Summary of antimicrobial prescribing guidance – managing common infections

PHE context, references and rationales for Clinical Commissioning Groups, Commissioning Support Units and Primary Care Providers

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Foreword – context and implementation

Recent developments

Between 2018 and 2020, a combined PHE/NICE 'Summary of antimicrobial prescribing guidance – managing common infections' will be produced for primary and secondary care. They will include combined table summaries, hosted on the NICE website and separate rational and evidence documents developed for the content hosted on each agencies' website and accessible through hyperlinks.

PHE statements are linked to graded references, rationale and full guidance where available. These can be found within this document and accessed through the table of contents.

As new syndromic NICE guidance is published, each PHE box in the NICE/PHE table summary will be replaced, and users will be referred to the new rationale and infographic developed by the NICE team. PHE will continue to do occasional updates based on user feedback or significant changes in the evidence base and a full review of their content every 3 years.

Audience

- primary care prescribers in general practice and out-of-hours settings, including doctors, nurses and pharmacists
- Clinical Commissioning Group (CCG) or Commissioning Support Unit (CSU) prescribing advisers who may be receiving queries from primary care prescribers
- those giving first point of contact or symptomatic advice for common infections

Aims

- to improve the management of common infections in primary care
- to minimise the emergence of antimicrobial resistance in the community

Production

The PHE table summaries are based on the best available evidence and have been produced in consultation with, general practitioners, nurses, pharmacists, specialists, patient representatives and professional societies and are in line with other guidelines, including NICE, PHE, SIGN and CKS

Implementation

The table summaries are designed to be printed out as posters for easy use in practice. The links to rationales and evidence are designed to be used as an educational tool for you, and your colleagues and trainees, or to share with patients.

The table summaries are intended to provide a 'quick reference' and are not all encompassing. Professional judgement should be used and patients involved in management decisions.

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The table summaries should not be used in isolation; they should be supported with patient information about safety netting, delayed/back-up antibiotics, infection severity and usual duration, clinical staff education, and audits. Materials are available on the RCGP TARGET and NICE websites.

Local adaptation

Major changes to the table summaries would be discouraged, but the format allows minor changes to be made by local guideline development groups. To ensure effective local implementation, dissemination should be agreed and planned at the local level between primary care clinicians, laboratories and secondary care providers.

Implications

This summary of antimicrobial prescribing guidance – managing common infections supports the 2017/19 NHS England Antibiotic Quality Premium ambition to reduce inappropriate antibiotic prescribing in the management of infections in primary care. Use of the table summaries should lead to more appropriate antimicrobial use. Public Health England works closely with the authors of the Clinical Knowledge Summaries and NICE Management of Infection Guidance - Public Health Advisory Committee.

Contact details

We welcome opinions on the advice given. Please email or post and feedback along with any evidence or references that support your requests for consideration.

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Developing and grading recommendations

The strength of each PHE 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, for example case reports or case series	C
Formal combination of expert opinion	D

The PHE Management of Common Infections Guidance was originally produced in 1999 by the South West GP Microbiology Laboratory Use Group, in collaboration with the Cheltenham & Tewkesbury Prescribing Group, the Association of Medical Microbiologists, general practitioners, nurses and specialists in the field, as part of the S&W Devon Joint Formulary Initiative. It has since been modified by the PHLS South West Antibiotic Guidelines Project Team, PHLS Primary Care Co-Ordinators, and members of the Clinical Prescribing Sub-Group of the Standing Medical Advisory Committee on Antibiotic Resistance. The guidance underwent a full systematic review and update in 2017, with input from Professor Cliodna McNulty; Dr Teh Li Chin; the Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI); the British Society for Antimicrobial Chemotherapy (BSAC); the British Infection Association (BIA); the Royal College of General Practitioners (RCGP); the Royal College of Nursing (RCN); general practitioners; specialists in the field; and patient representatives. Full consensus of the recommendations made was given by all guidance developers and reviewers prior to the dissemination of this guidance. All comments received have been reviewed and incorporated into the guidance, where appropriate.

For any further information regarding the review process and those involved in the development of this guidance, please email TARGETAntibiotics@phe.gov.uk.

Public Health England is an executive agency of the Department of Health, and is fully funded by the UK Government. The Primary Care Unit does not accept funding for the development of this guidance from pharmaceutical companies or other large businesses that could influence the development of the recommendations made.

Any conflicts of interest have been declared and considered prior to the development and dissemination of this guidance. For any detailed information regarding declared conflicts of interest, please email TARGETAntibiotics@phe.gov.uk.

General information

Principles of treatment

1. The PHE sections of the summary table are based on the best available evidence, but use professional judgement and involve patients in management decisions.
2. PHE sections of this summary table should not be used in isolation; it should be supported with patient information about safety netting, back-up antibiotics, self-care, infection severity and usual duration, clinical staff education, and audits. Materials are available on the RCGP TARGET website.
3. Prescribe an antibiotic only when there is likely to be clear clinical benefit, giving alternative, non-antibiotic self-care advice, where appropriate.
4. If person is systemically unwell with symptoms or signs of serious illness, or is at high risk of complications: give immediate antibiotic. Always consider possibility of sepsis, and refer to hospital if severe systemic infection
5. Use a lower threshold for antibiotics in immunocompromised, or in those with multiple morbidities; consider culture/specimens, and seek advice.
6. In severe infection, or immunocompromised, it is important to initiate antibiotics as soon as possible, particularly if sepsis is suspected. If patient is not at moderate to high risk for sepsis, give information about symptom monitoring, and how to access medical care if they are concerned.
7. Where an empirical therapy has failed or special circumstances exist, microbiological advice can be obtained from ☎ [insert phone number]
8. Limit prescribing over the telephone to exceptional cases.
9. Use simple, generic antibiotics if possible. Avoid broad spectrum antibiotics (for example co-amoxiclav, quinolones and cephalosporins) when narrow spectrum antibiotics remain effective, as they increase the risk of *Clostridium difficile*, MRSA and resistant UTIs.
10. Avoid widespread use of topical antibiotics, especially in those agents also available systemically (for example fusidic acid); in most cases, topical use should be limited.
11. Always check for antibiotic allergies. A dose and duration of treatment for adults is usually suggested, but may need modification for age, weight, renal function, or if immunocompromised. In severe or recurrent cases, consider a larger dose or longer course.
12. Avoid use of quinolones unless benefits outweigh the risk as new 2018 evidence indicates that they may be rarely associated with long lasting disabling neuro-muscular and skeletal side effects.
13. Refer to the BNF for further dosing and interaction information (for example the interaction between macrolides and statins), and check for hypersensitivity.
14. The PHE sections of the table summary support the 2017 to 2019 NHS England Antibiotic Quality Premium ambition to reduce inappropriate antibiotic prescribing in the management of infections in primary care.

Comments on selected antibiotics and doses recommended

Clarithromycin:

This guidance recommends clarithromycin as it has fewer side-effects than erythromycin, greater compliance with a twice daily regimen rather than a 4 times daily regimen, and generic tablets are of similar cost. Erythromycin is preferred in pregnancy.[1B-,2D,3B+] Azithromycin may be associated with greater development of resistance than other macrolides, as it has a greater half-life in comparison to clarithromycin and erythromycin so may provide more opportunity for resistant organisms to develop.

