTI giving a definition as: 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 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. Choice of antibiotics for lower UTI: NICE identified 3 RCTs comparing trimethoprim to other antibiotics for UTI in children, and one systematic review comparing short and long course of antibiotics for UTI in children that included studies assessing trimethoprim, nitrofurantoin and amoxicillin. The NICE guideline development group recommend trimethoprim, nitrofurantoin, amoxicillin, or cefalexin for empirical treatment of lower UTI in children. Duration of antibiotics for lower UTI: one systematic review found no difference in efficacy between short-courses (2-4 days) and longer courses (7-14 days) of antibiotics in children with lower UTI. Upper UTI: one systematic review combined two studies of co-amoxiclav treatment for 10-14 days compared with IV antibiotic treatment. No difference in efficacy was found.
2. Hodson EM, Willis NS, Craig JC. Antibiotics for acute pyelonephritis. *Cochrane Database of Systematic Reviews* 2007.
<http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD003772/frame.html> Accessed 23.09.14.
RATIONALE: Twenty three studies (3407 children) were eligible for inclusion. No significant differences were found in persistent kidney damage at six to 12 months (824 children: RR 0.80, 95% CI 0.50 to 1.26) or in duration of fever (808 children: mean

duration 2.05, 95% CI -0.84 to 4.94) between oral antibiotic therapy (10 to 14 days of cefixime, ceftibuten or co-amoxiclav) and IV therapy (3 days) followed by oral therapy (10 days).

Acute pyelonephritis

1. Grabe M, Bishop MC, Bjerkland-Johansen TE, Botto H, Cek M, Lobel B, Naber KG, Palou, J, Tenke, P, Wagenlehner F. Guidelines on Urological Infections. *European Association of Urology* 2009: 1-110.
RATIONALE: Expert consensus is that admission should be arranged for more severe cases of acute uncomplicated pyelonephritis (e.g. dehydrated, cannot take oral medication, signs of sepsis).
2. Public Health England and the British Infection Association recommends that people with acute pyelonephritis are admitted if there is no response to antibiotics within 24 hours. Lack of response to treatment is likely to be due to antibiotic resistance. The complications of acute pyelonephritis can be life-threatening.
3. Talan DA, Stamm WE, Hooton TM, Moran GJ, Burke T, Iravani A, Reuning-Scherer J and Church DA. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis in women. A randomized trial. *JAMA* 2000;283:1583-90.
RATIONALE: This randomized double-blind controlled trial found that 7 days of ciprofloxacin 500mg bd was as effective as 14 days co-trimoxazole. (E. coli isolates were 100% susceptible to ciprofloxacin in this study.)
4. Public Health England and the British Infection Association recommend ciprofloxacin and co-amoxiclav for the empirical 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 in acute pyelonephritis. Trimethoprim may be used if the causative organism is known to be susceptible to this antibiotic.
5. 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 doi:10.1093/jac/dkt177.
RATIONALE: This systematic review found that a shorter 7 day course of quinolones or beta lactam antibiotics was as effective as a 14 day course. However there was no direct comparison of 7 versus 14 days of trimethoprim or co-trimoxazole, and therefore we recommend 14 days of this antibiotic.
6. Chapman ALN, Seaton RA, Cooper MA et al. Good practice recommendations for outpatient parenteral antimicrobial therapy (OPAT) in adults in the UK: a consensus statement. *J Antimicrob Chemother* 2012;67:1053-62.
RATIONALE: If intravenous treatment is needed for an antibiotic resistant organism, outpatient based treatment can reduce hospitalisation and spread of antibiotic resistant pathogens. This document covers best practice when providing such a service.

Recurrent UTI in non-pregnant women

1. Albert X, Huertas I, Pereiró I, Sanfélix J, Gosalbes V, Perrota C. Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. *Cochrane Database of Systematic Reviews* 2004, Issue 3,
<http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD001209/frame.html>
Accessed 23.09.14.

RATIONALE: Nightly prophylaxis: pooled data from 10 RCTs of poor methodological quality calculated a Relative Risk of having one microbiological recurrence (MR) was 0.21 (95% CI 0.13 to 0.34), favouring antibiotic and the NNT was 1.85. over 6–12 months. But adverse effects do occur and 30% of women did not adhere to treatment. The benefit is lost as soon as prophylaxis stops. Post-coital antibiotics: one study of post-coital ciprofloxacin compared with ciprofloxacin prophylaxis found no significant difference between regimens on the rate of UTIs.

2. Stapleton A, Latham RH, Johnson C, Stamm WE. Postcoital antimicrobial prophylaxis for recurrent urinary tract infection. A randomized, double-blind, placebo- controlled trial. *JAMA* 1990;264(6):702-706.

RATIONALE: This small (n=27) RCT found that the relative risk of symptomatic recurrence was lower with post-coital co-trimoxazole (RR 0.15, 95% CI 0.04 to 0.58). Adverse event rates were low and not significantly different between antibiotic and placebo.

3. Grabe M, Bishop MC, Bjerkland-Johansen TE, Botto H, Cek M, Lobel B, Naber KG, Palou, J, Tenke, P, Wagenlehner F. Guidelines on Urological Infections. *European Association of Urology* 2015: 1-110.

RATIONALE: Standby antibiotics: expert opinion, based on one open prospective trial, is that standby antibiotics may be suitable if the rate of recurrences is not too common. Post-coital antibiotics: expert opinion is that the same antibiotics and same doses as for nightly prophylaxis can be used as a stat dose for post-coital prophylaxis of UTI. This guideline also provides evidence for long-term prophylaxis in recurrent UTI, and suggests that prophylaxis should be prescribed for a period of three to six months, then recurrence rate and need should be reviewed.

4. 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. There have been two recent systematic reviews examining the evidence for cranberry products for recurrent UTI. A 2012 Cochrane review of 24 studies (4473 participants) found a small trend towards fewer urinary tract infections in people taking cranberry juice or other products compared to placebo or no treatment but this was not significant (Jepson et al., 2012). Chi-Hung et al (*Arch Intern Med* 2012) examined 10 trials (1494 subjects, 9 community based): cranberry-containing products were significantly more effective in women with recurrent UTIs (RR, 0.53; 95% CI, 0.33-0.83) ($I^2 = 0\%$), female populations (RR, 0.49; 95% CI, 0.34-0.73) but there was substantial heterogeneity across trials. Many people in the Cochrane review studies stopped drinking the juice, suggesting it may be difficult to continue long term. Cranberry capsules may be more convenient than juice and high strength capsules may be most effective. Studies have demonstrated that compliance is better with capsules than with juice. Thus 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 they can make an informed decision. Advise patients taking warfarin to avoid taking cranberry products unless the health benefits are considered to outweigh any risks.

5. Chi-Hung W, Cheng-Chung F, Nai-Chuan C, Shi-Hung Liu S, Ping-Hsun Y, Tao-Yu W, et al. Cranberry-containing products for prevention of Urinary Tract Infections in susceptible populations. *Arch Intern Med* 2012; 172(13): 988-996.

RATIONALE: This systematic review with meta-analysis of randomised controlled trials included 1494 subjects in the qualitative analysis in 10 review trials, with all but one of the trials following subjects living in the community. Administration of cranberry-containing products differed significantly in form, daily dosage, proanthocyanidins

content, and dosing frequency. Results: cranberry-containing products seemed to be more effective in women with recurrent UTIs (RR, 0.53; 95% CI, 0.33-0.83) ($I^2 = 0\%$), female populations (RR, 0.49; 95% CI, 0.34-0.73) ($I^2 = 34\%$), children (RR, 0.33; 95% CI, 0.16-0.69) ($I^2 = 0\%$), cranberry juice users (RR, 0.47; 95% CI, 0.30-0.72) ($I^2 = 2\%$), and people using cranberry-containing products more than twice daily (RR, 0.58; 95% CI, 0.40-0.84) ($I^2 = 18\%$). The results suggest that cranberry-containing products are associated with protective effect against UTIs. However, this result should be interpreted in the context of substantial heterogeneity across trials.

6. Jepson RG, Williams G, Craig JC. Cranberries for preventing urinary tract infections. The Cochrane Library 2012. Issue 10 <http://summaries.cochrane.org/CD001321/cranberries-for-preventing-urinary-tract-infections> Accessed 23.09.14.

RATIONALE: This review identified 24 studies (4473 participants) comparing cranberry products with control or alternative treatments. There was a small trend towards fewer UTIs in people taking cranberry product compared to placebo or no treatment but this was not a significant finding. Many people in the studies stopped drinking the juice, suggesting it may not be an acceptable intervention. In the long term cranberry products (such as tablets or capsules) were also ineffective (although had the same effect as taking antibiotics), possibly due to lack of potency of the 'active ingredient'. However, four of the five studies in women with recurrent UTI (594 participants) which included a placebo group provided data that could be combined in a meta-analysis (Kontiokari 2001; Barbosa-Cesnik 2011; Stothers 2002; Sengupta 2011). Results showed a small, non-significant reduction in risk of repeat symptomatic UTI with cranberry treatment compared to placebo or no treatment (RR 0.74, 95%CI 0.42 to 1.31). Two studies in women with recurrent UTI (McMurdo 2009; NAPRUTI Study 2011) and one study in children (Uberos 2010) compared cranberry product with antibiotic prophylaxis. All three studies used either cranberry capsules or syrup, rather than cranberry juice. Analysis of the two studies in women showed that cranberry product compared to antibiotic were equally as effective in reducing the risk of repeat UTI in women (RR 1.31, 95% CI 0.85 to 2.02). The study in children also showed that the cranberry product were equally as effective in reducing the risk of repeat symptomatic UTI compared to antibiotics (RR 0.69, 95% CI 0.32 to 1.51).

7. Scottish Antimicrobial Prescribing Group, SAPG 2014. Guidance to improve the management of recurrent lower urinary tract infection in non-pregnant women. http://www.scottishmedicines.org.uk/files/sapg/Management_of_recurrent_lower_UTI_in_non-pregnant_women.pdf Accessed 23.09.14.

RATIONALE: This evidence based guidance gives a very good overview of the management of recurrent UTI, suggesting initial simple measures to limit UTI (including better hydration, post coital voiding, cranberry products, and standby antibiotics). Stresses the importance of confirming diagnosis of UTI and investigation of underlying causes and THEN advises low dose antibiotic prophylaxis with review at 6 months.

8. Rui L, Lindbaek M, Gjølstad S. Use of methenamine as preventative treatment in women with recurrent urinary tract infections. Is it effective? (*unpublished*).

RATIONALE: A retrospective study, in which a complete history of antibiotics dispensed from all Norwegian pharmacies from the Norwegian prescription database was analysed. The UTI antibiotics included were nitrofurantoin, pivmecillinam, trimethoprim, and ciprofloxacin, and any time span for use of methenamine was identified. A comparison was made between patients who received methenamine to those who did not. Initial findings reported by the author have suggested that the group with recurring UTIs have an average of 7.8 antibiotic prescriptions per year, and that the same group after starting methenamine have an average of 1.7 antibiotic prescriptions per year. Initial conclusions suggest that the use of methenamine hippurate is effective as prophylaxis for recurrent uncomplicated urinary tract infections in non-pregnant women.

9. 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; 95% CI 0.07-0.89; bacteriuria: RR 0.56; 95% CI 0.37-0.83). No benefits were reported in patients with renal tract abnormalities (symptomatic UTI: RR 1.54; 95% CI 0.38-6.20; bacteriuria: RR 1.29; 95% CI 0.54-3.07). 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 of seven days to six months (RR 0.14; 95% CI 0.05-0.38), 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. There is however a need for further well-conducted RCTs to look into long-term prophylaxis with methenamine hippurate.
10. British National Formulary (BNF). Methenamine hippurate. 2016 Oct. Available from: <http://www.evidence.nhs.uk/formulary/bnf/current/5-infections/51-antibacterial-drugs/5113-urinary-tract-infections/methenamine-hippurate>.
RATIONALE: A BNF formulary guideline, indicating the use of methenamine hippurate for prophylaxis and long-term treatment of chronic or recurrent lower urinary tract infection. This guideline states that use of methenamine hippurate should be avoided in patients with hepatic or renal impairment, and should be used with caution in pregnancy. Dosage is outlined as 1g every 12 hours. Child doses (6-12 years) are also listed as 500mg every 12 hours.

GASTRO-INTESTINAL TRACT INFECTIONS

Oral candidiasis

Note that oral candidiasis is uncommon in immunocompetent adults and therefore the evidence is taken from randomised controlled trials in children and immunocompromised adults. However anti-fungals are likely to be more effective in the immunocompetent adult population. Also note that as oral candidiasis is uncommon in immunocompetent adults, consider investigating for an underlying comorbidity or immunosuppressive illness.

1. Hoppe J, Treatment of oropharyngeal candidiasis in immunocompetent infants: A randomized multicentre study of Miconazole gel vs Nystatin suspension, Antifungals study group, *Pediatr Infect Dis J*. 1997 Mar;16(3):288-93.
RATIONALE: 227 patients under the age of 1 year were recruited to the trial. Cure by day 5 was achieved by 84.7% of 98 patients in the miconazole treatment arm compared with 21.2% of 85 treated with nystatin. At day 8 the cure rates were 96.9% versus 37.6% and at day 12 they were 99.0% versus 54.1%. There was not a statistically significant increase of side-effects (4.5% Miconazole / 3.5 Nystatin) or relapse rates with Miconazole.
2. Hoppe J, Hahn H, Randomized comparison of two nystatin oral gels with miconazole oral gel for treatment of oral thrush in infants. Antimycotics Study Group, *Infection* 1996, 24(2) 2136-139.
RATIONALE: 95 otherwise healthy patients under the age of one year were recruited to this trial. Clinical cure in Miconazole study group (given miconazole oral gel four times

daily for either 8, 10 or 14 days) 85.1% (27 patients) compared with 42 and 28% in branded nystatin groups (33 and 35 patients). Relapses were seen in nystatin groups (15 patients) but not in miconazole group.

3. Bensadoun R, Daoud J et al, Comparison of the efficacy and safety of miconazole 50-mg mucoadhesive buccal tablets with miconazole 500-mg gel in the treatment of oropharyngeal candidiasis. A prospective, randomized, single-blind, multicenter, comparative, phase III trial in patients treated with radiotherapy for head and neck cancer, *Cancer*. 2008 Jan 1;112(1):204-11.

RATIONALE: In this comparative trial of cancer patients oral candidiasis was effectively treated by both tablet and gel formulations. Clinical success was achieved in 56% of 141 patients who received 14 days of buccal tablet administration miconazole and 49% of 141 patients who received 14 days of the gel preparation. Other end-points of this study were largely non-significant but 29% of patients who used buccal preparation had side-effects versus 27% in the gel preparation group. However fewer people dropped out of study due to serious adverse events (3 versus 6 respectively) when using the buccal preparation.