Amoxicillin and metronidazole:

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

For metronidazole, the killing effect is dose-dependent (ie. it is the maximum concentration attained above the MIC that is most important).[4B+] Metronidazole has simple first-order kinetics, so doubling the dose doubles the plasma concentrations at the site of infection.[5D] Oral metronidazole is well tolerated and the side-effects reported at doses of 400mg TDS are either very rare or unknown.[6D] Metronidazole distributes well throughout the body with non-significant differences in the concentrations attained in saliva and crevice fluid compared to plasma.[7B+] Metronidazole has a volume of distribution of 0.5-1.0l/kg, so increasing body mass will decrease plasma concentrations.[8D] AUC/MIC>70 is only attainable against *Bacteroides fragilis* with a 400mg dose, and mouth anaerobes have similar susceptibility to this.[9B-] Evidence suggests that metronidazole 250mg TDS results in concentrations exceeding the MICs of isolated pathogens in crevice fluid. However, as it is more desirable to achieve crevice fluid concentrations several times that of the measured MICs, and the BMI of patients has increased since these trials were undertaken, this guidance recommends metronidazole 400mg 3 times daily.[10B+]

PHE references and rationale

Upper respiratory tract infections

Influenza:

1. National Institute for Health and Care Excellence (NICE). Amantadine, oseltamivir and zanamivir for the treatment of influenza. 2009 Feb. Available from: www.nice.org.uk/guidance/TA168.

    RATIONALE: A NICE guideline suggesting that oseltamivir and zanamivir are possible treatments for people with influenza if all of the following apply: the person is in an at risk group; the person has a flu-like illness and can start treatment within 48 hours (36 hours for zanamivir treatment in children) of the first sign of symptoms; the influenza virus is known to be going around; it is likely that a flu-like illness has been caused by the influenza virus. Healthcare professionals should discuss the choice of oseltamivir or zanamivir with the person being offered the treatment. The decision should take into account which antiviral the person would prefer, and any possible unwanted effects. If all else is equal, the cheapest antiviral should be used. If there is an outbreak of flu-like illness in a long-term residential or nursing home, oseltamivir and zanamivir may be offered to treat residents in at-risk groups who have symptoms of influenza. This could happen even if the influenza virus is not present in the wider community outside the home, but the healthcare team should be sure that the illness is influenza. This guideline also suggests that the recommended dose of oseltamivir for adolescents and adults is 75mg twice daily for 5 days.

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

    RATIONALE: A systematic review and meta-analysis of 22 randomised controlled trials and 1 unpublished report. Eight RCTs were included for amantadine, 6 were included for oseltamivir, and 9 were included for zanamivir. The study quality was variable, and gaps in the evidence limited the assessment of the clinical effectiveness of the interventions. For seasonal prophylaxis, there was limited evidence for the efficacy of amantadine in preventing symptomatic laboratory-confirmed influenza in healthy adults (RR 0.40; 60% reduction; 95% CI 0.08 to 2.03). Oseltamivir was effective in preventing SLCI, particularly when used in at risk elderly subjects (RR 0.08; 92% reduction; 95% CI 0.01 to 0.63). The preventative efficacy of zanamivir was most notable in at risk adults and adolescents (RR 0.17; 83% reduction; 95% CI 0.07 to 0.44), and healthy and at risk elderly subjects (RR 0.20; 80% reduction; 95% CI 0.02 to 1.72). The authors conclude that all 3 interventions show some efficacy for seasonal and post-exposure prophylaxis. However, weaknesses and gaps in the clinical evidence base are directly relevant to the interpretation of the health economic model, and rendered the use of advanced statistical analyses inappropriate.

3. Wellcome Trust: The Academy of Medical Sciences. Use of neuraminidase inhibitors in influenza. 2015 Oct. Available from: https://acmedsci.ac.uk/file-download/38069-561595082cd83.pdf.

> RATIONALE: A Wellcome Trust guideline recommending that if NIs are to be used in the treatment of influenza, treatment should commence within 48 hours of the first onset of symptoms. The authors conclude that, while the importance of initiating treatment as early as possible in those who do go on to develop severe disease is clear, the use of treatment in other scenarios must rely on clinical judgement, particularly because identifying these patients within 48 hours is not always possible.

4. Public Health England (PHE). PHE guidance on use of antiviral agents for the treatment and prophylaxis of seasonal influenza. 2016 Oct. Available from: www.gov.uk/government/uploads/system/uploads/attachment_data/file/580509/PHE_guidance_antivirals_influenza_2016_2017.pdf.

> RATIONALE: A PHE guideline advising that influenza is a viral infection affecting the lungs and airways. Complications include bacterial pneumonia and can be life threatening, especially in older people or those with certain underlying health conditions. It occurs most often during the winter in the UK, and peaks between January and March. There are 2 types of influenza: influenza A and influenza B, with influenza B causing a milder illness most often seen in children. PHE advise that risk factors for complicated influenza include: chronic neurological, hepatic, renal, pulmonary and chronic cardiac disease; diabetes mellitus; severe immunosuppression; age over 65 years; pregnancy (including up to 2 weeks' post-partum); children under 6 months of age; morbid obesity (BMI>40).

5. Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children (Review). *Cochrane Database Syst Rev*. 2014 Apr; 10(4):1-560. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008965.pub4/epdf.

> RATIONALE: A systematic review of 107 clinical study reports aiming to describe the potential benefits and harms of NIs for influenza in all age groups. The results indicate that treatment trials with oseltamivir or zanamivir do not settle the question of whether the complications of influenza (such as pneumonia) are reduced, because of a lack of diagnostic definitions. The authors conclude that the balance between benefits and harms should be considered when making decisions about the use of both NIs for either the prophylaxis or treatment of influenza.

6. Muthuri SG, Venkatesan S, Myles PR, Leonardi-Bee J, Al Khuwaitir TS, Al Mamun A et al. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. *Lancet Respir Med*. 2014 May; 2(5):395-404. Available from: www.ncbi.nlm.nih.gov/pubmed/24815805.

> RATIONALE: A meta-analysis including data from 29,234 patients from 78 studies of patients admitted to hospital between January 2nd, 2009, and March 14th, 2011. Compared with no treatment, neuraminidase inhibitor treatment (irrespective of timing) was associated with a reduction in mortality risk (adjusted odds ratio 0.81, 19% reduction;

95% CI 0.70 to 0.93; p=0.0024). Compared with later treatment, early treatment (within 2 days of symptom onset) was associated with a reduction in mortality risk (OR 0.48, 52% reduction; 95% CI 0.41 to 0.56; p<0.0001), as was early treatment versus no treatment (OR 0.50, 50% reduction; 95% CI 0.37 to 0.67; p<0.0001). These associations with reduced mortality risk were less pronounced and not significant in children. The authors conclude that they advocate the early instigation of neuraminidase inhibitor treatment in adults admitted to hospital with suspected or proven influenza infection.

Scarlet fever:

1. Public Health England (PHE). Guidelines for the public health management of scarlet fever outbreaks in schools, nurseries and other childcare settings. 2017 Oct. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_dat a/file/656687/Guidelines_for_the_public_health_management_of_scarlet_fever_outbreaks .pdf

   RATIONALE: Scarlet fever was once a dangerous disease in the UK, but antibiotic treatment means it is now much less serious. Following marked decreases in incidence over the last century, 3,000 to 4,000 cases were diagnosed each year in England during the early 2000s. In 2014, an unusual increase in incidence occurred with over 14,000 cases diagnosed in England with high incidence continuing into 2015 and 2016 and over 16,000 cases notified in each of these years. Scarlet fever is a common childhood infection caused by *Streptococcus pyogenes* (GAS). Under some circumstances GAS can cause non-invasive infections, such as: pharyngitis; impetigo; scarlet fever. On rare occasions they can cause severe disease, including: streptococcal toxic shock syndrome (TSS); necrotising fasciitis; invasive GAS (iGAS) infection. It is most common in children between the ages of 2 and 8 years, with 4 year olds most likely to develop the illness. Increases in scarlet fever can be expected during late winter and spring of each year, reflecting its normal seasonal pattern, although cases and outbreaks will occur throughout the year. The symptoms of scarlet fever are non-specific in early illness and may include sore throat, headache, fever, nausea, and vomiting. After 12 to 48 hours, the characteristic red, generalised pinhead rash develops, typically first appearing on the chest and stomach, rapidly spreading to other parts of the body, giving the skin a sandpaper-like texture. On more darkly-pigmented skin, the scarlet rash may be harder to spot, although the sandpaper-like texture should be present.
   Patients typically have flushed cheeks and pallor around the mouth, which may be accompanied by a "strawberry tongue". During convalescence, peeling of the skin occurs at the tips of fingers and toes, and less often over wide areas of the trunk and limbs. Although scarlet fever is usually a mild illness, patients can develop complications, such as: ear infection; throat abscess (quinsy); pneumonia; sinusitis; meningitis in the early stages; acute glomerulonephritis in the later stages; acute rheumatic fever in the later stages. Prompt treatment with appropriate antibiotics significantly reduces the risk of complications developing. There is greater risk of invasive disease if chickenpox is also present. Scarlet fever is highly contagious if not treated and children remain infectious for 2-3 weeks from rash if no antibiotics given. Recommendations include: prescribe an appropriate treatment course of antibiotics; advise **exclusion** from nursery/school/work for at least **24 hours** after the commencement of appropriate antibiotic treatment; consider

taking a throat swab to assist with differential diagnosis or if the patient is thought to be part of an outbreak, allergic to penicillin (to determine antimicrobial susceptibility), or in regular contact with vulnerable individuals such as the immunocompromised, the comorbid, or those with skin disease, who are at risk of complications of *S. pyogenes* including streptococcal toxic shock syndrome.

2. Clinical Knowledge Summaries (CKS). Scarlet fever. 2018 June. Available from: http://cks.nice.org.uk/scarlet-fever#!topicsummary.

    RATIONALE: A CKS guideline stating that scarlet fever most commonly affects children of school age, peaking at 4 years of age, and that it is usually a mild, self-limiting illness, which can be managed with analgesia. It recommends phenoxymethylpenicillin as the first line antibiotic at a dose of 500 mg for adults QDS for 10 days. It also lists amoxicillin and azithromycin as antibiotics for management in primary care. It also recommends offering paracetamol or ibuprofen, and encouraging the person to rest and drink adequate fluids. The NICE Sore throat (including pharyngitis and tonsillitis) guidance from Jan 2018 is recommending 250-500 mg Clarithromycin BD for 5 days in penicillin allergy. The CKS summary cites an article (*Clinical practice guideline for the diagnosis and management of Group A streptococcal pharyngitis: 2012 update by the Infectious Disease Society of America*) by Shulman et al which states that erythromycin, clarithromycin or azithromycin are all reasonable to use in people who are allergic to penicillin. We recommend using Clarithromycin in cases with penicillin allergy but have updated the duration based on the findings from the 2012 Altamimi review (below) which states a 5 day course for Clarithromycin should be adequate for acute streptococcal pharyngitis in children.

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

    RATIONALE: A meta-analysis of 22 trials, involving 7,470 patients. Trials were grouped by a short-course of cephalosporins (n=14), macrolides (other than azithromycin) (n=6), and penicillin (n=2). Cephalosporin trials were further grouped by the comparator, penicillin, or the same cephalosporin. Short-course cephalosporin treatment was superior for bacterial cure rate, compared with 10 days' penicillin (OR 1.47; 95% CI 1.06 to 2.03). For trials with short-course macrolide therapy (OR 0.79; 21% reduction; 95% CI 0.59 to 1.06), neither the macrolides nor the 10 day comparators showed superiority for bacterial cure rate. Short-course penicillin therapy was inferior in achieving bacterial cure versus 10 days of penicillin (OR 0.29; 71% reduction; 95% CI 0.13 to 0.63). Clinical cure rates mirrored bacteriological cure rates. The authors conclude that superior cure rates can be achieved with shorter courses of cephalosporins, but 5 days is inferior to 10 days with penicillin.

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

    RATIONALE: A meta-analysis of 11 randomised controlled trials, comparing short-course and long-course treatment (5 with penicillin V; 4 with oral cephalosporins; 1 with intramuscular ceftriaxone; 1 with clindamycin). In the primary analysis, microbiological eradication rates of GAS were inferior for short-course versus long-course treatment (OR

0.49; 51% reduction; 95% CI 0.32 to 0.74; 8 RCTs, n=1,607). This association was noted with penicillin V treatment (OR 0.36; 64% reduction; 95% CI 0.13 to 0.99; 3 RCTs, n=500), but was nonsignificant with cephalosporin treatment (OR 0.62; 38% reduction; 95% CI 0.38 to 1.03; 4 RCTs, n=1,018). Microbiological eradication was less likely with short-course treatment in trials involving primarily children and adolescents (OR 0.63; 37% reduction; 95% CI 0.40 to 0.98; 6 RCTs, n=1,258). Clinical success was inferior in patients who received short-course treatment (OR 0.49; 51% reduction; 95% CI 0.25 to 0.96; 5 RCTs, n=1,217). Adverse events did not differ between compared groups. The associations were consistent in the analyses involving all included RCTs. The authors conclude that short-course treatment for GAS tonsillopharyngitis, particularly with penicillin V, is associated with inferior bacteriological eradication rates.

5. Altamimi S, Khalil A, Khalaiwi KA, Milner RA, Pusic MV, Al Othman MA. Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children (Review). *Cochrane Database Syst Rev*. 2012 Aug; 15(8):1-58. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004872.pub3/epdf.
   RATIONALE: A systematic review and meta-analysis of 20 studies including over 13,000 cases, showing that short-course broad-spectrum antibiotics (including 5 days clarithromycin) are as efficacious as 10 days penicillin for sore throat symptom treatment and GABHS eradication. Ten days phenoxymethylpenicillin remains the treatment of choice for sore throat. Evidence suggests that the use of broader spectrum antibiotics will drive the emergence of bacterial resistance, will increase the risk of developing *Clostridium difficile* associated disease, and are associated with more adverse drug reactions. Five days clarithromycin or erythromycin should be reserved for those with true penicillin allergy.

Acute otitis externa:

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

2. Clinical Knowledge Summaries (CKS). Otitis externa. 2015 Jul. Available from: http://cks.nice.org.uk/otitis-externa#!topicsummary.
   RATIONALE: A CKS guideline stating that analgesia and localised heat (for example a warm flannel) should be used as first line measures for patients with acute otitis externa. These measures are sufficient for most cases of localised otitis externa, as folliculitis is usually mild and self-limiting. For topical treatment, acetic acid alone has not been compared with placebo for treating otitis externa in randomised controlled trials. One double-blind RCT found no statistically significant difference in efficacy between topical

acetic acid and a topical antibiotic-corticosteroid combination at day 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. Aluminium acetate has also not been compared with placebo for the treatment of otitis externa. Two RCTs found no clinically important difference between topical aluminium acetate and topical antibiotics with or without corticosteroid. However, these results should be interpreted with caution because of the very low methodological quality of the studies. For oral antibiotics, flucloxacillin should only be prescribed if disease extends outside the ear canal, at a dose of 250-500mg, 4 times daily, for 7 days.

3. Kaushik V, Malik T, Saeed SR. Interventions for acute otitis externa (Review). *Cochrane Database Syst Rev.* 2010 Jan; 20(1):1-121. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004740.pub2/epdf.
RATIONALE: A systematic review and meta-analysis of 19 low quality randomised controlled trials, only 2 of which are from primary care and, therefore, probably included more severe or chronic cases. It is important to note that over half of the trials involved ear cleaning, which the authors stress is likely not to be wholly generalizable to primary care. This meta-analysis demonstrates that topical treatments alone are adequate for treating most cases of acute otitis externa. Acetic acid was as effective, and comparable to antibiotics/steroids for the first 7 days, but inferior after this point. The authors conclude that it is important to instruct patients to use drops for at least 1 week, and to continue for up to 14 days if symptoms persist.