4. Pons V, Greenspan D, et al. Oropharyngeal candidiasis in patients with AIDS: randomized comparison of fluconazole versus nystatin oral suspensions. *Clin Infect Dis*. 1997;24(6):1204-1207.

RATIONALE: Cure was achieved at day 14 in 87% of 83 HIV positive patients who were treated with fluconazole and 52% of 84 patients who received nystatin. Mycological clearance was achieved in 60% of the fluconazole arm and 6% of patients treated with nystatin; 18% of patients relapsed on fluconazole contrasted with 44% on nystatin respectively at day 28. GI side effects were comparable but two patients in the fluconazole arm developed deranged LFTs, one having to withdraw.

5. Flynn PM, Cunningham CK et al, Oropharyngeal candidiasis in immunocompromised children: a randomized, multicenter study of orally administered fluconazole suspension versus nystatin. The Multicenter Fluconazole Study Group. *J Pediatr*. 1995 Aug;127(2):322-8.

RATIONALE: 91% of patients treated with fluconazole were cured at day 14 compared with 51% of patients treated with nystatin. Mycologically there was organism eradication in 76% on fluconazole versus 11% on nystatin. Both regimens were tolerated well with similar relapse rates.

6. BHIVA British HIV Association and British Infection Association Guidelines for the Treatment of Opportunistic Infection in HIV-seropositive Individuals 2011

http://www.bhiva.org/documents/Guidelines/OI/hiv_v12_is2_Iss2Press_Text.pdf (Accessed 13.11.14).

RATIONALE: This recommends fluconazole treatment for oral candidiasis in HIV positive patients. Patients with extensive/severe candidiasis or with a background of HIV should receive oral fluconazole therapy. If patients are systemically unwell or have not responded to oral fluconazole consider referral to secondary care.

7. Clinical Knowledge Summaries (CKS). Candida - oral. 2013 Jul. Available from:

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

RATIONALE: CKS recommends for localized or mild oral candidal infection, prescribe topical treatment for 7 days (and advise the person to continue treatment for 2 days after symptoms resolve). CKS advise that miconazole oral gel 20mg/mL QDS should be offered first-line, or 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 7 days, and continued for a further 7 days if candida infection is persistent. CKS recommendations for the assessment and treatment of oral candidal infection are in line with expert opinion, as there is a lack of direct evidence from randomized controlled

trials (RCTs) to support the use of topical miconazole or nystatin, or oral fluconazole in the treatment of oral candidiasis in otherwise healthy adults. However, its use is supported by pharmacological principles, historical use, and extrapolation of clinical data from trials in other groups (such as infants and people who are immunosuppressed).

Eradication of *Helicobacter pylori*

Helicobacter pylori treatment requires a proton pump inhibitor to increase the PH so that antibiotics are active in the acidic environs of the stomach, plus two antibiotics. Amoxicillin, clarithromycin, metronidazole, levofloxacin, tetracycline hydrochloride are all suitable. Tripotassium dicitratobismuthate (De-nol tab[®]), bismuth subsalicylate, rifabutin and furazolidone are alternative third line agents. Previous use of quinolones or clarithromycin, metronidazole significantly increase resistance and decrease efficacy of regimens so clinicians should enquire if they have previously been used for any infection, and choose a regimen accordingly.

1. NICE. Dyspepsia and gastro-oesophageal reflux disease: Investigation and management of dyspepsia, symptoms suggestive of gastro-oesophageal reflux disease, or both. *National Institute for Health and Clinical Excellence*. September 2014.

<http://www.nice.org.uk/guidance/cg184/chapter/1-recommendations###helicobacter-pylori-testing-and-eradication> Accessed 30.09.14.

RATIONALE: NICE give guidance on when to consider H pylori test and treat in primary care and the treatment regimens based on an extensive systematic review of the efficacy of regimens in countries with similar resistant rates to the UK. First-line H pylori eradication: NICE recommend a twice daily full-dose PPI (Esomeprazole 20mg, Lansoprazole 30mg, Omeprazole 20-40mg, Pantoprazole 40mg, Rabeprazole 20mg) plus amoxicillin (as very little resistance) with either clarithromycin or metronidazole for first line therapy in patients who are not allergic to penicillin. A similar regimen with amoxicillin is recommended second line using amoxicillin with the second agent (clarithromycin or metronidazole that has not previously been used). Second-line in patients previously exposed to metronidazole and clarithromycin they recommend PPI plus tetracycline plus levofloxacin.

NICE recommend that consideration should be given to avoiding clarithromycin or levofloxacin if previously used for other infections.

In penicillin allergic patients NICE recommend a twice daily full-dose PPI with clarithromycin and metronidazole. In allergic patients who have had clarithromycin previously for another infection NICE recommend PPI plus, bismuth, plus tetracycline plus metronidazole. In penicillin allergic patients who relapse full-dose PPI plus metronidazole plus levofloxacin (if penicillin allergic patients have had a quinolone previously for another infection NICE recommend PPI plus, bismuth, plus tetracycline plus metronidazole).

Duration of treatment: although 14-day triple therapy gives almost a 10% higher eradication rate, the absolute benefit of H pylori therapy is modest in NUD and undiagnosed dyspepsia and the longer duration of therapy does not appear cost effective. In patients with PUD increasing the course to 14 days also gives a nearly 10% higher eradication rate, but does not appear cost effective.

MALToma: expert opinion is that for MALT lymphoma, the increased efficacy of a 14-day regimen will reduce the need for chemotherapy and/or gastric resection.

2. Malfertheiner P, Megraud F, O'Morain C, Bazzoli F, El-Omar E, Graham D, Hunt R, Rokkas T, Vakil N, Kuipers EJ, The European Helicobacter Study Group (EHSg). Current concepts in the management of *Helicobacter pylori* infection: the Maastricht III Consensus Report. *Gut* 2007;56:772-781.

RATIONALE: MALToma: sixty two percent of patients with low grade gastric MALT lymphoma have complete remission after H pylori eradication within 12 months. Second-

line treatment: bismuth-based quadruple therapy is a preferred option.

3. Moayyedi P, Soo S, Deeks JJ, Delaney B, Harris A, Innes M, Oakes R, Wilson S, Roalfe A, Bennett C, Forman D. Eradication of *Helicobacter pylori* for non-ulcer dyspepsia. *The Cochrane library* 2006. Issue 2

<http://mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD002096/frame.html>

Accessed 23.09.14.

RATIONALE: Pooled data from 17 RCTS (n=3566) found there was a 10% relative risk reduction in dyspepsia symptoms in people with non-ulcer dyspepsia randomized 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).

4. Delaney BC, Qume M, Moayyedi P, Logan RFA, Ford AC, Elliott C, McNulty C, Wilson S, Hobbs FDR. Helicobacter pylori test and treat versus proton pump inhibitor in initial management of dyspepsia in primary care: multicentre randomised controlled trial (MRC-CUBE trial). *BMJ* 2008;336:651-654.

RATIONALE: At 12 months, there were no significant differences in QALYs, costs, or dyspeptic symptoms between the group assigned to initial H pylori test and treat and the group assigned to initial acid suppression (n=699).

5. Fischbach L and 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;26:343-357.

RATIONALE: Pooled data found that the efficacy of a PPI + clarithromycin + metronidazole was reduced more by resistance to clarithromycin than by resistance to metronidazole. Metronidazole resistance reduced efficacy by 18% while clarithromycin resistance was estimated to reduce efficacy by 35%. Clarithromycin resistance reduced the efficacy of a PPI + clarithromycin + amoxicillin by 66%.

6. McNulty CAM, Lasseter G, Shaw I, Nichols T, D'Arcy S, Lawson A, Glocker E. Is Helicobacter pylori antibiotic resistance surveillance needed and how can it be delivered? *Aliment Pharmacol Ther* 2012; 35: 1221–1230.

RATIONALE. This study determined the prevalence of H. pylori antibiotic resistance in patients attending endoscopy in England and Wales, and the feasibility of an antibiotic resistance surveillance programme testing. H.pylori were cultured in 6.4% of 2063 patients attending Gloucester and Bangor hospitals. Resistance to amoxicillin, tetracycline and rifampicin/rifabutin was below 3% at all centres. Clarithromycin, metronidazole and quinolone resistance was significantly higher in HRU (68%, 88%, 17%) and Bangor isolates (18%, 43%, 13%) than Gloucester (3%, 22%, 1%). Each previous course of these antibiotics was associated with an increase in the risk of antibiotic resistance to that agent [clarithromycin: RR = 1.5 (P=0.12); metronidazole RR = 1.6 (P=0.002); quinolone RR = 1.8 (P=0.01)].

7. Luther J, Higgins PDR, Schoenfield PS, Moayyedi P, Vakil N, Chey WD. Empiric quadruple vs. triple therapy for primary treatment of *Helicobacter pylori* infection: systematic review and meta-analysis of efficacy and tolerability. *Am J Gastroenterol* 2010;105:65-73.

RATIONALE: Pooled data from 9 RCTs (n=1679) found that eradication rates were comparable between clarithromycin triple therapy (77%) and bismuth-containing quadruple therapy (78%). Most trials of 7-10 days duration.

8. Drugs.com. Helidac accessed online via <http://www.drugs.com/mtm/helidac.html>

RATIONALE: In the UK bismuth is available as De-nol tab[®] (tripotassium dicitratobismuthate) or as bismuth subsalicylate (Pepto-Bismol[®]). Bismuth subsalicylate (Pepto-Bismol[®]) is non-prescribable and is available over the counter as a chewable lozenge or liquid. Astellas have plans in late 2015 or early 2016 to discontinue De-Nol tab from the UK market for commercial reasons, however De-Nol may still be available via other suppliers in the future. In the US, there is a licensed proprietary HP eradication

regimen based on Pepto Bismol. The Helidac Therapy Pack consists of a 14 day course of Pepto Bismol (two 262.4mg-chewable tablets), metronidazole 250mg and tetracycline 500mg, all taken four times daily. This pack is taken in conjunction with an H2 antagonist. HP eradication rates with Helidac in patients with a history of duodenal ulcer disease have been reported to be in the 80% range, and 77-82% in patients with active duodenal ulcer disease (Luther, 2010). A proton pump inhibitor may be preferred to an H2 antagonist for concomitant use with the Pepto Bismol regimen. However, there is no clinical experience in UK of using Pepto Bismol as part of a HP eradication regimen and this use, like that of De-Nolab, would be off-label.

9. Dore MP, Lu H, Graham DY. Role of bismuth in improving Helicobacter pylori eradication with triple therapy. *Gut*. 2016 May;65(5):870-8. doi: 10.1136/gutjnl-2015-311019. Epub 2016 Feb 4.

RATIONALE: This review describes the increasing antibiotic resistance worldwide and added value of using bismuth with resistance is high. It estimates that the addition of bismuth to form a quadruple therapy can increase eradication by 30-40% in populations with high resistance.

10. Public Health England recommends that oxytetracycline is not substituted for tetracycline hydrochloride as part of the quadruple therapy regimen. Oxytetracycline is thought to have different mucus penetration properties to tetracycline hydrochloride. In addition, the treatment studies have been done with tetracycline hydrochloride. If third line treatment is required clinicians may also consider changing the PPI to rabeprazole, as it has a different metabolism to the other PPIs which may be metabolised rapidly in some patients, causing treatment failure.

11. Fuccio L, Minardi ME, Zagari RM, Grilli D, Magrini N, Bazzoli F. Meta-analysis: duration of first-line proton-pump inhibitor based triple therapy for Helicobacter pylori eradication. *Annals Internal Medicine* 2007; 147: 553-562.

RATIONALE: Pooled data found that extending the course of triple therapy from 7-14 days increased eradication rates only by about 5% (no statistically significant difference). The authors concluded that this is unlikely to be a clinically useful difference.

Infectious diarrhoea

1. The Griffin Report. Report of the Independent Investigation Committee June 2010. Review of the major outbreak of *E. coli* O157 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 www.griffininvestigation.org.uk Accessed 23.09.14.

2. Farthing M, Feldman R, Finch R, Fox R, Leen C, Mandal B, Moss P, Nathwani D, Nye F, Percival A, Read R, Ritchie L, Todd WT, Wood M. The management of infective gastroenteritis in adults. A consensus statement by the British Society for the Study of Infection. *J Infect* 1996;33:143-52.

RATIONALE: Empirical treatment for patients well enough to be managed in primary care is not recommended because 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.

3. Public Health England and the British Infection Association recommend that, if campylobacter is strongly suspected as the cause of diarrhoea, consider empirical treatment with clarithromycin. Quinolones are not recommended because there is increasing resistance of campylobacter to quinolones, and broad spectrum antibiotics such as quinolones are not recommended for empirical therapy because they are associated with an increased risk of *Clostridium difficile*, MRSA, and antibiotic resistance including resistant UTIs.

4. *E. coli* O157 Independent Investigation Committee. Review of the major outbreak of *E. coli* O157 in Surrey, 2009. <http://www.griffininvestigation.org.uk/> Accessed 23.09.14.

RATIONALE: The Griffin report recommends that *E coli* O157 should be suspected in any child presenting with bloody diarrhoea.

Clostridium difficile

1. Updated Guidance on the Management and treatment of *Clostridium difficile* infection. Public Health England. <https://www.gov.uk/government/publications/clostridium-difficile-infection-guidance-on-management-and-treatment> Accessed 23.09.14.

RATIONALE: Supportive care should be given, including attention to hydration, electrolytes and nutrition. Antiperistaltic agents should be avoided in acute infection. This is because of 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.

Mild disease

Patients with mild disease may not require specific *C. difficile* antibiotic treatment. If treatment is required, oral metronidazole is recommended (dose: 400–500mg tds for 10–14 days) as it has been shown to be as effective as oral vancomycin in mild to moderate CDI (Zar et al., 2007; Louie et al., 2007; Bouza et al., 2008).

Moderate disease

For patients with moderate disease, a 10- to 14-day course of oral metronidazole is the recommended treatment (dose: 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 (HICPAC, 1995; American Society of Health-System Pharmacists, 1998; Gerding, 2005).

Severe disease

For patients with severe CDI, oral vancomycin is preferred (dose: 125mg qds for 10–14 days). This is because of relatively high failure rates of metronidazole in recent reports and a slower clinical response to metronidazole compared with oral vancomycin treatment (Wilcox and Howe, 1995; Musher et al., 2005; Lahue and Davidson, 2007; Zar et al., 2007). Two double-blind randomised studies reported that vancomycin is superior to metronidazole in severe cases of CDI (Louie et al., 2007; Bouza et al., 2008). A pooled analysis of these two phase 3 studies has shown that metronidazole was overall inferior to vancomycin (Johnson et al., 2012).