4. Thorp MA, Kruger J, Oliver S, Nilssen EL, Prescott CA. The antibacterial activity of acetic acid and Burow's solution as topical ontological preparations. *J Laryngol Otol.* 1998 Oct; 112(10):925-928. Available from: www.ncbi.nlm.nih.gov/pubmed/10211213.
RATIONALE: A prospective study demonstrating little evidence to support the use of 1 agent over another in the treatment of acute otitis externa. Both acetic acid and Burow's solution have shown a similar efficacy compared to other topical treatments, such as antibiotics and corticosteroids, although caution should be taken due to the lack of quality in these studies. Based on the fact that acetic acid is recommended as first line treatment for mild otitis externa, whilst aluminium is for more resistant cases or extensive swelling and requires specialist referral for ear wick insertion, acetic acid's availability compared to aluminium acetate would suggest that this is the better first line option. Although there are no trials of acetic acid versus placebo, there are trials comparing its use to a topical antibiotic-corticosteroid combination, which show equivalence. Only 1 study was found from a literature search which compared the efficacy between acetic acid and Burow's solution. This was a small (n=20) in vitro study, which compared the activity of 1, 2 and 3 percent acetic acid with Burow's solution (aluminium acetate 13%) on an agar plate with the following organisms: *Pseudomonas aeruginosa*; *Staphylococcus aureus*; *Proteus mirabilis*; *Streptococcus pyogenes*. The activity of each agent was ascertained by the size of the zone of inhibition of bacterial growth. Burow's solution showed significantly larger average zones of inhibition than acetic acid (p<0.001). Both the 2 and 3 percent

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acetic acid, as well as the Burow's solution, were active against all the organisms.

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

   RATIONALE: A hospital outpatient randomised controlled trial demonstrating superiority of topical steroid-antibiotic therapy, as all patients in the betamethasone-neomycin group showed symptom improvement, but 5 patients worsened in the group receiving betamethasone alone. Neomycin sulphate with corticosteroid is suggested as a combination therapy, as it contains an antibiotic that is not used orally. Neomycin is active against Pseudomonas and Staphylococci, which are the most common bacterial causes.

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

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

Lower respiratory tract infections

General references:

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

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

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2. Patel SN, McGeer A, Melano R, Tyrrell GJ, Green K, Pillai DR et al. Susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. *Antimicrob Agents Chemother*. 2011 Aug; 55(8):3703-3708. Available from:
    www.ncbi.nlm.nih.gov/pmc/articles/PMC3147653/.

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

3. Fluoroquinolone and quinolone antibiotics: PRAC recommends restrictions on use. Pharmacovigilance Risk Assessment Committee. 5 October 2018. Available from:
    www.ema.europa.eu/documents/referral/quinolone-fluoroquinolone-article-31-referral-recommendation-provided-prac_en.pdf

    RATIONALE: This document outlines recommendations related to the safety of fluoroquinolone and quinolone antibiotics based on an evaluation of feedback from patients, health care professionals and experts presented at a review meeting in June 2018. The committee found that patients treated with these antibiotics can suffer long term, disabling side effects (involving muscles, tendons, bones and nervous system). The PRAC recommendations will be sent to EMA's Committee for Medicinal Products for Human Use (CHMP), which will adopt the Agency's final opinion. Recommendations state that these antibiotics should not be used when infections might get better without treatment or are not severe; for preventing traveller's diarrhoea or recurring lower urinary tract infections; in those who have previously had had serious side effects from these antibiotics; to treat mild or moderately severe infections unless other antibacterial medicines commonly recommended for these infections cannot be used. They suggest use with caution especially for the elderly, patients with kidney problems, patients who have had an organ transplantation or those who are being treated with a systemic corticosteroid. These patients are at higher risk of tendon injury caused by fluoroquinolone and quinolone antibiotics. Healthcare professionals should advise patients to stop treatment with a fluoroquinolone antibiotic at the first sign of a side effect involving muscles, tendons or bones (such as inflamed or torn tendon, muscle pain or weakness, and joint pain or swelling) or the nervous system (such as feeling pins and needles, tiredness, depression, confusion, suicidal thoughts, sleep disorders, vision and hearing problems, and altered taste and smell).

Acute exacerbation of COPD:

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

influenza, S. pneumoniae, or S. aureus.

1. Ram FSF, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC. Antibiotics for exacerbations of chronic obstructive pulmonary disease (Review). *Cochrane Database Syst Rev.* 2006 Apr; 1:1-52. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004403.pub2/epdf.

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

2. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med.* 1987 Feb; 106(2):196-204. Available from: www.ncbi.nlm.nih.gov/pubmed/3492164.

    RATIONALE: A randomised, double-blind, crossover trial, in which the effects of broad-spectrum antibiotic and placebo therapy in 535 patients with exacerbations of chronic obstructive pulmonary disease were compared. The success rate with placebo was 55%, and with antibiotic was 68%; the rate of failure with deterioration was 19% with placebo, and 10% with antibiotic, suggesting that there is a significant benefit associated with antibiotic treatment for exacerbations of COPD.

3. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2016 Jan. Available from: http://goldcopd.org/global-strategy-diagnosis-management-prevention-copd-2016/.

    RATIONALE: An international guideline, citing 1 systematic review and 2 randomised controlled trials, which recommend that antibiotics should be given to patients with exacerbations of COPD who have 3 cardinal symptoms (increase in dyspnoea; sputum volume; sputum purulence), or have 2 of the cardinal symptoms if increased purulence of sputum is 1 of them, or if the patient requires mechanical ventilation. The recommended length of antibiotic therapy is usually 5 to 10 days, and the choice of antibiotic should be based on the local bacterial resistance pattern.

4. National Institute for Health and Care Excellence (NICE). Chronic obstructive pulmonary disease in over 16s: diagnosis and management. 2010 Jun. Available from: www.nice.org.uk/guidance/cg101.

    RATIONALE: A NICE guideline, advising that the role of antibiotics should be to treat exacerbations of COPD associated with a history of more purulent sputum. Patients with exacerbations without more purulent sputum do not need antibiotic therapy, unless there is consolidation on a chest radiograph, or clinical signs of pneumonia. Initial empirical treatment should be an aminopenicillin (for example amoxicillin), a macrolide, or a tetracycline. When initiating empirical antibiotic treatment, prescribers should always take account of any guidance issued by their local microbiologists. When sputum has been

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sent for culture, the appropriateness of antibiotic treatment should be checked against laboratory culture and sensitivities, when they become available.

5. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ*. 2010 Mar; 340(2096):1-11. Available from: www.bmj.com/content/bmj/340/bmj.c2096.full.pdf.

    RATIONALE: A systematic review and meta-analysis of 24 studies, 22 involving patients with symptomatic infections, and 2 involving healthy volunteers, aiming to investigate subsequent antibiotic resistance in individuals prescribed antibiotics in primary care. In 7 studies of respiratory tract bacteria (n=2,605), pooled ORs were 2.4 (95% CI 1.4 to 3.9) and 2.4 (95% CI 1.3 to 4.5) for the same time periods. The authors state that risk factors for resistance include: indiscriminate or poor use of antibiotics; quantity of antibiotic prescribed, especially for longer durations and multiple courses; exposure to antibiotics, with the strongest association in the first month, with reduced association at subsequent time points, and a small but important residual association within 12 months; receiving 1 or more courses of antibiotics in 12 months, especially if a further antibiotic treatment is necessary. The authors conclude that primary care antibiotic prescriptions make an important contribution to antimicrobial resistance. Primary care clinicians and patients may wish to consider this evidence when discussing the benefits and risks of prescribing and consuming antibiotics.

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

    RATIONALE: A prospective study discussing the MRC dyspnoea scale as a way of classifying chronic obstructive pulmonary disease. The questionnaire consists of 5 statements regarding perceived breathlessness: Grade 1 – "I only get breathless with strenuous exercise"; Grade 2 – "I get short of breath when hurrying on the level or up a slight hill"; Grade 3 – "I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking at my own pace on the level"; Grade 4 – "I stop for breath after walking 100 yards, or after a few minutes on the level"; Grade 5 – "I am too breathless to leave the house". The authors conclude that the MRC dyspnoea scale is a simple and valid method of categorising patients with COPD in terms of their disability, and could be used to complement FEV1.

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

    RATIONALE: A meta-analysis of 21 double-blind, randomised studies, in which the authors concluded that a short-course of antibiotic treatment was as effective as the traditional longer treatment in patients with mild to moderate exacerbations of chronic bronchitis and COPD. At early follow-up (<25 days), the summary odds ratio (OR) for clinical cure with short treatment (less than or equal to 5 days) versus conventional treatment (more than 5 days) was 0.99 (95% CI 0.90 to 1.08). At late follow-up, the

summary OR was 1 (95% CI 0.91 to 1.10). No trials of amoxicillin or doxycycline were included in this meta-analysis, however there is no microbiological reason that a 5 day course of these agents would be inferior to a 5 day course of clarithromycin in acute exacerbations of COPD.

8. Hunter MH, King DE. COPD: Management of acute exacerbations and chronic stable disease. *Am Fam Physician*. 2001 Aug; 64(4):603-613. Available from:https://pdfs.semanticscholar.org/5497/e2bbe9dbe1c3eb3d3027af8c7995755c18a3.pdf

   RATIONALE: An editorial, providing information on the epidemiology, pathophysiology, prognostic indicators, pharmacologic management and treatment of both acute exacerbations and chronic stable COPD. The authors state that findings from numerous clinical studies suggest that antibiotic therapy has a small but important effect on clinical recovery, so administration should be considered at the beginning of treatment for exacerbations of COPD. Treatment recommendations include: amoxicillin 500mg TDS; doxycycline 200mg stat, then 100mg once daily; clarithromycin 500mg twice daily.

Acute cough & bronchitis**:**

1. Smith SM, Fahey T, Smucny J, Becker LA. Antibiotics for acute bronchitis (Review). *Cochrane Database Syst Rev*. 2014 Mar; 1(3):1-60. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000245.pub3/epdf.

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

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

   RATIONALE: A pragmatic cluster randomised controlled trial, aiming to establish whether an interactive booklet on respiratory tract infections in children reduces re-consultation for the same illness episode, reduces antibiotic use, and affects future consulting intentions, while maintaining parental satisfaction with care. 528 children were included, all of whom had presented to primary care with an acute respiratory tract infection, excluding those with suspected pneumonia, asthma, or a serious concomitant illness, or those needing immediate hospital admission. Results indicated that utilising an information booklet during primary care consultations for children with RTIs significantly decreases antibiotic

use (ARR 21.3%; 95% CI 13.7 to 28.9; p<0.001). Re-consultation occurred in 12.9% of children in the intervention group, and in 16.2% in the control group (ARR 3.3%; no statistical significance). There was no detriment noted in patient satisfaction in the intervention group.

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

    RATIONALE: A NICE guideline describing strategies for limiting antibiotic prescribing in self-limiting respiratory tract infections, and advises in which circumstances antibiotics should be considered. A no antibiotic or delayed antibiotic prescribing strategy should be agreed for patients with acute cough/chronic bronchitis. In the 2 randomised controlled trials included in the review, the delay was 7 to 14 days between symptom onset and commencement of 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 advice from a professional if their condition worsens or becomes prolonged. There has been no systematic review of the evidence of length of antibiotic treatment for acute cough or bronchitis, when antibiotics are prescribed. However, evidence for the efficacy of 5 days antibiotic treatment for pneumonia has been recorded, therefore it is reasonable to consider that 5 days would also be effective in bronchitis. This guideline provides information on identifying those patients with RTIs who are likely to be at risk of developing complications. It is stated that if the patient is older than 65 years with acute cough and 2 or more of the following criteria, or older than 80 years with acute cough and 1 or more of the following criteria, a no or delayed antibiotic prescribing strategy should not be considered: hospitalisation in the previous year; type 1 or type 2 diabetes; history of congestive heart failure; current use of oral glucocorticoids.

4. Cals JW, Ament AJ, Hood K, Butler CC, Hopstaken RM, Wassink GF et al. C-reactive protein point of care testing and physician communication skills training for lower respiratory tract infections in general practice: economic evaluation of a cluster randomized trial. *J Eval Clin Pract*. 2011 Dec; 17(6):1059-1069. Available from: www.ncbi.nlm.nih.gov/pubmed/20666881.

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

5. NICE clinical guideline 191. Pneumonia in adults: diagnosis and management. Issued December 2014. www.nice.org.uk/guidance/cg191 [Accessed: 17 Nov, 2017].

    RATIONALE: For people presenting with symptoms of lower respiratory tract infection in

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

6. Clinical Knowledge Summaries (CKS). Chest infections – adult. 2015 Nov. Available from: https://cks.nice.org.uk/chest-infections-adult#!topicsummary.

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

Community-acquired pneumonia:

1. NICE clinical guideline 191. Pneumonia in adults: diagnosis and management. Issued December 2014. Available from: www.nice.org.uk/guidance/cg191 [Accessed: 17 Nov, 2017].

    RATIONALE: A NICE guideline stating that for people presenting with symptoms of lower respiratory tract infections in primary care, a C-reactive protein (CRP) test should be considered, if after clinical assessment a diagnosis of pneumonia has not been made and it is not clear whether or not antibiotics should be prescribed. The results of the CRP test should be used to guide antibiotic prescribing in people without a clinical diagnosis of pneumonia, as follows: do not routinely offer antibiotic therapy if the CRP concentration is less than 20mg/litre; consider a delayed antibiotic prescription if the CRP concentration is between 20mg/litre and 100mg/litre; offer antibiotic therapy if the CRP concentration is greater than 100mg/litre. This guideline includes information on diagnosis, severity assessment, microbiological profile, and therapeutic management in both community and hospital settings. Assessing severity using CRB65 scores, in addition to clinical judgement, allows patients to be stratified according to increasing risk of mortality (score 0: mortality risk 1%; score 1-2: mortality risk 1-10%; score 3-4: mortality risk >10%). Patients with a CRB65 score >1 are deemed to have moderately severe CAP and should be assessed with a view to hospital admission, especially if the score is >2. Patients with moderately severe CAP should receive antibiotics, which also cover atypical organisms. For patients treated at home, 5 days' treatment is appropriate with safety net advice to return for urgent review if they are worsening, or at 3 days if they are not improving. With

moderate to severe pneumonia, 7 to 10 days' treatment should be considered, based on severity and response. NICE advise that glucocorticosteroids should not be given unless indicated for another condition. Explain to patients with community-acquired pneumonia that, after starting treatment, their symptoms should steadily improve, although the rate of improvement will vary with the severity of the pneumonia. Most people can expect the following: at 1 week fever should have resolved; at 4 weeks chest pain and sputum production should have substantially reduced; at 6 weeks cough and breathlessness should have substantially reduced; at 3 months most symptoms should have resolved, but fatigue may still be present; at 6 months most people will feel back to normal.

2. Torres A, Blasi F, Peetermans WE, Viegi G, Welte T. The aetiology and antibiotic management of community-acquired pneumonia in adults in Europe: a literature review. *Eur J Clin Microbiol Infect Dis*. 2014 Feb; 33(7):1065-1079. Available from: www.ncbi.nlm.nih.gov/pmc/articles/PMC4042014/.