We recommend using any of the following to indicate severe CDI and so to use oral vancomycin in preference to metronidazole:

- WCC more than $15 \times 10^9/L$;
- acutely rising blood creatinine (e.g. more than 50% increase above baseline);
- temperature more than 38.5°C; or
- evidence of severe colitis (abdominal signs, radiology).

Recurrent disease

Recurrent disease may occur in up to 20% of patients, up to half of which may actually be reinfections rather than relapse. The same antibiotic can be used for a second course. 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, such as 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 (six weeks in total) (Tedesco *et al.*, 1985). Clearly, this may provide a considerable selective pressure for vancomycin resistance, e.g. in enterococci. Fidaxomicin should also be considered for patients with severe CDI who are considered at high risk for recurrence; these include elderly patients with multiple comorbidities who are receiving concomitant antibiotics (Hu et al, 2009; Wilcox 2012).

Fidaxomicin is very expensive and may not be of additional benefit for some strains of *C. difficile* (e.g. ribotype O157). Its role in multiple recurrences is unclear. Local cost-

effectiveness based decision making should determine its use, or seek specialist advice.

2. Howell MD, Novack V, Grgurich P, Soulliard D, Novack L, Pencina M, Talmor D (2010). Iatrogenic gastric acid suppression and the risk of nosocomial *Clostridium difficile* infection. *Arch Intern Med* 170: 784-90.

RATIONALE: There is increasing evidence that acid-suppressing medications, in particular proton pump inhibitors (PPIs) may be a risk factor for CDI. Notably, Howell et al. (2010) reported a correlation between the degree of acid suppression and risk of CDI (i.e. a 'dose response' effect), which ranged from none (Odds Ratio 1), to H₂ receptor antagonists (OR 1.53, 95% CI 1.12-2.10) to once daily PPI (OR 1.74, 1.39-2.18) to more frequent PPI (OR 2.36, 1.79-3.11). It remains possible that these associations are confounded by other CDI risk factors (Cohen et al, 2010). 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/reviewing the need for PPIs in patients with or at high risk of CDI.

3. 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;55:495-501.

RATIONALE: This retrospective review of 102 patients given a 5-day course of metronidazole for *Clostridium difficile* infection found that 70.3% responded by the end of the 5 day course. Twenty-one of the remaining 30 patients eventually responded to metronidazole, but needed longer treatment courses.

4. National Institute of Clinical Excellence (2012). *Clostridium difficile* infection: fidaxomicin. Available at: <http://www.nice.org.uk/Advice/ESNM1> Accessed 23.09.14.

RATIONALE: Until recently there were only two main alternatives (metronidazole or vancomycin) for the treatment of CDI (Cohen et al, 2010). Oral fidaxomicin was approved for the treatment of CDI in Europe in 2012 (Johnson & Wilcox, 2012; Wilcox, 2012), and has been reviewed by the National Institute for Clinical Excellence (NICE; the information published by NICE is not formal guidance) and the Scottish Medicines Consortium (SMC). Two, phase 3, multi-centred, randomised, double-blind trials had almost identical designs and compared oral fidaxomicin (dose: 200mg bd for 10–14 days) with oral vancomycin (dose: 125mg qds for 10–14 days) (Louie et al, 2011; Cornely et al, 2012). The studies had essentially similar results. Fidaxomicin was non-inferior to vancomycin in the initial clinical cure of CDI (relative risk (RR) 0.88 (95% CI 0.64, 1.19), p=0.396), but was superior in reducing recurrence (RR 0.54 (95% CI 0.42, 0.71), p<0.001) and sustained clinical cure (RR 0.68 (95% CI 0.56, 0.81), p<0.001) (all modified intention to treat analysis of combined study results) (Crook et al, 2012). The side-effect profile of fidaxomicin appears similar to that of oral vancomycin. The acquisition cost of fidaxomicin is considerably higher than vancomycin (which is more expensive than metronidazole). Therefore local decision makers need to take into account the benefits versus increased costs.

Traveller's diarrhoea

1. Dupont HL. Systematic review: prevention of travellers' diarrhoea. *Aliment Pharmacol Ther* 2008;27:741-51.

RATIONALE: Expert opinion is that people travelling to a high-risk area whose condition could be worsened by a bout of diarrhoea may be considered for standby antibiotics.

2. Centres for Disease Control and Prevention – Travellers' Health: Yellow Book. <http://wwwn.cdc.gov/travel/yellowBookCh4-Diarrhea.aspx> Accessed 23.09.14.

RATIONALE: High-risk countries are defined as most of Asia, the Middle-East, Africa, Mexico, Central and Southern America. Expert opinion is that bismuth subsalicylate (Pepto-Bismol) can be used for prophylaxis: one trial 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.

3. de Bruyn, G., Hahn, S. and Borwick, A. Antibiotic treatment for travellers' diarrhoea. The Cochrane Library. Issue 3. 2000 John Wiley & Sons, Ltd.
<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002242/abstract> Accessed 23.09.14.
RATIONALE: Of 20 RCTs identified, ten RCTs evaluated short-courses of quinolones, three RCTs evaluated stat doses of quinolones, and one RCT evaluated azithromycin for travellers' diarrhoea.
4. Steffen R, Mathewson JJ, Ericsson CD, Du Pont HL, Helminger A, Balm TK, Wolff K, Witassek F. Traveller's diarrhoea in West Africa and Mexico: faecal transport systems and bismuth subsalicylate for self-therapy. *J Infect Dis* 1988;157(5):1008-13.
RATIONALE: A two-day treatment course of bismuth reduced the number of stools by 17% compared with placebo.

Threadworm

1. CKS (2011) Threadworm. Clinical Knowledge Summaries.
<http://cks.nice.org.uk/threadworm#!scenario> Accessed 05.01.15.
RATIONALE: there is no good trial evidence regarding the efficacy of anthelmintics in the treatment of threadworm. The limited data available are from relatively old, small studies comparing mebendazole with either placebo, or with drugs that are not available in the UK. There are few contraindications to the use of mebendazole, and the manufacturer reports that post-marketing surveillance has revealed no serious safety concerns [ABPI Medicines Compendium, 2005; BNF 65, 2013]. The British National Formulary for Children recommends mebendazole for treating threadworm infection in children over 6 months; however, it is not licensed for use in children less than 2 years of age [BNF 65, 2013]. Mebendazole does not kill eggs, therefore adequate personal and environmental hygiene is essential to prevent reinfestation from recently swallowed eggs, or eggs already in the environment. The recommendation to treat people who cannot take or do not wish to take an anthelmintic with physical removal of the eggs combined with strict hygiene measures is based on expert opinion [Ibarra, 2001]. CKS found no published studies regarding the efficacy of these methods. It is based on the life cycle of the threadworm (adults survive for about 6 weeks) and the long viability of eggs (up to 2 weeks). Washing or wiping at 3 hourly intervals is intended to prevent reinfection [Ibarra, 2001]. However washing or wiping this frequently may be impractical, and the role that reinfection plays in reinfestation is likely to be minimal. Therefore washing or wiping twice a day may be more realistic. Piperazine, an alternative anthelmintic indicated for the eradication of threadworm in adults and children aged over 3 months, was discontinued by the manufacturer in 2012.

GENITAL TRACT INFECTIONS

STI screening

1. National Chlamydia Screening Programme <http://www.chlamydia-screening.nhs.uk/ps/> Accessed 23.09.14.
2. BASHH and MedFASH. Standards for the management of sexually transmitted infections (STIs). *British Association of Sexual Health and HIV and the Medical Foundation for AIDS and Sexual Health*. 2010. www.medfash.org.uk Accessed 23.09.14.

Chlamydia trachomatis

1. National Chlamydia Screening Programme <http://www.chlamydia-screening.nhs.uk/ps/> Accessed 23.09.14.

2. SIGN. Management of genital *Chlamydia trachomatis* infection: a national clinical guideline. *Scottish Intercollegiate Guidelines Network* 2009.

<http://www.sign.ac.uk/guidelines/fulltext/109/index.html> Accessed 23.09.14.

RATIONALE: Treatment of partners: the treatment of partners prior to resuming sexual intercourse is the strongest predictor for preventing re-infection. Treatment in pregnancy: expert opinion is that azithromycin 1g stat is the first-line treatment for Chlamydia in pregnant women.

3. BASHH. UK National Guidelines for the Management of Genital Tract Infection with *Chlamydia trachomatis*. *British Association for Sexual Health and HIV*.

<http://www.bashh.org/documents/65.pdf> Accessed 23.09.14.

RATIONALE: Treatment of partners: partners should also be treated for C trachomatis infection. Re-testing: expert opinion is that a test of cure is not routinely recommended, but should be performed in pregnancy, or where non-compliance or re-exposure are suspected. The higher rate of positive tests after treatment during pregnancy is attributed to either less efficacious treatment regimen, non-compliance, or re-infection.

4. Lau CY, Qureshi AK. Azithromycin versus doxycycline for genital chlamydial infections: a meta-analysis of randomised controlled trials. *Sexually transmitted diseases*. 2002;29:497-502.

RATIONALE: Pooled data (12 RCTs, n=1543) found that microbiological cure was achieved in 97% of people taking azithromycin and 98% of those taking doxycycline, $p = 0.296$; no significant difference.

5. Brocklehurst P, Rooney G. Interventions for treating genital Chlamydia trachomatis infection in pregnancy. *Cochrane Database of Systematic Reviews* 1998. Issue 4.

<http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD000054/frame.html> Accessed 23.09.14.

RATIONALE: Pooled data from four RCTs found that 8% of women taking azithromycin (11/145) failed to achieve microbiological cure compared with 19% of women taking erythromycin (27/145); OR 0.38, 95% CI 0.19 to 0.74). Pooled data from three RCTs found that 9% of women taking amoxicillin (17/199) failed to achieve microbiological cure compared with 15% of women taking erythromycin (28/191); OR 0.54, 95% CI 0.28 to 1.02.

6. UKTIS. The treatment of infections in pregnancy. *National Teratology Information Service*. 2012. (Tel: 0844 892 0909, http://www.uktis.org/html/maternal_exposure.html Accessed 23.09.14.

RATIONALE: **Azithromycin:** There are few published data on the use of **azithromycin** in human pregnancy however the currently available data do not indicate that the use of azithromycin in pregnancy is associated with an increased risk of malformations. An increased incidence of cardiovascular defects and pyloric stenosis have been suggested for macrolides as a class, although causality has not been established conclusively. **Erythromycin:** Erythromycin is a broad spectrum macrolide antibiotic. The majority of studies do not support an association between erythromycin exposure and any malformation or any other adverse fetal effect, however associations have been made with an increased incidence of cardiovascular defects and pyloric stenosis, although causality has not been conclusively established. **Amoxicillin:** there is no evidence to suggest that penicillins are associated with an increased risk of malformations or other forms of fetal toxicity in human pregnancy.

7. GRASP Steering Group. GRASP 2014 report: Surveillance of antimicrobial resistance to *Neisseria gonorrhoeae*.

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/476582/GRASP_2014_report_final_111115.pdf Accessed 18.05.16.

RATIONALE: This report describes the latest data on trends in and epidemiology of

antimicrobial resistance and decreased susceptibility in gonococcal infection in England and Wales using data collected through GRASP in 2014. In 2014 in England, compared to 2013, the number of new gonorrhoea diagnoses increased by 19% (especially among men who have sex with men) and young adults. Ciprofloxacin resistance is now endemic in England and Wales, accounting for 37.3% of all gonorrhoea isolates tested in 2014, an increase from 29.3% in 2013. 1.4% of isolates exhibited decreased susceptibility to cefixime; no isolates were confirmed to have resistance to ceftriaxone (MIC ≥ 0.125 mg/L). However, in early 2015, one isolate was confirmed to have resistance to ceftriaxone (MIC 0.25mg/L). As resistance to cephalosporins is increasing and treatment failures have been reported with cefixime, if gonorrhoea is suspected, ceftriaxone (500mg IM stat) is the cephalosporin of choice.

8. Ross JDC, Cronjé HS, Paszkowski T, Rakoczi I. Moxifloxacin versus ofloxacin plus metronidazole in uncomplicated pelvic inflammatory disease: results of a multicentre, double blind, randomised trial. *Sex Transm Infect* 2006;82(6):446-51.

RATIONALE: This trial in 564 patients with uncomplicated PID in hospitals from 13 countries, compared oral metronidazole 500mg twice daily with either oral ofloxacin 400mg twice daily or moxifloxacin 400mg once daily. Clinical resolution with 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*.

9. Ison CA, Mouton JW, Jones K. Which cephalosporin for gonorrhoea? *Sex Transm Infect* 2004;80:386-88.

RATIONALE: This study used previously published pharmacokinetic data on cefixime, ceftriaxone and cefuroxime to model the length of time tissue concentrations to these drugs would be above the MIC₉₀ (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 in *Neisseria gonorrhoeae*.

10. British Association for Sexual Health and HIV.

- 2006 UK National Guideline for the Management of Genital Tract Infection with *Chlamydia trachomatis*. <http://www.bashh.org/documents/65.pdf> Accessed 23.09.14.
Covers the symptoms and signs of Chlamydia and recommended diagnostic tests.
- 2005 United Kingdom National Guideline for the Management of Pelvic Inflammatory Disease. <http://www.bashh.org/documents/118/118.pdf> Accessed 23.09.14

Recommended regimens: the recommended regimens for outpatient management are either ofloxacin plus metronidazole for 14 days, or a stat dose of IM ceftriaxone plus metronidazole and doxycycline 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. Treatment of partners: partners should be screened for gonorrhoea and chlamydia.

- 2010 National guideline for the management of epididymo-orchitis
<http://www.bashh.org/documents/3546.pdf> Accessed 23.09.14.

11. Meads C, Knight T, Hyde C and Wilson J. The clinical effectiveness and cost-effectiveness of antibiotic regimens for pelvic inflammatory disease. West Midlands Health Technology Assessment group. 2004.

http://www.rep.bham.ac.uk/2004/Pelvic_Inflammatory_Disease.pdf Accessed 23.09.14.

RATIONALE: This systematic review identified 34 trials of antibiotic treatment for PID. Most studies were small, open-label, and of poor methodological study. One small trial was found that compared oral ofloxacin plus metronidazole with clindamycin plus gentamicin. The cure rate was 15/15 for ofloxacin plus metronidazole plus 17/18 for clindamycin plus gentamicin. The systematic 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-analysis of these six studies found no difference in cure rates between IM ceftriaxone plus doxycycline and the comparator antibiotics.