   RATIONALE: A literature review providing up-to-date information on the aetiology of community-acquired pneumonia and its antibiotic management in adults across Europe. *Streptococcus pneumoniae* was the most commonly isolated pathogen in patients with CAP, and was identified in 12 to 85% of patients. Other frequently identified pathogens were *Haemophilus influenzae*, gram-negative enteric bacilli, respiratory viruses, and *Mycoplasma pneumoniae*. The authors found several age-related trends: *S. pneumoniae*, *H. influenzae*, and respiratory viruses were more frequent in elderly patients aged >65 years, whereas *M. pneumoniae* was more frequent in those aged <65 years. Limited data on antibiotic resistance was available in the studies, however penicillin resistance of *S. pneumoniae* was reported in 8.4 to 20.7% of isolates, and erythromycin resistance was reported in 14.7 to 17.1% of isolates.

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

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

4. Public Health England (PHE). English surveillance programme for antimicrobial utilisation and resistance (ESPAUR): Report 2016. 2016 Nov. Available from: www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report.

   RATIONALE: An ESPAUR report, stating that antimicrobial resistance is stable in pneumococcal infections, and that the key antibiotics recommended to treat upper and

lower respiratory tract infections include amoxicillin, phenoxymethylpenicillin, erythromycin, clarithromycin, azithromycin, and doxycycline. This report provides line charts that demonstrate that, by 2015, *K. pneumoniae* resistance to co-amoxiclav had risen to between 20% and 30%, third generation cephalosporins were recorded at a resistance rate of 10%, with carbapenems at a resistance rate of just over 0%. This report also suggests that there is less resistance to combined treatment, compared to 1 antimicrobial alone (2.0% versus 18.5%, respectively).

5. Pakhale S, Mulpuru S, Verheij TJ, Kochen MM, Rohde GG, Bjerre LM. Antibiotics for community-acquired pneumonia in adult outpatients (Review). *Cochrane Database Syst Rev*. 2014 Oct; 1(10):1-71. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002109.pub4/pdf.

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

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

   RATIONALE: A prospective double-blind trial, in which 65 adults with community-acquired pneumonia requiring hospitalisation were enrolled, aiming to study whether doxycycline is as efficacious as levofloxacin in the treatment of community-acquired pneumonia in general medical wards. 30 patients were prescribed 500mg levofloxacin for 5 days, and 35 patients were prescribed 100mg doxycycline twice daily for 5 days. Results indicated that length of stay was less in the doxycycline group in comparison to the levofloxacin group (4.0 + 1.82 days, and 5.7 + 2.05 days, respectively; p<0.0012). Failure rate was similar in both groups (p=0.893). The authors conclude that 100mg doxycycline can be used as an effective and economical alternative therapy to levofloxacin in the empirical treatment of community-acquired pneumonia.

Meningitis

Suspected meningococcal disease:

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

   RATIONALE: A NICE guideline stating that primary healthcare professionals should

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

2. Theilen U, Wilson L, Wilson G, Beattie JO, Qureshi S, Simpson D. Management of invasive meningococcal disease in children and young people: summary of SIGN guidelines. BMJ. 2008;336(7657):1367-70. Available from: www.bmj.com/content/336/7657/1367

   RATIONALE: A summary of the SIGN guidelines suggesting that antibiotics should be administered to reduce the risk of mortality. Parenteral antibiotics (either benzylpenicillin or cefotaxime) should be administered, if time, before hospital admission, and a non-blanching rash. Antibiotics should not be delayed pending investigation, but should be administered as soon as invasive meningococcal disease is suspected.

3. Sudarsanam T, Rupali P, Tharyan P, Abraham OC, Thomas K. Pre-admission antibiotics for suspected cases of meningococcal disease (Review). *Cochrane Database Syst Rev*. 2008 Jan; 23(1):1-40. Available from:
   http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005437.pub2/epdf.

   RATIONALE: A systematic review of randomised controlled trials aiming to study the effectiveness and safety of pre-admission antibiotics versus no pre-admission antibiotics or placebo, and different pre-admission antibiotic regimens in decreasing mortality, clinical failure, and morbidity in people with suspected meningococcal disease. The authors state that meningococcal disease can lead to disability or death within hours after onset. Pre-admission antibiotics aim to reduce the risk of serious disease and death by preventing delays in starting therapy before confirmation of the diagnosis. No RCTs were found that compared pre-admission antibiotics versus no pre-admission antibiotics or placebo. One open-label, non-inferiority RCT, conducted during an epidemic in Niger, evaluated a single-dose of intramuscular ceftriaxone versus a single-dose of intramuscular long-acting chloramphenicol. Ceftriaxone was not inferior to chloramphenicol in reducing mortality (RR 1.2; 95% CI 0.6 to 2.6; n=503, 308 with confirmed meningococcal meningitis and 26 deaths), clinical failures (RR 0.8; 92% effectiveness; 95% CI 0.3 to 2.2; n=477, 18 clinical failures), or neurological sequelae (RR 1.3; 95% CI 0.6 to 2.6; n-477, 29 with sequelae). No adverse effects of treatment were reported, and estimated treatment costs were similar. No data was available on disease burden due to sequelae. The authors conclude that there is no reliable evidence to support or refute the use of pre-admission antibiotics for suspected cases of non-severe meningococcal disease. Evidence of moderate quality from 1 RCT indicated that single intramuscular injections of ceftriaxone and long-acting chloramphenicol were equally effective, safe, and economical in reducing serious outcomes. The choice between these antibiotics should be based on affordability, availability and patterns of antibiotic resistance. Further RCTs comparing different pre-admission antibiotics, accompanied by intensive supportive measures, are ethically

justifiable in participants with severe illness, and are needed to provide reliable evidence in different clinical settings.

4. Saeed K. 'One for all' concerns regarding NICE antibiotic guidelines on suspected bacterial meningitis. *Br J Gen Pract*. 2011 Oct; 61(591):606. Available from: www.ncbi.nlm.nih.gov/pmc/articles/PMC3177115/pdf/bjgp61-606.pdf.

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

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

   RATIONALE: A review article, stating that, for the antibiotics administered in bacterial meningitis, it is the duration of time that antibiotic concentrations in the cerebrospinal fluid exceed the minimum bactericidal concentration for that antibiotic that determines the rate of bactericidal activity. Taking this into consideration, the following dosages are recommended for IV or IM administration (if a vein cannot be accessed). For benzylpenicillin, a child under 1 year should be given a stat dose of 300mg, a child between 1 and 9 years should be given a stat dose of 600mg, and an adult or child over the age of 10 should be given a stat dose of 1.2g. In true penicillin allergy, cefotaxime should be given at a dose of 50mg/kg for children under 12 years, and a dose of 1g should be given for adults or children over the age of 12.

Gastrointestinal tract infections

Oral candidiasis:

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

   RATIONALE: A systematic review and meta-analysis of 17 studies involving 2,273 patients, aiming to assess the efficacy and safety of miconazole for treating oral candidiasis. 355 patients with thrush, 306 patients with cancer, 1,020 patients with HIV, 454 patients with denture stomatitis, and 138 patients with unidentified conditions were included. Results indicated that miconazole was superior to nystatin in clinical and mycological outcomes (clinical OR 13; 95% CI 3.05 to 55.29; mycological OR 6.40; 95% CI 1.38 to 29.6). For HIV-infected patients, there were no significant differences in the efficacy between miconazole and other antifungals. The heterogeneity among trials was acceptable (clinical outcome I^2 0%; mycological outcome I^2 32%). A fixed-effect model

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was used for the meta-analysis, and no statistical differences were found in clinical or mycological efficacy between miconazole and the other antifungals (clinical OR 0.75; 25% difference; 95% CI 0.53 to 1.06; mycological OR 1.01; 95% CI 0.74 to 1.38). For cancer-associated oral candidiasis, 1 trial compared miconazole buccal tablets with miconazole oral gel. No clinical differences were found between the 2 formulations. For denture stomatitis, 5 trial data were pooled to compare miconazole and natural substances: 2 trials for evaluating clinical outcome; 3 for evaluating mycological outcome. The heterogeneity between trials was acceptable (clinical I^2 31%; mycological I^2 0%), and a fixed-effect model was used for the meta-analysis. Results indicated that miconazole was clinically more efficacious than the natural substances (OR 3.01; 95% CI 1.35 to 6.72), whereas no statistical differences were found for mycological outcome (OR 1.5; 95% CI 0.72 to 3.12). No significant differences were found in the safety evaluation between miconazole and other treatments, but the relapse rate of miconazole oral gel may be lower than that of other formulations. The authors conclude that miconazole may be an optimal choice for the treatment of oral candidiasis, and that miconazole oral gel may be more effective than other formulations with regard to long-term results.

2. Farah CS, Ashman RB, Challacombe SJ. Oral candidosis. *Clin Dermatol*. 2000 Sep; 18(5):553-562. Available from: www.sciencedirect.com/science/article/pii/S0738081X00001450?via%3Dihub.

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

3. Nelson M, Dockrell DH, Edwards S. British HIV Association and British Infection Association guidelines for the treatment of opportunistic infection in HIV-seropositive individuals 2011. *HIV Medicine*. 2011 May; 12(2):1-5. Available from: www.bhiva.org/documents/Guidelines/OI/hiv_v12_is2_Iss2Press_Text.pdf.

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

4. Clinical Knowledge Summaries (CKS). Candida – oral. 2017 May. Available from http://cks.nice.org.uk/candida-oral#.

   RATIONALE: A CKS guideline recommending that, for localised or mild oral candida infection, topical treatment for 7 days should be prescribed. This guideline advises that for adults and children over the age of 2 years, miconazole oral gel (24mg/ml) 2.5ml QDS should be offered as first line treatment, or 1ml nystatin suspension 100,000units/mL QDS, if miconazole is not tolerated. Oral fluconazole 50mg OD should be prescribed in extensive or severe cases, or 100mg OD for HIV or immunosuppression. All treatment

should be prescribed for 7 days, and continued for a further 7 days (micronazole) or 2 days (nystatin) if candida infection is persistent. The recommendations provided for the assessment and treatment of oral candida infection are in line with expert opinion, as there is a lack of direct evidence from randomised controlled trials to support the use of topical miconazole or nystatin, or oral fluconazole in the treatment of oral candidiasis in otherwise healthy adults. However, their use is supported by pharmacological principles, historical use, and extrapolation of clinical data from trials in other groups (infants; immunosuppression).

5. Bensadoun RJ, Daoud J, El Gueddari B, Bastit L, Gourmet R, Rosikon A et al. Comparison of the efficacy and safety of miconazole 50-mg mucoadhesive buccal tablets with miconazole 500mg gel in the treatment of oropharyngeal candidiasis: a prospective, randomized, single-blind, multicentre, comparative, phase 3 trial in patients treated with radiotherapy for head and neck cancer. *Cancer*. 2008 Jan; 112(1):204-211. Available from: www.ncbi.nlm.nih.gov/pubmed/18044772.

    RATIONALE: A randomised controlled trial of cancer patients, in whom oral candidiasis was effectively treated by both tablet and gel formulations of miconazole. Clinical success was achieved in 56% of 141 patients who received 14 days 50mg mucoadhesive buccal tablet administration miconazole, and 49% of 141 patients who received 14 days of the 500mg gel preparation, administered in 4 equal doses. Other end-points of this study were largely non-significant, but 29% of patients who used buccal preparation experienced side-effects, versus 27% in the gel preparation group. However, fewer participants dropped out of the study due to adverse events (3 versus 6, respectively) when using the buccal preparation.

6. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016 Jan; 62(4):1-50. Available from: www.ncbi.nlm.nih.gov/pmc/articles/PMC4725385/.

    RATIONALE: An international consensus document providing the following recommendations. For mild disease, clotrimazole lozenges, 10mg 5 times daily, or miconazole mucoadhesive buccal, 50mg tablets applied to the mucosal surface over the canine fossa, once daily for 7 to 14 days, are recommended. Alternatives for mild disease include nystatin suspension (100,000U/mL) 4-6mL 4 times daily, or 1-2 nystatin pastilles (200,000U each) 4 times daily, for 7 to 14 days. For moderate to severe disease, oral fluconazole, 100-200mg daily, for 7 to 14 days, is recommended. For fluconazole-refractory disease, itraconazole solution, 200mg once daily, or posaconazole suspension, 400mg twice daily for 3 days, then 400mg daily for up to 28 days, are recommended. Alternatives for fluconazole-refractory disease include voriconazole, 200mg twice daily, or AmB deoxycholate oral suspension, 100mg/mL 4 times daily. If required for patients who have recurrent infection, fluconazole, 100mg 3 times weekly, is recommended. For HIV-infected patients, antiretroviral therapy is strongly recommended to reduce the incidence of recurrent infections. For denture-related candidiasis, disinfection of the denture, in addition to antifungal therapy, is recommended. The authors state that the use of effective antiretroviral therapy has dramatically decreased the incidence of oesophageal candidiasis in HIV-infected patients.

7. Flynn PM, Cunningham CK, Kerkering T, San Jorge AR, Peters VB, Pitel PA. Oropharyngeal candidiasis in immunocompromised children: A randomized, multicenter study of orally administered fluconazole suspension versus nystatin. *J Pediatr*. 1995 Aug; 127(2):322-328. Available from: www.sciencedirect.com/science/article/pii/S0022347695703217.

    RATIONALE: A randomised controlled trial, demonstrating 14 day cure in 91% of patients treated with fluconazole suspension 2 to 3mg/kg per day, compared with 51% of patients treated with nystatin 400,000 units per day in a QDS regimen, both for 14 days. Mycologically, there was organism eradication in 76% of patients on fluconazole, versus 11% on nystatin. Both regimens were tolerated well, with similar relapse rates.

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

    RATIONALE: A randomised controlled trial of fluconazole versus nystatin oral suspensions. Cure was achieved at day 14 in 87% of 83 HIV-positive patients who were treated with fluconazole 100mg once daily, and 52% of 84 patients who received nystatin 500,000 units per day. Mycological clearance was achieved in 60% of the fluconazole group, and 6% of the patients treated with nystatin. 18% of patients relapsed with fluconazole, compared with 44% on nystatin, at day 28. Gastrointestinal side-effects were comparable, but 2 patients in the fluconazole group developed deranged liver function tests, and 1 had to withdraw.

Infectious diarrhoea:

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

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

2. Farthing M, Feldman R, Finch R, Fox R, Leen C, Mandal B et al. The management of infective gastroenteritis in adults. A consensus statement by an expert panel convened by the British Society for the Study of Infection. *J Infect*. 1996 Nov; 33(3):143-152. Available from: www.journalofinfection.com/article/S0163-4453(96)92057-5/abstract.

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

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

    RATIONALE: A PHE guideline, recommending that, if campylobacter is strongly suspected as the cause of diarrhoea, empirical treatment with clarithromycin 250-500mg BD for 5 to 7 days should be considered. Quinolones are not recommended as there is increasing resistance of campylobacter to quinolones, and broad-spectrum antibiotics are not recommended for empirical treatment due to an increased risk of *Clostridium difficile*, MRSA, and antibiotic-resistant UTIs.

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

    RATIONALE: A meta-analysis of 11 randomised controlled trials, involving 479 patients, which provides evidence that, when compared with placebo, treating diarrhoea caused by campylobacter with erythromycin, norfloxacin, or ciprofloxacin, shortens the duration of diarrhoea by 1.32 days (95% CI 0.64 to 1.99; p<0.001). Duration of symptoms was 41 hours shorter (2.4 versus 4.1 days) if treated within 3 days of the start of symptoms, in comparison to commencement of treatment after 3 days.