12. Ross JDC, Cronjé HS, Paszkowski T, Rakoczi I. Moxifloxacin versus ofloxacin plus metronidazole in uncomplicated pelvic inflammatory disease: results of a multicentre, double blind, randomised trial. *Sex Transm Infect* 2006;82(6):446-51.

RATIONALE: This trial in 564 patients with uncomplicated PID in hospitals from 13 countries, compared oral metronidazole 500mg twice daily with either oral ofloxacin 400mg twice daily or moxifloxacin 400mg once daily. Clinical resolution with 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*.

13. Arredondo JL, Diaz V, Gaitan H *et al*. Oral clindamycin and ciprofloxacin versus intramuscular ceftriaxone and oral doxycycline in the treatment of mild-to-moderate pelvic inflammatory disease in outpatients. *Clin Infect Dis* 1997;24(2):720-727.

RATIONALE: In this clinical trial in South American outpatients, clinical cure was attained with 97% (65/67) in the oral clindamycin and ciprofloxacin group compared to 95% (61/64) in the ceftriaxone and doxycycline group.

Epididymitis

1. BASHH. UK National Guidelines for the Management of Epididymo-orchitis. *British Association for Sexual Health and HIV*. <http://www.bashh.org/documents/3546.pdf> Accessed 22.09.14.

RATIONALE: In men under 35 years epididymo-orchitis is most often caused by a sexually transmitted pathogen such as *Chlamydia trachomatis* or *Neisseria gonorrhoeae*. For those over 35 years the cause is most often non-sexually transmitted Gram negative enteric organisms causing urinary tract infections. Particular risks include recent instrumentation or catheterisation. There is crossover between these groups and complete sexual history taking is imperative.

Vaginal Candidiasis

1. Nurbhai M, Grimshaw J, Watson M, Bond CM, Mollison JA, Ludbrook A. Oral versus intravaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (thrush). *Cochrane Database of Systematic Reviews* 2007, Issue 4. <http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD002845/frame.html> Accessed 23.09.14.

RATIONALE: No statistically significant differences were observed in clinical cure rates of antifungals administered by the oral or the intravaginal route. At short-term follow-up, 74% cure was achieved with oral treatment and 73% cure with intra-vaginal treatment (OR 0.94, 95% CI 0.75 to 1.17).

2. UKTIS. Use of **fluconazole in pregnancy**. *The UK Teratology Information Service*. 2008. (Tel:

0844 892 0909, <http://www.uktis.org/docs/fluconazole.pdf>) Accessed 23.09.14.

RATIONALE: Fluconazole is a triazole antifungal commonly used in the treatment of candidiasis. Data on the outcomes of over 1,700 pregnancies exposed to low dose fluconazole (150mg as a single dose) show no increased incidence of spontaneous abortions or malformations and no pattern of defects. However, there may be an increased risk of malformations associated with high dose chronic therapy (>400mg/day). First-line treatment of candidal infection in pregnancy is with a topical imidazole such as **clotrimazole**. Fluconazole (150mg as a single dose) may be a suitable second-line treatment if clotrimazole is ineffective.

3. Young GL, Jewell D. Topical treatment for vaginal candidiasis (thrush) in pregnancy. *Cochrane Database of Systematic Reviews* 2001, Issue 4.
<http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD000225/frame.html>
Accessed 23.09.14.

RATIONALE: This Cochrane review found that topical imidazole appears more effective than nystatin at treating vaginal candidiasis in pregnancy. In addition, treatment for only four days was less effective than treatment for seven days (OR 11.7, 95% CI 4.21 to 29.15).

4. Schaefer C, Peters P, Miller RK. Drugs during pregnancy and lactation: treatment options and risk assessment. *Academic Press*. 2007.
RATIONALE: Clotrimazole and miconazole are the topical antifungals of choice during pregnancy. There is no evidence of an increased risk of spontaneous miscarriage or malformations with use of clotrimazole or miconazole during pregnancy.
5. Public Health England and the British Infection Association recommend 6 nights treatment with clotrimazole 100mg pessaries during pregnancy because this is the quantity in one original pack of clotrimazole 100mg pessaries.

Bacterial vaginosis

1. Joesoef MR, Schmid GP, Hillier SL. Bacterial vaginosis: review of treatment options and potential clinical implications for therapy. *Clin Infect Dis*. 1998; 28(1):57-65.
RATIONALE: Pooled data from five RCTs found no significant difference between cumulative cure rates 5-10 days after finishing treatment for metronidazole 400mg BD for 7 days (86%), intravaginal metronidazole 5g BD for 5 days (81%) or intravaginal clindamycin 5g at night for 7 days (85%).
2. McDonald HM, Brocklehurst P, Gordon A. Antibiotics for treating bacterial vaginosis in pregnancy. *Cochrane Database of Systematic Reviews* 2007, Issue 1.
<http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD000262/frame.html>
Accessed 23.09.14.
RATIONALE: Pooled data from 10 RCTs indicated that both oral and intravaginal antibiotics are effective at eradicating bacterial vaginosis in pregnant women. Oral antibiotics compared with placebo (seven trials, n=3244) OR 0.15, 95% CI 0.13 to 0.17. Intravaginal antibiotics compared with placebo (three trials, n=1113) OR 0.27, 95% CI 0.21 to 0.35.
3. Joesoef MR, Schmid GP. Bacterial vaginosis: review of treatment options and potential clinical implications for therapy. *Clin Infect Dis* 1995;20(Suppl 1):S72-S79.
RATIONALE: The 2g single dose is less effective than the 7-day course at 4-week follow up. When data from studies that only directly compared the two dose regimens were pooled, the cumulative cure rates 3-4 weeks after completion of treatment were 62% for the single-dose regimen and 82% for the 7-day regimen (p < 0.005).
4. UKTIS. Use of metronidazole in pregnancy. *The UK Teratology Information Service*. 2008. (Tel: 0844 892 0909, <http://www.uktis.org/docs/Metronidazole.pdf>) Accessed 23.09.14.

RATIONALE: The available data (almost exclusively based on oral treatment) does not indicate an increased risk of adverse fetal effects associated with metronidazole use during pregnancy. The manufacturer advises avoidance of the 2g stat regimen during pregnancy.

5. BASHH. National guideline for the management of bacterial vaginosis. *British Association for Sexual Health and HIV*. 2006. <http://www.bashh.org/documents/62/62.pdf> Accessed 23.09.14.

RATIONALE: No reduction in relapse rate was reported from two studies in which male partners of women with BV were treated with metronidazole, tinidazole, or clindamycin.

Gonorrhoea

Antimicrobial resistance to *Neisseria gonorrhoeae* continues to evolve at an increasing rate. The British Association for Sexual Health and HIV (BASHH) now recommend ceftriaxone 500mg IM with azithromycin 1g as first line treatment, followed by routine test of cure (TOC) at least 14 days after treatment. If there are persisting symptoms or signs, refer to GUM clinic and test with culture test of cure at least 72 hours after completing of therapy.

1. Public Health England (PHE) GRASP Steering Committee and British Association for Sexual Health and HIV (BASHH). CEG Position Statement on the Treatment of Gonorrhoea. 2015 Dec. Available from:

<http://www.bashh.org/BASHH/Guidelines/Guidelines/BASHH/Guidelines/Guidelines.aspx>.

RATIONALE: In December 2015, BASHH recommended that dual treatment with ceftriaxone plus azithromycin is advised for the treatment of gonorrhoea (irrespective of the results of chlamydia testing) in order to mitigate against the selection of gonococci with reduced susceptibility to cephalosporins. The rationale is that it is difficult for an organism to develop simultaneous resistance to two different antimicrobial classes, meaning the 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, for example 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 easier selection of ceftriaxone resistance. Co-infection with rectal chlamydia: BASHH recommend specific treatment of each infection, i.e. ceftriaxone combined with azithromycin for the gonorrhoea, with the addition of doxycycline for the concurrent rectal chlamydia. Of 15, 758 reported cases of PID in 2013, only 323 (2%) involved gonococci. BASHH believe that it is reasonable to continue the use of ceftriaxone and doxycycline in this patient group: given the small subset of patients with *N. gonorrhoeae*, it is unlikely to impact on measures to delay the development of widespread ceftriaxone resistance. BASHH stress the importance of TOC for all patients, but particularly for those not treated with dual gonococcal therapy.

2. Bignell C, Fitzgerald M. UK national guideline for the management of gonorrhoea in adults. *Int J HIV AIDS*. 2011 Oct; 22(10):541-547. Available from:

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

RATIONALE: The British Association for Sexual Health and HIV (BASHH) UK gonorrhoea guideline was updated in 2011. It offers advice on diagnosis, treatment and health promotion for anogenital and pharyngeal gonorrhoea. Nucleic acid amplification tests (NAATs) are now being used more for diagnosis and are increasing detection rates in the pharynx and rectum. First line treatment using ceftriaxone with azithromycin is now advised, along with routine test of cure (TOC). 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 *C. trachomatis* or receive

presumptive treatment for this infection; all patients identified with gonorrhoea should have partner notification carried out according to the published standards of the BASHH Clinical Standards Unit; all patients identified with gonorrhoea should be offered written information about STIs and their prevention; and all patients with gonorrhoea should receive first-line treatment or the reasons for not doing so documented.

3. 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*. 2015 Nov; 5:1-9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26022269>.
RATIONALE: A 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. This paper concludes that, given the global threat of antimicrobial resistance, GPs should remain aware of national treatment guidelines, and remain alert to treatment failure in their patients.

Trichomoniasis

1. BASHH. UK National Guideline on the Management of *Trichomonas vaginalis*. *British Association for Sexual Health and HIV*. 2007. <http://www.bashh.org/documents/87/87.pdf> Accessed 23.09.14.
RATIONALE: Treatment of partners: the recommendation to also treat partners for trichomoniasis, irrespective of the results of investigations is based on two prospective RCTs.
2. UKTIS. Use of metronidazole in pregnancy. *The UK Teratology Information Service*. 2008. (Tel: 0844 892 0909, <http://www.uktis.org/docs/Metronidazole.pdf>) Accessed 23.09.14.
RATIONALE: 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 adverse fetal effects associated with metronidazole use in human pregnancy. Where possible, the results of culture and sensitivity tests should be available before making a treatment choice. However if treatment is required before test results become available, then penicillins or cephalosporins may be used if considered clinically appropriate. The manufacturer advises avoidance of the 2g stat regimen during pregnancy.
3. Du Bouchet I, Spence MR, Rein MF, Danzig MR, McCormack WM. Multicentre comparison of clotrimazole vaginal tablets, oral metronidazole, and vaginal suppositories containing sulphamamide, aminacrine hydrochloride, and allantoin in the treatment of symptomatic trichomoniasis. *Sex Transm Dis* 1997;24:156-160.
RATIONALE: In this randomized, open-label trial (n=168) clotrimazole vaginal tablets were not found 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).
4. Forna F, Gulmezoglu MU. Interventions for treating trichomoniasis in women. *Cochrane Database of Systematic Reviews*. 2003. Issue 2. <http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD000218/frame.html> Accessed 23.09.14.
RATIONALE: Pooled data from two RCTs (n=294) found an 88% cure rate in women treated with metronidazole 2g stat compared with a 92% cure rate in women treated with metronidazole for 5 or 7 days. Relative risk of no parasitological cure 1.12, 95% CI 0.58 to 2.16.

Pelvic inflammatory disease

1. RCOG. Management of Acute Pelvic Inflammatory Disease. Green Top Guideline No.32. *Royal College of Obstetricians & Gynaecologists*. 2008. Available from: <http://www.rcog.org.uk/womens-health/clinical-guidance/acute-pelvic-inflammatory-disease-pid>.
RATIONALE: Recommended regimens – the recommended regimens are broad spectrum to cover *N. gonorrhoea*, *C. trachomatis*, and anaerobes. For outpatient management, either ofloxacin plus metronidazole for 14 days, or a stat dose of IM cefotaxime plus metronidazole and doxycycline for 14 days are recommended. Broad-spectrum treatment is warranted in PID because of 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. Ceftriaxone is therefore recommended. Although the combination of doxycycline and metronidazole (without IM ceftriaxone) has previously been used in the UK to treat PID, there are no clinical trials that adequately assess its effectiveness and its use is not recommended.
2. BASHH. UK National Guideline for the management of PID. *British Association for Sexual Health and HIV*. 2005. <http://www.bashh.org/documents/118/118.pdf> Accessed 23.09.14.
RATIONALE: Recommended regimens: the recommended regimens for outpatient management are either ofloxacin plus metronidazole for 14 days, or a stat dose of IM ceftriaxone plus metronidazole and doxycycline 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. Treatment of partners: partners should be screened for gonorrhoea and chlamydia.
3. GRASP Steering Group. GRASP 2014 report: Surveillance of antimicrobial resistance to *Neisseria gonorrhoeae*.
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/476582/GRASP_2014_report_final_111115.pdf Accessed 18.05.16.
RATIONALE: This report describes the latest data on trends in and epidemiology of antimicrobial resistance and decreased susceptibility in gonococcal infection in England and Wales using data collected through GRASP in 2014. In 2014 in England, compared to 2013, the number of new gonorrhoea diagnoses increased by 19% (especially among men who have sex with men) and young adults. Ciprofloxacin resistance is now endemic in England and Wales, accounting for 37.3% of all gonorrhoea isolates tested in 2014, an increase from 29.3% in 2013. 1.4% of isolates exhibited decreased susceptibility to cefixime; no isolates were confirmed to have resistance to ceftriaxone (MIC ≥ 0.125 mg/L). However, in early 2015, one isolate was confirmed to have resistance to ceftriaxone (MIC 0.25mg/L). As resistance to cephalosporins is increasing and treatment failures have been reported with cefixime, if gonorrhoea is suspected, ceftriaxone (500mg IM stat) is the cephalosporin of choice.
4. Meads C, Knight T, Hyde C and Wilson J. The clinical effectiveness and cost-effectiveness of antibiotic regimens for pelvic inflammatory disease. West Midlands Health Technology Assessment group. 2004. www.rep.bham.ac.uk Accessed 23.09.14.
RATIONALE: This systematic review identified 34 trials of antibiotic treatment for PID. Most studies were small, open-label, and of poor methodological study. One small trial was found that compared oral ofloxacin plus metronidazole with clindamycin plus gentamicin. The cure rate was 15/15 for ofloxacin plus metronidazole plus 17/18 for clindamycin plus gentamicin. The systematic review found one trial of ceftriaxone plus doxycycline was found, two trials of cefoxitin plus probenecid and doxycycline, and three trials of cefoxitin plus doxycycline compared to other antibiotics. Meta-analysis of these six studies found no difference in cure rates between IM cephalosporin plus doxycycline

and the comparator antibiotics.

5. Ison CA, Mouton JW, Jones K. Which cephalosporin for gonorrhoea? *Sex Transm Infect* 2004;80:386-88.

RATIONALE: This study used previously published pharmacokinetic data on cefixime, ceftriaxone and cefuroxime to model the length of time tissue concentrations to these drugs would be above the MIC₉₀ (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 in *Neisseria gonorrhoea*.

6. Ross JDC, Cronjé HS, Paszkowski T, Rakoczi I. Moxifloxacin versus ofloxacin plus metronidazole in uncomplicated pelvic inflammatory disease: results of a multicentre, double blind, randomised trial. *Sex Transm Infect* 2006;82(6):446-51.

RATIONALE: This trial in 564 patients with uncomplicated PID in hospitals from 13 countries, compared oral metronidazole 500mg twice daily with either oral ofloxacin 400mg twice daily or moxifloxacin 400mg once daily. Clinical resolution with 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*.

SKIN INFECTIONS

Impetigo

1. Public Health England and the British Infection Association recommend that topical antibiotics are reserved only for treatment of very localised lesions because fusidic acid is an antibiotic that is also used systemically. There are concerns that widespread use of topical fusidic acid will lead to increased resistance, rendering systemic fusidic acid (used for severe staphylococcal infections such as osteomyelitis or systemic MRSA) ineffective. If a topical antibiotic is used, a short course (such as 5 days) reduces exposure and the risk of resistance. Since few agents are effective against MRSA, mupirocin should be reserved for such cases.
2. Public Health England and the British Infection Association recommend flucloxacillin for first-line treatment of impetigo because it is a narrow-spectrum antibiotic that is effective against Gram positive organisms, including beta-lactamase producing *Staphylococcus aureus*, and it demonstrates suitable pharmacokinetics, with good diffusion into skin and soft tissues. Clarithromycin is recommended for people with penicillin allergy because it is also active against most staphylococcal and streptococcal species.
3. Koning S, Verhagen AP, van Suijlekom-Smit LWA, Morris AD, Butler C, van der Wouden JC. Interventions for impetigo. *Cochrane Database of Systematic Reviews*. 2003. Issue 2. <http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD003261/frame.html> Accessed 23.09.14.

RATIONALE: Many RCTs identified by this Cochrane review were of poor methodological quality. Pooled data from four RCTs found no difference in cure rates between topical mupirocin and topical fusidic acid (OR 1.22, 95% CI 0.69 to 2.16). Most RCTs that compared topical compared with oral antibiotics used mupirocin. However, mupirocin is reserved for MRSA and should not be used first-line for impetigo. Topical fusidic acid was significantly better than oral erythromycin in one study, but no difference was seen between fusidic acid and oral cefuroxime in a different arm of the same study.

Topical bacitracin was significantly worse than oral cefalexin in one small study, but there was no difference between bacitracin and erythromycin or penicillin in two other studies. The results of one non-blinded RCT suggested that topical fusidic acid was more effective than topical hydrogen peroxide, but this did not quite reach statistical significance.

4. Public Health England and the British Infection Association recommend that topical retapamulin or polymixin are reserved for use in areas where there are rising rates of resistance to fusidic acid. Polymixin (contains bacitracin) has less robust RCT evidence than fusidic acid. Although topical retapamulin has been demonstrated to be non-inferior to topical fusidic acid for the treatment of impetigo in one randomized controlled trial, it is more expensive and there are less safety data available (it is a black triangle drug).
5. Denton M, O'Connell B, Bernard P, Jarlier V, Williams Z, Santerre Henriksen A. 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;61:586-588.

RATIONALE: Of *S. aureus* isolates from the UK, only 75.6% were susceptible to fusidic acid. A diagnosis of impetigo was associated with reduced fusidic acid susceptibility.

Eczema

1. Birnie AJ, Bath-Hextall FJ, Ravenscroft JC, Williams HC. Interventions to reduce *Staphylococcus aureus* in the management of atopic eczema. *Cochrane Database of Systematic Reviews*. 2008. Issue 3.
<http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD003871/frame.html>
Accessed 23.09.14.

RATIONALE: Most RCTs identified by this Cochrane review were of 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 *S aureus* in 4 trials (n=302) but not in a further 9 trials (n=677).

2. National Collaborating Centre for Women's and Children's Health (2007) Atopic eczema in children: management of atopic eczema in children from birth up to the age of 12 years (full NICE guideline). National Institute for Health and Clinical Excellence.
<http://guidance.nice.org.uk/CG57> Accessed 23.09.14.

RATIONALE: In view of the lack of robust trial evidence, the Guidance Development Group's view was that flucloxacillin should normally be the first-line treatment for active *S. aureus* and streptococcal infection because it is active against both. If sensitive, erythromycin or clarithromycin should be used when there is local resistance to flucloxacillin and in children with a penicillin allergy because it is as effective as cephalosporins and less costly. It is the view of the GDG that topical antibiotics, including those combined with topical corticosteroids, should be used to treat localised overt infection only, and for no longer than two weeks.

Cellulitis

1. Clinical Resource Efficiency Support Team (CREST) *Guidelines on the management of cellulitis in adults*. Clinical Resource Efficiency Support Team, Northern Ireland. 2005.
<http://www.acutemed.co.uk/docs/Cellulitis%20guidelines,%20CREST,%202005.pdf> Accessed 23.09.14.

RATIONALE: This is an excellent review on the diagnosis and management of cellulitis. Expert consensus is that people with Class I disease (who have no signs of systemic toxicity and no uncontrolled co-morbidities) can usually be managed on an outpatient basis with oral antibiotics. Flucloxacillin is bactericidal against both streptococci and staphylococci. Therefore flucloxacillin 500mg QDS (or clarithromycin

500mg BD for those with penicillin allergy) are suitable oral antibiotics because they cover staphylococci and streptococci, the most commonly implicated pathogens. Clindamycin 300mg QDS is also recommended as a further alternative for people with penicillin allergy, who do not respond or in more severe disease. Most cases of uncomplicated cellulitis can be treated successfully with 1-2 weeks of treatment. 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 with decreased temperature, white cell count, and decreasing erythema and induration. (Eron et al JAC 2003) Those with class III (significant systemic upset, such as acute confusion, tachycardia, tachypnoea, hypotension or unstable co-morbidities, or Class IV (patients with sepsis syndrome or severe life threatening infections should be admitted urgently.

2. British Lymphology Society. Consensus document on the management of cellulitis in lymphoedema. 2015 Apr. Available from: <http://thebls.com/documents/1.pdf>.
RATIONALE: An expert consensus document on the management of cellulitis in lymphoedema. The authors state that flucloxacillin 500mg should be prescribed in the presence of clinical infection (e.g. pus formation, folliculitis or crusted dermatitis). They also state that if the patient is allergic to penicillin, clarithromycin 500mg or clindamycin 300mg should be prescribed. Doxycycline 200mg is recommended as an alternative if the patient is penicillin-hypersensitive and taking statins (e.g. 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. Jones, G.R. Principles and practice of antibiotic therapy for cellulitis. *CPD Journal Acute Medicine*. 2002;1(2):44-49.
RATIONALE: Oral agents will be as effective as intravenous agents for cellulitis if they can maintain the free antibiotic level above the MIC of the pathogen for more than 40% of the dose interval. Flucloxacillin 500mg, clarithromycin 500mg and clindamycin 300mg are suitable oral doses.
4. Morris AD. Cellulitis and erysipelas. *Clinical Evidence*. 2007. London. BMJ Publishing Group.
RATIONALE: This systematic review found no RCTs of antibiotics compared with placebo of sufficient quality for inclusion. Although 11 RCTs were identified that compared antibiotic treatments, these studies were small and only powered to demonstrate equivalence, not superiority, between antibiotics. Two RCTs using intravenous flucloxacillin were found, but none using oral flucloxacillin. Oral azithromycin was compared with erythromycin, flucloxacillin, and cefalexin in three RCTs. Oral co-amoxiclav was compared with fleroxacin (available in Germany) in one sub-group analysis.
5. Fischer RG and Benjamin DK Jr. Facial cellulitis in childhood: a changing spectrum. *Southern Medical Journal*. 2002;95: 672-674.
RATIONALE: Buccal cellulitis is commonly due to *Haemophilus influenzae* infection, although rates are decreasing following the Hib immunization programme. Public Health England and the British Infection Association recommends co-amoxiclav for empirical treatment of facial cellulitis because it is broader spectrum than flucloxacillin and also covers anaerobes and other less common causes of facial cellulitis.
6. Kilburn SA, Featherstone P, Higgins B, Brindle R. Interventions for cellulitis and erysipelas. *Cochrane Database of Systematic Reviews*. 2010. Issue 6.
<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004299.pub2/pdf> Accessed 23.09.14.
RATIONALE: This review included 25 studies with a total of 2488 participants. The primary outcome 'symptoms were rated by participant or medical practitioner or proportion symptom-free' was commonly reported. No two trials examined the same

drugs, therefore the review grouped similar types of drugs together. Three studies with a total of 88 people comparing a penicillin with a cephalosporin showed no difference in treatment effect (RR 0.99, 95% CI 0.68 to 1.43). Macrolides/streptogramins were found to be more effective than penicillin antibiotics (Risk ratio (RR) 0.84, 95% CI 0.73 to 0.97). In 3 trials involving 419 people, 2 of these studies used oral macrolide against intravenous (iv) penicillin demonstrating that oral therapies can be more effective than iv therapies (RR 0.85, 95% CI 0.73 to 0.98).

Leg ulcer

1. O'Meara S, Al-Khurdi D, Ovington LG. Antibiotics and antiseptics for venous leg ulcers. *Cochrane Database of Systematic Reviews*. 2010. Issue 1.
<http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD003557/frame.html>
Accessed 23.09.14.
RATIONALE: Most studies identified by this Cochrane review were of poor methodological quality. Use of antibiotics did not promote healing compared to placebo in four trials of people with leg ulcers without visible signs of infection.
2. RCN The nursing management of patients with venous leg ulcers. Recommendations. *Royal College of Nursing*. 2006
http://www.rcn.org.uk/development/practice/clinicalguidelines/venous_leg_ulcers Accessed 23.09.14.
RATIONALE: Expert consensus is that swabbing (and so by definition antibiotic therapy) is unnecessary unless there is evidence of clinical infection such as inflammation, redness, or cellulitis; increased pain; purulent exudates; rapid deterioration of the ulcer; pyrexia; or foul odour.
3. Public Health England. *Investigation of skin and superficial and non-surgical wound swabs*. UK Standards for Microbiology Investigations SMI B 11. Issue 5.2
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/343916/B_11i_5.2.pdf Accessed 22.09.14.
RATIONALE: Wound swabs should be taken from clinically infected ulcers before starting antibiotics. Taking swabs after starting antibiotics may affect the swab results. Sensitivity results can help guide the appropriate use of further antibiotics if the infection is not clinically improving on empirical treatment.

PVL-SA

1. HPA. Guidance on the diagnosis and management of PVL-associated *Staphylococcus aureus* infections (PVL-SA) in England. 2nd Edition. 2008.
<https://www.gov.uk/government/collections/panton-valentine-leukocidin-pvl-guidance-data-and-analysis> Accessed 23.09.14.
RATIONALE: Expert opinion based on review of the literature and experiences of colleagues in the UK, Europe, the USA, and Canada.
2. 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;43: 2384–90.
RATIONALE: In this study the Staphylococcus Reference Unit tested 515 UK isolates of *S. aureus* for PVL and 8 (1.6%) were positive for the PVL locus. A further 470 isolates were selected to explore the association of PVL-positive *S. aureus* with clinical disease. Of these, 23 (4.9%) were PVL positive and most were associated with skin and soft tissue infections (especially abscesses in which 7 of 16, 45% were positive). The PVL genes were also detected in isolates responsible for community-acquired pneumonia, burn infections, bacteraemia, and scalded skin syndrome.

Bites (human or animal)

1. CKS. Bites – human and animal. *Clinical Knowledge Summaries*. 2007.
<http://cks.nice.org.uk/bites-human-and-animal> Accessed 23.09.14.
RATIONALE: Expert opinion is that prophylaxis for animal bites is not required unless bite to the hand, foot, and 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 (e.g. those who are diabetic, cirrhotic, asplenic, immunosuppressed, people with a prosthetic valve or a prosthetic joint).
2. Medeiros I, Saconat H. Antibiotic prophylaxis for mammalian bites. *Cochrane Database of Systematic Reviews*, 2001 Issue 2
http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD001738/pdf_fs.html Accessed 23.09.14.
RATIONALE: Human bites: only one trial (n=48) analyzed human bites, and the infection rate in the antibiotic group (0%) was significantly lower than the infection rate in the control group (47%); OR 0.02, 95% CI 0.00 to 0.33. Dog bites: pooled results from six RCTs (n=463) found that the infection rate was not reduced after the use of prophylactic antibiotics (4%) compared with the control group (5.5%); OR 0.74, 95% CI 0.30 to 1.8). Cat bites: one small study (n=11) reported a lower infection rate in the treatment group who received prophylactic antibiotics (0%) compared with the control group (67%).
3. First-line antibiotic. Public Health England and the British Infection Association recommend co-amoxiclav for treatment or prophylaxis of human or animal bites because it is a broad-spectrum antibiotic that is effective against the most commonly isolated organisms from human bites (alpha- and beta-haemolytic streptococci, *S. aureus*, corynebacteriae, and *Eikenella corrodens*) and animal bites (such as *Pasteurella* spp. [57% of dog bites and 75% of cat bites], streptococci, staphylococci, moraxellae, neisseriae, and anaerobes).
4. First-line antibiotics in penicillin allergy for animal bites. Public Health England and the British Infection Association recommend metronidazole PLUS doxycycline for adults with penicillin allergy who require treatment or prophylaxis of an animal bite. Doxycycline has activity against *Pasteurella* species (the most common pathogen), staphylococci and streptococci. Metronidazole is included to cover anaerobes. Macrolides are not recommended for animal bites because they do not adequately cover *Pasteurella* spp. Seek specialist advice for children under the age of 12 years (doxycycline contraindicated).
5. First-line antibiotics in penicillin allergy for human bites. Public Health England and the British Infection Association recommend metronidazole plus either doxycycline or clarithromycin for adults and children with penicillin allergy who require treatment or prophylaxis of a human bite. Both doxycycline and clarithromycin are active against staphylococci and streptococci (the most common pathogens). Metronidazole is included to cover anaerobes. Doxycycline, but not clarithromycin is active against *Eikenella* species, which is also a common pathogen isolated from human mouths.
6. Public Health England and the British Infection Association recommend that people with penicillin allergy are reassessed at 24 and 48 hours after starting a course of antibiotic treatment because the recommended regimen covers the majority, but not all, of the likely pathogens from an animal or human bite.

Scabies

1. HPA. The management of scabies in the community. *Health Protection Agency North West*. 2005. <http://www.wirralct.nhs.uk/attachments/article/25/ScabiesInTheCommunity.pdf> Accessed 22.09.14.
RATIONALE: Treatment of all contacts: expert opinion is 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 re-infestation. Two treatments, 7 days apart: expert opinion is that two treatment sessions are needed to treat scabies effectively.

2. ABPI Medicines Compendium. Lyclear Dermal Cream. Datapharm Communications Ltd. 2008. <http://www.medicines.org.uk/EMC/medicine/10439/SPC/Lyclear+Dermal+Cream/> Accessed 23.09.14.
3. Strong M, Johnstone P. Interventions for treating scabies. *Cochrane Database of Systematic Reviews*. 2007. Issue 3
<http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD000320/frame.html> Accessed 23.09.14.
RATIONALE: Permethrin: topical permethrin appeared more effective than oral ivermectin, topical crotamiton, and topical lindane. The greatest body of evidence is for topical permethrin compared with lindane (n=735, five RCTs: RR 0.32, 95% CI 0.13 to 0.75). Malathion: no RCTs were found that evaluated the efficacy of malathion for the treatment of scabies. Malathion has only been evaluated in uncontrolled studies.

Dermatophyte infection – skin

1. ABPI Medicines Compendium. Lamisil AT 1% cream. 2009. Datapharm Communications Ltd.
<http://www.medicines.org.uk/EMC/searchresults.aspx?term=Lamisil&searchtype=QuickSearch> Accessed 23.09.14.
RATIONALE: Terbinafine cream is not licensed for the treatment of Candida infection.
2. Public Health England Fungal skin and nail infections: diagnosis & laboratory investigation. Quick reference guide for primary care for consultation and local adaptation. 2009
<https://www.gov.uk/government/publications/fungal-skin-and-nail-infections-diagnosis-and-laboratory-investigation> Accessed 22.09.14.
RATIONALE: The recommendation to send skin scrapings to confirm the diagnosis before starting oral treatment is based on expert opinion and clinical experience.
3. Bell-Syer SEM, Hart R, Crawford F, Torgerson DJ, Tyrrell W, Russel I. Oral treatments for fungal infection of the foot. *Cochrane Database of Systematic Reviews*. 2002. Issue 2
www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD003584/frame.html Accessed 23.09.14.
RATIONALE: Terbinafine: one RCT (n=41) found that oral terbinafine, 250mg a day for 6 weeks, was more effective than placebo for treating athlete's foot. At 8 weeks, 65% of the terbinafine group were cured, compared with none of the placebo group (relative risk [RR] of cure with terbinafine 25, 95% CI 2 to 384). Itraconazole: one RCT (n=77) found that oral itraconazole, 400mg a day for 1 week, was more effective than placebo. At 9 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). Terbinafine vs itraconazole: Pooled data from three RCTs (n=222) found no difference in cure rates between oral terbinafine 250mg a day for 2 weeks (76% cured), and itraconazole 100mg a day for 4 weeks (71% cured); risk difference 5%, 95% CI -6 to +27.
4. Crawford F and Hollis S. Topical treatments for fungal infections of the skin and nails of the foot. *Cochrane Database of Systematic Reviews* 2007. Issue 3.
<http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD001434/frame.html> Accessed 23.09.14.
RATIONALE: Terbinafine and imidazoles: pooled data (8 RCTs; n=962) found little difference between allylamines (e.g. terbinafine for 1-2 weeks) and imidazoles (for 4-6 weeks) at 2 weeks after baseline. But at 6 weeks after baseline, there was a relative reduction in treatment failure with allylamines compared with imidazoles (RR 0.63, 95%

CI 0.42 to 0.94). Treatment with an imidazole for 4-6 weeks reduced the risk of treatment failure by 60% compared with placebo at 6 weeks (Risk Ratio 0.40, 95% CI 0.35 to 0.46; n=1235). Treatment with an allylamine for 1-4 weeks reduced the risk of treatment failure by 67% compared with placebo at 6 weeks (Risk Ratio 0.33, 95% CI 0.24 to 0.44; n=1116) Undecanoates: this systematic review identified two RCTs of undecanoates compared with placebo (n=283). There was a 71% relative reduction in the risk of treatment failure at 6 weeks with 4 weeks treatment with undecanoates compared with placebo (Risk Ratio 0.29, 95% CI 0.12 to 0.70).

5. Gupta AK, Cooper EA. Update in antifungal therapy of dermatophytosis. *Mycopathologia*. 2008 Nov-Dec;166(5-6):353-67.

RATIONALE: Topical medications applied once or twice daily are the primary treatment indicated for tinea corporis/cruris, and tinea pedis/manuum. Use of oral antifungals may be practical where the tinea involvement is extensive or chronic, or where application of a topical is not feasible. For tinea unguium (onychomycosis) and tinea capitis, oral therapies are the primary treatments recommended. Topical amorolfine and ciclopirox formulations have been approved for use in milder onychomycosis cases, and their role in the treatment of the different clinical forms of onychomycosis is currently being defined. Relapse of infection remains a problem, particularly with tinea pedis/unguim. Appropriate follow-up duration and education of patients on proper foot hygiene are also important components in providing effective therapy.

Dermatophyte infection - nail

1. Roberts DT, Taylor WD, Boyle J. Guidelines for treatment of onychomycosis. *Brit J Dermatol* 2003;148:402-410.

RATIONALE: Confirmation of diagnosis: only 50% of cases of nail dystrophy are fungal, and it is not easy to identify these clinically. The length of treatment needed (6-12 months) is too long for a trial of therapy.

2. Chung CH, Young-Xu Y, Kurth T, Orav JE, Chan AK. The safety of oral antifungal treatments for superficial dermatophytosis and onychomycosis: a meta-analysis. *Am J Med* 2007;120:791-798.

RATIONALE: Pooled data from about 20,000 participants 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).

3. CKS. Fungal nail infection (onychomycosis) *Clinical Knowledge Summaries* 2009.

<http://cks.nice.org.uk/fungal-nail-infection#azTab> Accessed 23.09.14.

RATIONALE: Non-dermatophyte nail infection: there is limited evidence that both terbinafine and itraconazole are effective. Candidal nail infection: there is evidence that itraconazole is effective for candidal nail infection. There is weak evidence that terbinafine is also effective. Specialist advice for children: this is because fungal nail infection is rare in children, and the preferred treatments are not licensed for use in children.

4. Public Health England Mycology Reference Laboratory recommends itraconazole for non-dermatophyte infections because although some of the infecting organisms are not particularly susceptible to this agent in vitro, it does reach high concentrations in nail tissue. It can be given as a pulse therapy regimen rather than continuous treatment.
5. Reinel D. Topical treatment of onychomycosis with amorolfine 5% nail lacquer: comparative efficacy and tolerability of once and twice weekly use. *Dermatology*. 1992; 184(1):21-24.

RATIONALE: One RCT (n=456) without a placebo control found that 46% of those randomised to amorolfine applied once a week for 6 months achieved mycological cure of dermatophyte infection compared with 54% of those who applied topical amorolfine twice a week.

6. Crawford F & Ferrari J. Fungal toenail infections. In *Clinical Evidence Concise*. London. BMJ Publishing Group. 2006; 15: 561-63.

RATIONALE: Terbinafine vs itraconazole: one systematic review pooled data from two randomized controlled trials (n=501). At 1-year follow-up, the cure rate following 12 weeks of treatment was greater for people with dermatophyte onychomycosis treated with oral terbinafine 250mg once a day (69%) compared with oral itraconazole 200mg daily (48%). Absolute risk reduction 21%, 95% CI 13% to 29%. Pulsed vs continuous itraconazole: four small RCTs were identified that found no statistically significant difference between continuous and pulsed itraconazole for dermatophyte onychomycosis.

7. Crawford F and Hollis S. Topical treatments for fungal infections of the skin and nails of the foot. *Cochrane Database of Systematic Reviews* 2007. Issue 3.

<http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD001434/frame.html>

Accessed 23.09.14.

REVIEW: This review concluded that there is little evidence that topical anti-fungals are effective in the management of onychomycosis or fungally infected toe nails. The majority of available data demonstrate low cure rates after long treatment times with ciclopiroxolamine. Amorolfine and butenafine 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 for toe nail infections.

8. In 2014 amorolfine 5% nail lacquer cost between £11.35 and £19.99, compared to £10.20 for a three month course of oral terbinafine.

Varicella zoster/chicken pox

Herpes zoster/shingles

1. DH. Immunisation against infectious diseases – The Green book. Chapter 34. Varicella. Department of Health 2006. <https://www.gov.uk/government/publications/varicella-the-green-book-chapter-34> Accessed 23.09.14.

RATIONALE: Pregnant women are at greater risk of varicella pneumonia, and there is a risk to the fetus 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 fetal 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 to assess the need for varicella immunoglobulin and antiviral treatment.

2. Klassen TP and Hartling L. Aciclovir for treating varicella in otherwise healthy children and adolescents. *Cochrane Database of Systematic Reviews*. 2005. Issue 4.

<http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD002980/frame.html>

Accessed 23.09.14.

RATIONALE: Pooled data from three studies who enrolled participants within 24 hours of rash onset found 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. Chicken Pox. In: Clinical Evidence Concise. London. BMJ Publishing Group. 2006;15:267-79.

RATIONALE: One systematic review was identified that found one RCT (n=148 adults) which compared early versus late administration of aciclovir 800mg five times a day compared with placebo. It found 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. It found no significant difference in time to full crusting of lesions if aciclovir was given 24–72 hours after the rash ($P > 0.2$).

4. Public Health England recommends that treatment with aciclovir should be considered (if it can be started within 24 hours of the rash) in those with severe chickenpox (including secondary cases) and in those at increased risk of complications (adults and adolescents aged 14 years and over, smokers, people on steroids).

5. Hope-Simpson RE. Postherpetic neuralgia. *Brit J Gen Pract* 1975;25:571-75.

RATIONALE: Study showing that incidence of post-herpetic neuralgia in a general practice population increases with age with a third of cases being among those over 80 years.

6. 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 aciclovir and valaciclovir on prolonged pain. *J Infect Dis* 1998;127(Suppl 1):S81-S84.

RATIONALE: A study of two databases (n=1076) 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 of the onset of cutaneous herpes zoster. Aciclovir HR 2.2, 95% CI 1.03 to 4.71. Valaciclovir HR 1.40, 95% CI 1.04 to 1.87.

7. Wood MJ, Kay R, Dworkin RH, Soong S-J, Whitley RJ. Oral aciclovir therapy accelerates pain resolution in patients with herpes zoster: A meta-analysis of placebo-controlled trials. *Clin Inf Dis* 1996;22:341-7.

RATIONALE: Meta-analysis of four RCTs (n=691) found greatest benefit in those aged over 50 years, in whom pain resolved twice as fast with aciclovir compared with placebo. Oral aciclovir also reduced the incidence of post herpetic neuralgia.

8. International Herpes Management Forum. Improving the management of varicella, herpes zoster, and zoster-associated pain. 2002. www.ihmf.org Accessed 23.09.14.

RATIONALE: Antiviral treatment is recommended for ophthalmic shingles to prevent the potentially sight-threatening complications than can occur following herpes zoster involving the trigeminal nerve. Aciclovir, famciclovir, and valaciclovir have all been shown to reduce the complications of ophthalmic shingles in RCTs.

9. Dworkin RH, Johnson JW, Bruer J et al. Recommendations for the management of Herpes Zoster. *Clin Infect Dis* 2007;44(Suppl 1):S1-S26.

RATIONALE: Expert opinion is that 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 RCTs supports treatment for all those over 50 years to prevent the incidence of post-herpetic neuralgia.

10. 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;39:1546-1553.

RATIONALE: This randomized double-blind controlled trial (n=1141) in people aged 50 years and over within 72 hours of onset of herpes zoster found that valaciclovir 1g three times a day for 7 or 14 days reduced the time to resolution of pain compared with

aciclovir 800mg five times a day for 7 days. Median time to cessation of pain was 38 days for valaciclovir for 7 days compared with 51 days for aciclovir ($p=0.001$), and was 44 days for valaciclovir for 14 days.

11. Shen MC, Lin HH, Lee SS, Chen YS, Chiang PC, Liu YC. Double-blind, randomized, aciclovir-controlled, parallel-group trial comparing the safety efficacy of famciclovir and aciclovir in patients with uncomplicated herpes zoster. *J Microbiol Immunol Infect* 2004;37:75-81.

RATIONALE: In this small study ($n=55$), famciclovir and aciclovir were comparable in healing of lesions and cessation of acute-phase pain.

Cold sores

1. Sprurance SL, Nett R, Marbury T, Wolff R, Johnson J, Spaulding T. Aciclovir cream for the treatment of herpes labialis: results of two randomized, double-blind, vehicle-controlled, multicentre clinical trials. *Antimicrob Agents Chemother* 2002;46:2238-2243.

RATIONALE: Aciclovir 5% cream reduced the mean duration and pain of an episode by about half a day.

2. Sprurance SL, Rea TL, Thoming C, Tucker R, Saltzman R, Boon R. Penciclovir cream for the treatment of herpes simplex labialis. A randomized, double-blind, multicentre, placebo-controlled trial. *JAMA* 1997;277:1374-1379.

RATIONALE: Penciclovir 1% cream reduced the mean duration of cold sores by 0.7 days.

3. Raborn GW, Martel AY, Lassonde M, Lewis MA, Boon R, Sprurance SL. Effective treatment of herpes simplex labialis with penciclovir cream: combined results of two trials. *J Am Dent Assoc* 2002;133:303-309.

RATIONALE: Penciclovir cream reduced the mean duration of cold sores by 1 day.

4. Arduino PG and Porter SR. Oral and perioral herpes simplex type 1 (HSV-I) infection: review of its management. *Oral Dis* 2006;12(3):254-70.

RATIONALE: Prophylaxis with oral antivirals may be of use for those with frequent, severe episodes, or predictable triggers e.g. sunlight, or for immunocompromised individuals (i.e. at higher risk of complications). Seek specialist advice if long-term prophylaxis is being considered.

EYE INFECTIONS

Conjunctivitis

1. Sheikh A and Hurwitz B. Antibiotics versus placebo for acute bacterial conjunctivitis. *Cochrane Database of Systematic Reviews* 2006. Issue 2.

<http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD001211/frame.html>

Accessed 23.09.14.

RATIONALE: Meta-analysis of five RCTs ($n=1034$) found that antibiotics (one trial each of ocular polymixin plus bacitracin, ciprofloxacin, norfloxacin, fusidic acid, and chloramphenicol) improve early clinical remission rates (Risk Ratio on days 2 to 5 1.24, 95% CI 1.05 to 1.45). Clinical remission rates compared with placebo are lower if remission is assessed later (Risk Ratio on days 6 to 10 1.11, 95% CI 1.02 to 1.21). However, most cases resolve spontaneously, with clinical remission being achieved in 65% (95% CI 59 to 70%) by days 2 to 5 in those receiving placebo.

2. American Academy of Ophthalmology Corneal/External Disease Panel. Preferred Practice Pattern Guidelines. Conjunctivitis. *American Academy of Ophthalmology*. 2008.

RATIONALE: this guideline contains a useful table of signs and symptoms for all causes

of conjunctivitis.

3. ABPI Medicines Compendium. *Summary of product characteristics for Fucithalmic*. 1997. Datapharm Communications Ltd.
<http://www.medicines.org.uk/EMC/searchresults.aspx?term=Fucithalmic&searchtype=QuickSearch> Accessed 23.09.14.
RATIONALE: Fucithalmic 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 include *Streptococcus*, *Neisseria*, *Haemophilus*, *Moraxella* and *Corynebacteria*.
4. Rose PW, Harnden A, Brueggemann AB, Perera R, Sheikh A, Crook D, Mant D. Chloramphenicol treatment for acute infective conjunctivitis in children in primary care: a randomised double-blind placebo-controlled trial. *Lancet* 2005;366:37-43.
RATIONALE: This study (n=326) found that most children presenting with acute infective conjunctivitis in primary care will get better by themselves, and there is no statistically significant difference between using placebo or chloramphenicol. Clinical cure by day 7 occurred in 83% of children given placebo compared with 86% of children given chloramphenicol. Risk difference 3.8%, 95% CI -4.1% to 11.8%.
5. Reitveld RP, ter Riet G, Bindels PJ, Bink D, Sloos JH, van Weert HC. The treatment of acute infectious conjunctivitis with fusidic acid: a randomised controlled trial. *Br J Gen Pract* 2005;55:924-930.
RATIONALE: This primary care-based study (n=163) found no statistically significant difference in clinical cure rates at 7 days in people using fusidic acid (62%) compared with placebo (59%). Adjusted risk difference 5.3%, 95% CI -11% to 18%.
6. Walker S, Daiper CJ, Bowman R, Sweeney G, Seal DV, Kirkness CM. Lack of evidence for systemic toxicity following topical chloramphenicol use. *Eye* 1998;12:875-879.
RATIONALE: Despite widespread prescribing of topical chloramphenicol, the incidence of aplastic anaemia in the UK remains low, and epidemiological data do not suggest an association between aplastic anaemia and topical chloramphenicol. Furthermore, a study of chloramphenicol levels in 40 patients found that chloramphenicol failed to accumulate to detectable levels in serum following one and two weeks of topical treatment.

References – dental infections

This guidance is based on the Scottish Dental Clinical Effectiveness Programme guide to drug prescribing in dentistry.

To provide evidence for the guidance a literature review using Medline and Cochrane has been conducted, by Dr Joanne Hooker, up to October 2011 searching for Gingivitis; Antibiotics & dental abscess; Mucosal ulceration; Metronidazole; Oral Inflammation; Microbial flora & oral cavity; Oral hygiene; Oral microbial pathogens; Acute necrotising ulcerative gingivitis; Ludwig's angina; Dentoalveolar abscess; Mucositis; Odontogenic infection; Antimicrobials & dentistry; Pericoronitis; Periodontal disease; Mouthwash/mouthrinse; Periodontitis; Chlorhexidine; Anti-plaque/anti-gingivival; Hydrogen peroxide; Antimicrobial susceptibility; Saline solution. Where only expert opinion was available, the guidance was based on the literature on the main pathogens and their antimicrobial susceptibility profiles in the UK.

Dosage of antimicrobials recommended in this guidance:

- **Clarithromycin:** We recommend clarithromycin as it has less side-effects than erythromycin, greater compliance as twice rather than four times daily and generic tablets are similar cost. In children erythromycin may be preferable as clarithromycin syrup is twice the cost. Azithromycin has a greater half life in comparison to clarithromycin and erythromycin and thus provides 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 appropriate. We recommend a higher dose of 500mg amoxicillin and 400mg metronidazole. The rationale for this is when antimicrobials are considered appropriate, it is important to have sufficient concentrations at the site of infection. For β -lactams such as amoxicillin, the killing effect of the antibiotic is time-dependent (i.e. the time period for which concentrations of the antibiotic at the site of infection are above the Minimum Inhibitory Concentration (MIC) that is required 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, so it is the maximum concentration attained above the MIC that is important (Lewis et al, 2000). Metronidazole has simple first-order kinetics, so doubling the dose doubles the

plasma concentrations (Cudmore et al, 2004). Oral metronidazole is well tolerated and the side-effects reported at doses of 400mg TDS are either very rare or unknown (eMC medicine, 2014). Metronidazole distributes well throughout the body with non-significant differences in the concentrations attained in saliva and crevice fluid compared to plasma (Pahkla, 2005). Metronidazole has a volume of distribution of 0.5-1.0l/kg, so increasing body mass will decrease plasma concentrations (Lamp, 1999). $AUC/MIC > 70$ is only attainable against *Bacteroides fragilis* with a 400mg dose, and mouth anaerobes have similar susceptibility to *Bacteroides fragilis* (Wexler, 2015). 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, we recommend metronidazole 400mg three times daily (Poulet et al, 2005).

1. 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. *Diagnostic Microbiology and Infectious Disease*. 2000 Jan. 37: 51-55. Available from:

<http://www.ncbi.nlm.nih.gov/pubmed/10794941>.

RATIONALE: Using an in vitro infection model inside of an anaerobic chamber, this group simulated the human serum pharmacokinetic profile of oral metronidazole regimens. They found that the rapid bactericidal activity in vitro of metronidazole administered as a simulated extended release formulation at 750-1500mg/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* spp. and demonstrates a prolonged postantibiotic effect (>3 hours). This supports the 400mg TDS dosing regimen over the 200mg, as 400mg will attain about twice the tissue concentrations than 200mg and, as killing rate is concentration dependent, this will be improved.

2. Levison ME, Levison JH. Pharmacokinetics and pharmacodynamics of antibacterial agents. *Infect Dis Clin North Am*. 2009 Dec. 23(4): 791-797.

Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3675903/>.

RATIONALE: A review article describing how the pharmacodynamics of an antimicrobial drug relates its pharmacokinetics to the time course of the antimicrobial effects at the site of infection. This article discusses how for some groups of antibiotics (aminoglycosides; fluoroquinolones; daptomycin; colistin; metronidazole; azithromycin; ketolides), it is the amount of drug (based on the C_{max} and AUC relative to the MIC) rather than the dosing frequency that determines the efficacy for these drugs. Therefore, it is the maximum concentration attained above the MIC that is important.

3. Cudmore SL, Delgaty KL, Hayward-McClelland SF, Petrin DP, Garber GE. Treatment of infections caused by metronidazole-resistant *Trichomonas vaginalis*. *Clinical Microbiology Reviews*. 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 TDS, 500mg BD or 2g single dose) of oral metronidazole. This article states that concentration of metronidazole in serum, specifically peak concentration in plasma and minimum lethal concentration (MLC), are dependent on dosage. All oral dose regimens (250mg TDS, 500mg BD or 2g single dose) achieve peak concentrations in plasma in 1-2 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 MLC before slow, steady elimination.

4. eMC Medicine. Flagyl 400mg Tablets. 2014 Oct. Available from: <https://www.medicines.org.uk/emc/medicine/21216>.
RATIONALE: A website outlining the therapeutic indications and side-effects of 400mg metronidazole tablets. This website states that the frequency of adverse events are either rare, very rare or not known. Serious adverse reactions occur rarely with standard recommended regimens.
5. Pahkla ER, Koppel T, Saag M, Pahkla R. Metronidazole concentrations in plasma, saliva and periodontal pockets in patients with periodontitis. *J Clin Periodontol*. 2005 May. 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. Eleven patients with severe generalised adult periodontitis participated in the study, and metronidazole concentrations in all fluids were measured 2 hours after last dose. This study concluded that metronidazole penetrates well into gingival crevice fluid and saliva, therefore, general pharmacokinetic data of metronidazole can also be applied in the treatment of periodontal disease and in the design of respective treatment regimens.
6. Lamp KC, Freeman CD, Klutman NE, Lacy MK. Pharmacokinetics and pharmacodynamics of the nitromidazole antimicrobials. *Clin Pharmacokinet*. 1999 May. 36(5): 353-357. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10384859>.
RATIONALE: This review covers the pharmacokinetics of metronidazole, and highlights 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.
7. Wexler H. Metronidazole resistance in *Bacteroides fragilis*: an integrated approach. National Institute of Health. 2015 Nov. Available from: <http://grantome.com/grant/NIH/R21-AI109545-02>.
RATIONALE: This large laboratory study determined susceptibility of 579 different anaerobes. The MICs were similar in oral bacteria to other anaerobes.
8. 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. 2005 Feb. 55(3): 347-351. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15695539>.
RATIONALE: A prospective, parallel-group, very small but detailed randomised study showing that metronidazole 500mg three times daily alone or in combination with spiramycin (1,500,000 units plus 250mg MZ) is an effective treatment for active periodontitis. The metronidazole at 250mg and 500mg three times daily consistently exceeded the MICs for the pathogens isolated in the corresponding sites. Most of the bacterial species were eradicated during treatment and at follow-up. This study concluded that the currently used metronidazole dose of 250mg TDS 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, we recommend 400mg three times daily.

Mucosal ulceration and inflammation (simple gingivitis)

1. An extensive literature search using Medline and Cochrane failed to find any robust clinical evidence on saline mouthwash. The recommendations are, therefore, based on expert opinion from the Scottish Dental Clinical Effectiveness Programme which recommends salt solution (half a teaspoon of salt dissolved in warm water) or compound sodium chloride mouthwash (prescribe 300ml) and dilute with an equal volume of water) as required until symptoms resolve. NB advise patient to spit out mouthwash after rinsing.
2. The Scottish Dental Clinical Effectiveness Programme (2011).
RATIONALE: Recommends chlorhexidine 0.2% mouthwash or chlorhexidine oromucosal solution, alcohol free 0.2% (300ml): rinse 10ml for one minute twice each day. Spit out mouthwash after use. Leave 30 minute interval between using chlorhexidine mouthrinse and using toothpaste due to staining of teeth and dilution of chlorhexidine. This recommendation is based on the trials outlined below in references 3 – 6.
3. 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;37: 829-39. (The Netherlands).
RATIONALE: This systematic review from the Netherlands aimed to evaluate the effects of 0.12% chlorhexidine versus 0.2% chlorhexidine in the management of gingival inflammation and plaque control. Medline, Pub-Med and Cochrane 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% regarding the reduction of plaque.
4. Lang NP, Hase JC, Grassi M, Hammerle CHF, Weigel C, Kelty E, Frutig F. Plaque formation and gingivitis after supervised mouthrinsing with 0.2% delmopinol hydrochloride, 0.2% chlorhexidine digluconate and placebo for 6 months. *Oral Diseases*, 1998;4;105-113 (Switzerland).
RATIONALE: Double-blind, randomised six month clinical trial. This study of 162 patients with gingivitis, based in Switzerland, compared the effects of 0.2% chlorhexidine mouthwash or 0.2% delmopinol mouthwash (which inhibits adhesion of oral micro-organisms to the tooth surface reducing plaque formation) to placebo on plaque formation and gingivitis.. Both were more effective than placebo, however, chlorhexidine was statistically significantly more effective (in relation to the clinical outcome parameters measured to quantify gingivitis and plaque formation). The trial also concluded that the long-term use of chlorhexidine was found to be less tolerated by the subjects.
5. Gunsolley JC. A meta-analysis of six-month studies of antiplaque and antigingivitis agents. A meta-analysis of the efficacy of anti-gingivitis and anti-plaque agents in sixth-month trials. *J Am Dent Assoc* 2006;137:1649-57.
RATIONALE: Seven studies, conducted between 1989 and 2005 (including 2258 subjects in total) looked at chlorhexidine 0.12% mouthwash and evaluated its efficacy at reducing gingival inflammation by using the Modified Gingival Index scoring system*. Chlorhexidine had the most consistent results. *The Modified Gingival Index is a statistically sensitive scoring system that allows the non-invasive assessment of subtle signs of the severity and extent of gingival inflammation (Lobene, RR et al).
6. Lobene, RR; Weatherford, T; Ross, NM; Lamm, RA; Menaker, L. A modified gingival index for use in clinical trials. *Clinical Preventative Dentistry*. 1986 Vol 8 No.1 (USA)
7. Scottish Dental: Clinical Effectiveness Programme 2011.
RATIONALE: Formal expert opinion. Recommends 6% hydrogen peroxide (300ml): dilute 15ml in half a glass of warm water three times each day. Rinse for up to 3 minutes and spit out mouthwash after use. Continue until inflammation has resolved and normal oral hygiene measures can be resumed.

8. Hasturk H, Warbington M, Van Dyke TE. Efficacy of a fluoridated hydrogen peroxide-based mouthrinse for the treatment of gingivitis: a randomised controlled clinical trial. *J Periodontol* 2004;75:57-65.

RATIONALE: This American placebo controlled trial in 99 patients looked at the effects of fluoridated hydrogen peroxide-based mouthrinse for the treatment of gingivitis (over 28 days) and teeth whitening (over 5 months). There was a statistically significant improvement in gingival inflammation in the mouthrinse group compared with placebo ($p=0.004$).

Acute necrotising ulcerative gingivitis (ANUG)

1. The mainstay of treatment is local antiseptics and hygiene measures; adjunctive antibiotics are only required in cases of systemic involvement or where there is failure to improve following primary dental management. Metronidazole recommended; amoxicillin is an alternative.

2. Duckworth R, Waterhouse JP, Britton DE, Nuki K, Sheiham A, Winter R, Blake GC. Acute ulcerative gingivitis. A double-blind controlled clinical trial of metronidazole. *Br Dent J* 1966;21;120:599-602.

RATIONALE: In this double-blinded clinical trial 33 patients with ANUG were treated for 2 days with metronidazole (200mg TDS) and 33 patients with phenoxymethylpenicillin (250mg QDS). There was no placebo group. There was no difference in the initial response rate but at 12 month follow-up there were significantly more recurrences in the phenoxymethylpenicillin group (8/21 vs. 0/20 of those who completed the follow survey). This data supports the use of metronidazole in the treatment of ANUG.

3. Wade AB, Blake GC, Miza KB. Effectiveness of metronidazole in treating the acute phase of ulcerative gingivitis. *Dent Pract* 1966;16:440-444.

RATIONALE: In this double-blinded clinical trial 25 patients with ANUG were treated for 2 days with metronidazole (200mg TDS) and 25 patients used sodiumperborate mouth rinse (one sachet TDS). There was no placebo group. The initial response was significantly better in the metronidazole group but there was no long term follow up. This data may support the use of systemic metronidazole over topical mouth rinse in the treatment of ANUG.

4. Loesche WJ, Syed SA, Laughon BE, Stoll J. The bacteriology of acute necrotizing ulcerative gingivitis. *J Periodontol* 1982;53:223-230.

RATIONALE: In this small longitudinal study a total of eight patients with ANUG were included. Those systemically ill ($n=3$) were treated with metronidazole (200mg TDS) and those with local symptoms only received standard periodontal therapy. Those systemically ill had more microbiological findings initially. Metronidazole treatment reduced the number of anaerobes but at a 2-3-month follow-up these had reverted to pre-treatment levels. This study supports the efficacy of metronidazole on anaerobic pathogens in the treatment of ANUG and highlights the efficacy of standard periodontal treatment.

5. Preshaw PM. Antibiotics in the treatment of periodontitis. *Dental Update* 2004;31:448-456.

RATIONALE: Informal expert opinion (UK). This review recommends root surface instrumentation, chemical plaque control (chlorhexidine mouthwash) and oral hygiene advice as the gold standard treatment. Metronidazole (400mg 3 times daily for 3 days) can be added in the acute stages.

6. Kuriyama T; Williams, DW; Yanagisawa, M; Iwahara, K; Shimizu, C; Kakagawa, K; Yamamoto, E; Karasawa, T. Antimicrobial susceptibility of 800 anaerobic isolates from patients with dentoalveolar infection to 13 oral antibiotics. *Oral Microbiol Immunol* 2007;22:285-288 (Japan & Wales).

RATIONALE: A clinical study looking at the antimicrobial susceptibility of 800 anaerobic

isolates from dentoalveolar infections. Strict anaerobes predominate, *P. intermedia* (a common pathogen in ANUG) found to be 100% susceptible to metronidazole. This supports the use of metronidazole in this condition. *Fusobacterium* species has good susceptibility to amoxicillin/clavulanic acid, a wide range of cephalosporins, clindamycin and metronidazole.

7. Dahlen G. Microbiology and treatment of dental abscesses and periodontal-endodontic lesions. *Periodontol 2000* 2002;28:206-239. (Sweden).

RATIONALE: Metronidazole is effective against strict anaerobes (the common pathogens seen in ANUG). Four studies demonstrated that *Prevotella*, *Porphyromonas* species and *Fusobacterium* species were 100% susceptible to metronidazole. This study highlighted the benefits of metronidazole in the face of β -lactamase-producing anaerobes and also the penicillin allergic patient.

Pericoronitis

1. Pericoronitis is the inflammation and infection of perimolar soft tissue, often provoked by emerging molar teeth. Formal expert opinion from the Scottish Dental Clinical Effectiveness Programme 2011 indicates that this condition should be managed by referral to a dentist for local surgical treatment primarily with irrigation or incision and debridement of the lesion. Antibiotics can be added where there is systemic involvement or on-going symptoms. Public Health England recommends metronidazole 400mg TDS for 3 days. If metronidazole is not tolerated an alternative is amoxicillin 500mg TDS for 3 days (in adults the dose can be doubled in severe infections). See note above references.

2. Ellison SJ. The role of phenoxymethylpenicillin, amoxicillin, metronidazole and clindamycin in the management of acute dentoalveolar abscesses – a review. *Br Dent J* 2009;206:247-62.

RATIONALE: Drawing from conclusions derived from this British literature review and literature search of over 5,000 references worldwide using Embase, Medline and Cochrane (search criteria antibiotics and dental) this review recommends the use of metronidazole 200mg TDS for 3 days as first line treatment in pericoronitis. Public Health England, however, recommends 400mg TDS. See note above references.

3. Sixou J-L, 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;12:5794–5797.

RATIONALE: This French study looked at the microbial flora isolated from samples taken from 35 patients with pericoronitis and evaluated their susceptibility to amoxicillin, pristinamycin (a macrolide) and metronidazole (alone or in combination with the macrolide 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 metronidazole.

4. Dahlen G. Microbiology and treatment of dental abscesses and periodontal-endodontic lesions. *Periodontol 2000* 2002;28:206-239. (Sweden).

RATIONALE: This informal expert review evaluated 7 studies looking at the microbial findings in pericoronitis and concluded that anaerobic species predominate, sharing a similar microbiological profile to that of a dental abscess.

Dental abscess

There are few randomised controlled trials or systematic reviews looking at outcomes of dental abscess with and without antibiotics. The guidance is mainly based on expert opinion and laboratory susceptibility data of the organisms usually found in the dental conditions described.

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;69:660.

RATIONALE: In the management of localized acute apical abscess in the permanent dentition, the abscess should be drained through a pulpectomy or incision and drainage. This analysis indicated that antibiotics are of no additional benefit. In the event of systemic complications (e.g., 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;28:206-239.

RATIONALE: This review recommends 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 and is aimed at limiting spread and preventing serious complications.

3. Ellison SJ. The role of phenoxymethylpenicillin, amoxicillin, metronidazole and clindamycin in the management of acute dentoalveolar abscesses – a review. *Br Dent J* 2009;206:247-62.

RATIONALE: This British literature review and literature search of over 5,000 references worldwide using Embase, Medline and Cochrane (search criteria antibiotics and dental) concluded that there is little evidence-based antibiotic prescribing in the case of dental infections and to help control increasing antimicrobial resistance it is important to only prescribe antimicrobials if indicated. Antimicrobials should be prescribed if systemic sign of acute dental abscess include: pyrexia, trismus, lymphadenopathy, gross facial or ocular oedema, dysphagia, tachycardia or rigors.

4. Kuriyama T, Absi EG, Williams DW, Lewis MAO. An outcome audit of the treatment of acute dentoalveolar infection: impact of penicillin resistance. *Br Dent J* 2005;198:759-63 (UK).

RATIONALE: 112 patients with dentoalveolar infection underwent incisional or dental pulp chamber drainage and were assigned to one of six different antibiotic regimes. No significant difference in outcome was found with any regime, and the presence of penicillin-resistant strains did not influence the outcome where surgical management was already established (Student-T analysis for the comparison of clinical improvement scores) questioning the indication for antibiotics at all. However this study did not look at cases where antibiotics were not prescribed where adequate drainage had been achieved, and reinforced that it would be unethical to undertake such a study where systemic signs of infection were evident.

5. Preshaw PM. Antibiotics in the treatment of periodontitis. *Dental Update* 2004;31:448-56.

RATIONALE: Informal expert opinion. Scientific research demonstrating the impervious nature of dental biofilms to antibiotics (microorganisms can survive concentrations 500-1000 times greater than required for systemic delivery, Walker 2002) illustrated the rationale for definitive surgical management prior to considering this as an adjunct and Preshaw reinforces that in most cases systemic treatment is not required.

6. Robertson D, Smith AJ. The microbiology of the acute dental abscess. *Med Microbiol.* 2009;58:155-62.

RATIONALE: Informal expert opinion, literature review. Despite few well controlled trials, the literature available supports the use of urgent surgical management of the dental abscess in combination with antimicrobial agents where there is evidence of cellulitis or sepsis.

7. Scottish Dental Clinical Effectiveness Programme, 2011.

RATIONALE: Formal expert opinion. The Scottish guidance recommends a dosage

regimen of 250mg amoxicillin TDS. Expert opinion at Public Health England and Department of Health Advisory Group on Antimicrobial Resistance & Healthcare Associated Infection is to increase concentrations at the site of infection above the minimum inhibitory concentration needed to eradicate the infecting bacteria, especially for more resistant *Bacteroides* spp. In severe infection double the dose of amoxicillin (from 500mg – 1g TDS) or in the case of phenoxymethylpenicillin (500mg – 1g QDS).

8. 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;12:41-6.

RATIONALE: This German study looking at the susceptibility of microbiological samples taken from 140 patients with dentoalveolar disease (periodontitis or odontogenic abscess) showed 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.

9. Kuriyama T, Absi EG, Williams DW, Lewis MAO. An outcome audit of the treatment of acute dentoalveolar infection: impact of penicillin resistance. *Br Dent J* 2005;198:759-63 (UK).

RATIONALE: A clinical study looking at the antimicrobial susceptibility of 800 anaerobic isolates from dentoalveolar infections in Japan. The study concluded 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. However, resistance to amoxicillin was seen in β -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 the 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 the development of resistance.

10. Kulik EM, Lenkeit K, Chenaux S, Meyer J. Antimicrobial susceptibility of periodontopathogenic bacteria. *J Antimicrob Chemother* 2008;61:1087-1091.

RATIONALE: A laboratory-based microbiological study in Switzerland (where antibiotic use is among the lowest in Europe) looking at the resistance profiles of three predominant periodontopathogenic bacteria isolated from dental abscesses over a fourteen year period to 2005, concluded 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.

11. Martin MV, Longman LP, Hill JB, Hardy P. Acute dentoalveolar infections: an investigation of the duration of antibiotic therapy. *British Dental Journal*, 1997;183:135-37.

RATIONALE: This British study looked 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 the resolution of systemic symptoms (swelling and temperature) after 2-3 days and then at 10 days and found 98.6% of cases had resolution of symptoms at the first review (when antibiotics were discontinued), furthermore these patients did not need an additional course of antibiotics at a later stage. This study shows that if drainage has been established antibiotics may not be needed beyond 2-3 days. We recommend clinical review at 3 days, if possible, when antibiotics may be stopped if symptoms have resolved, or continued for 5 days duration.

12. Scottish Dental Clinical Effectiveness Programme 2011.

RATIONALE: Formal expert opinion. Avoid clindamycin, clarithromycin, cephalosporins

and amoxicillin/clavulanate as first line agents (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 a 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.

13. Ellison SJ. An outcome audit of three day antimicrobial prescribing for the acute dentoalveolar abscess. *Br Dent J*. 2011 Dec. 211(12): 591-594.

RATIONALE: This describes 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% (188) with systemic involvement were given 3 days amoxicillin 250mg TDS (first-line) or metronidazole 200mg TDS (second-line). The combination of drainage and three day antibiotic regimen in these patients showing associated signs of systemic symptoms was effective in 100% of cases where review was obtained.

Acknowledgements

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2010 major review and evidence searches by Ms Hannah Jones, Dr Simon Hurding, and Clare Colligan with overview by Dr Clodna McNulty.

In 2012 there was a major review in collaboration with the Scottish antimicrobial Prescribing Group led by Dr Clodna McNulty and Dr Jacqueline Sneddon.

Dr Clodna McNulty has led the subsequent antibiotic guidance review process, with assistance from Dr Philippa Moore and reviewers below.

In 2014 Dr Chris Brookes, undertook the oral candidiasis literature search and wrote the guidance under the supervision of Dr Philippa Moore, Consultant Microbiologist, Gloucestershire Royal Hospital and Dr Clodna McNulty

In 2016, there was a minor review, in collaboration with the South West Regional Microbiology Group (SWRMG) and Dr Teh Li Chin, led by Prof Clodna McNulty

In 2017, there was a minor review, in collaboration with experts in the field, regarding the update of the section on urinary tract infections, references and associated rationales.

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Abbreviations

ABPI	The Association of the British Pharmaceutical Industry
ANUG	Acute necrotising ulcerative gingivitis
AOM	Acute otitis media
AUC	Area under the curve
BASHH	British Association for Sexual Health & HIV
BD	Twice daily
BNF	British National Formulary
BP	Blood pressure
BSAC	British Society of Antimicrobial Chemotherapy
BTS	British Thoracic Society
CAP	Community acquired pneumonia
CFU	Colony forming units
CI	Confidence interval
CKS	Clinical Knowledge Summaries
COPD	Chronic obstructive pulmonary disease
CPD	Continuing Professional Development
CRB65	Confusion, respiratory rate, blood pressure, age >65
CREST	Clinical Resource Efficiency Support Team
CRP	C reactive protein
DH	Department of Health
DU	Duodenal ulcer
EHSB	European Helicobacter Study Group
ESBL	Extended spectrum beta-lactamases
GDG	Guidance Development Group
GFR	Glomerular filtration rate
GORD	Gastro-oesophageal reflux disease
GRASP	Gonococcal Resistance to Antimicrobials Surveillance Programme
GU	Gastric ulcer
GUM	Genitourinary medicine
HIV	Human immunodeficiency virus
HSV	Herpes simplex virus
IHMF	International Herpes Management Forum
IM	Intramuscular
IV	Intravenous
MALToma	Mucosa-Associated Lymphoid Tissue lymphoma
MARTI	Managing acute respiratory tract infection
Mg	Milligrams
MIC	Minimum inhibitory concentration
MRSA	Methacillin-resistant Staphylococcus aureus
MSU	Mid stream urine
MTZ	Metronidazole
MUT	Managing Urinary Tract
NHS	National Health Service

NICE	National Institute for Health and Care Excellence
NNT	Number needed to treat
NPV	Negative predictive value
OD	Once daily
OE	Otitis externa
OM	Otitis media
OPAT	Outpatient Parenteral Antimicrobial Therapy
PHE	Public Health England
PHLS	Public Health Laboratory Service
PID	Pelvic inflammatory disease
PPI	Proton pump inhibitor
PVL	Panton-Valentine Leukocidin
QDS	Four times daily
RCGP	Royal College of General Practitioners
RCT	Randomised Controlled Trial
RR	Relative risk
RS	Rhinosinusitis
Rx	Treatment
SAPG	Scottish Antimicrobial Prescribing Group
SDCEP	Scottish Dental Clinical Effectiveness Programme
SIGN	Scottish Intercollegiate Guidelines Network
SSTI	Skin and soft tissue infection
Stat	Single dose
STD	Sexually transmitted disease
STI	Sexually transmitted infection
TARGET	Treat antibiotics responsibly: Guidance, Education, Tools
TDS	Three times daily
UKTIS	United Kingdom Teratology Information Service
UTI	Urinary tract infection
WCC	White cell count