5. Ordonez-Mena JM, McCarthy ND, Fanshawe TR. Comparative efficacy of drugs for treating giardiasis: a systematic update of the literature and network meta-analysis of randomized clinical trials. *J Antimicrob Chemother*. 2017. Available from: www.ncbi.nlm.nih.gov/pubmed/29186570

    RATIONALE: Giardiasis is the commonest intestinal protozoal infection worldwide. The first-choice therapy has been metronidazole. However, this recent metanalysis indicates that single- dose tinidazole is the best available treatment for giardiasis in symptomatic and asymptomatic children and adults. This metanalysis was done in 2017 and included 60 RCTs from 58 reports including 6714 patients, 18 treatments and 42 treatment comparisons. Tinidazole was associated with higher parasitological cure than metronidazole [relative risk (RR) 1.23, 95% CI 1.12-1.35] and albendazole (RR 1.35, 95% CI 1.21-1.50). Taking into consideration clinical efficacy, side effects and amount of the evidence, tinidazole was found to be the most effective drug.

Helicobacter pylori:

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

    RATIONALE: A systematic review and meta-analysis examining duodenal ulcer healing in 3,910 patients across 34 trials. Findings indicated that *H. pylori* eradication therapy was superior to ulcer healing drugs (UHDs) (RR of ulcer persisting 0.66; 34% superiority; 95% CI 0.58 to 0.76) and no treatment (2 trials; 207 patients; RR 0.37; 63% superiority; 95% CI

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0.26 to 0.53). In gastric ulcer healing, no significant differences were detected between eradication therapy and UHDs (15 trials; 1,974 patients; RR 1.23; 95% CI 0.90 to 1.68). In preventing duodenal ulcer recurrence, no significant differences were detected between eradication therapy and maintenance therapy with UHDs (4 trials; 319 patients; RR 0.73; 27% difference; 95% CI 0.42 to 1.25), but eradication therapy was superior to no treatment (27 trials; 2,509 patients; RR 0.20; 80% superiority; 95% CI 0.15 to 0.26). In preventing gastric ulcer recurrence, eradication therapy was superior to no treatment (12 trials; 1,476 patients; RR 0.31; 69% superiority; 95% CI 0.22 to 0.45), therefore, test and treat for *H. pylori* is advised in patients with a past history of gastric ulcers.

2. National Institute for Health and Care Excellence (NICE). Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. 2014 Sep. Available from: www.nice.org.uk/guidance/cg184.

    RATIONALE: A NICE guideline recommending that patients of any age with gastro-oesophageal symptoms that are unexplained or unresponsive to treatment should be referred to a specialist. Unexplained is defined as "a symptom(s) and/or sign(s) that has not led to a diagnosis being made by the primary care professional after initial assessment of the history, examination and primary care investigations". Clinicians should offer *H. pylori* test and treat to patients with dyspepsia. Clinicians should leave a 2 week washout period after PPI use before testing for *H. pylori* with a urea breath test or stool antigen test. NICE recommend that patients with reflux-like symptoms should be treated in a similar way to those with dyspepsia, using full dose PPI for 4 weeks, before considering treatment for *H. pylori*. Clinicians should offer patients who need long-term management of dyspepsia symptoms an annual review of their condition, and should encourage them to try stepping down or stopping treatment (unless there is an underlying condition or co-medication that needs continued treatment). Clinicians should test for *H. pylori* using a carbon-[13]urea breath test or stool antigen test, or laboratory-based serology where performance has been locally validated. Clinicians should not use office-based serology tests for *H. pylori*, as their performance is routinely inadequate. Clinicians should discuss treatment adherence with the patient and should emphasise its importance. Clinicians should offer patients who test positive for *H. pylori* a 7 day, twice daily course of treatment with a PPI, amoxicillin, and either clarithromycin or metronidazole. Choose the treatment regimen with the lowest acquisition cost and take into account previous exposure to clarithromycin and metronidazole. All triple regimens have similar outcomes and are slightly better than quadruple regimens. Offer patients who are allergic to penicillin a 7 day, twice daily course of treatment with a PPI, clarithromycin and metronidazole. Offer patients who are allergic to penicillin and who have had previous exposure to clarithromycin a 7 day, twice daily course of treatment with a PPI, metronidazole and levofloxacin. Offer patients who still have symptoms after first line eradication treatment a 7 day, twice daily course of treatment with a PPI, amoxicillin and either clarithromycin or metronidazole (whichever was not used first line). Offer patients who have had previous exposure to clarithromycin and metronidazole a 7 day, twice daily course of treatment with a PPI, amoxicillin and a quinolone or tetracycline. Offer patients who are allergic to penicillin (and who have not had previous exposure to a quinolone) a 7 day, twice daily course of treatment with a PPI, metronidazole and levofloxacin. Offer patients who are allergic to penicillin and who have had previous

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exposure to a quinolone a PPI, a bismuth salt (tripotassium dicitratobismuthate or bismuth subsalicylate), metronidazole and tetracycline. NICE document evidence from 1 study, stating that increasing the duration of PPI/amoxicillin/quinolones from 7 to 10 days results in improved second line *H. pylori* eradication when using standard or double dosing for the 10 day regimen. Evidence from other studies has shown that increasing the duration of a quadruple regimen from 7 to 14 days does not improve second line *H. pylori* eradication. Clinicians should consider referral for those patients who have *Helicobacter pylori*, which has not responded to second line eradication therapy.

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

   RATIONALE: A consensus report providing expert opinion on the most appropriate management and diagnostic tests for *Helicobacter pylori*. The report advises that younger patients without alarm symptoms should be offered test and treat for *H. pylori* if local prevalence is over 20%, and also states that *H. pylori* eradication is most beneficial in patients with gastro-duodenal ulcer disease. Both *H. pylori* infection and NSAID use are independent risk factors for the development of peptic ulcer disease and associated bleeding. These conditions are uncommon in those who do not have either risk factor, but there is an increased risk when both factors are present. In naïve users of NSAIDs, it is clearly beneficial to eradicate *H. pylori*, but there is no clear benefit for those who are already long-term users. However, results from a meta-analysis showed that eradication seems less effective than *H. pylori* treatment with a maintenance PPI for preventing NSAID-associated ulcers. Clinicians should test for *H. pylori* in patients with unexplained iron-deficiency anaemia, idiopathic thrombocytopenic purpura, and vitamin B12 deficiency. Two meta-analyses have supported the association between these conditions, with 1 illustrating a clear link between *H. pylori* infection and iron-deficiency anaemia, and the other showing that *H. pylori* eradication increases haemoglobin levels in patients with this condition. Systematic reviews have demonstrated that an overall platelet response has been recorded in more than 50% of patients successfully treated for *H. pylori* infection, and response rates are increasing in countries with a high prevalence of *H. pylori* infection in background populations. This report states that there is a negative association between the prevalence of *H. pylori* and GORD. The sequelae of GORD, such as Barrett's oesophagus and oesophageal adenocarcinoma, are less common in infected individuals, and eradication of *H. pylori* in populations of infected patients, on average, neither causes nor exacerbates symptoms of GORD. Therefore, the presence of GORD should not dissuade practitioners from *H. pylori* eradication treatment, where indicated. Long-term treatment with PPIs in *H. pylori* positive patients is associated with the development of corpus-predominant gastritis. This accelerates the process of losing specialised glands, leading to atrophic gastritis. Eradication of *H. pylori* in patients receiving long-term PPI treatment heals gastritis and prevents the progression to atrophic gastritis. However, there is no evidence that this reduces the risk of gastric cancer. Finally, this report emphasises that urea breath tests (UBTs) and stool helicobacter antigen tests (SATs) are the most accurate tests and should be used in preference to serology.

4. Moayyedi P, Soo S, Deeks J, Delaney B, Harris A, Innes M et al. Eradication of *Helicobacter*

pylori for non-ulcer dyspepsia. *Cochrane Database Syst Rev*. 2006 Apr; 19(2):1-42. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002096.pub4/epdf.

RATIONALE: A systematic review and meta-analysis of 17 randomised controlled trials (n=3,566), which found that there was a 10% relative risk reduction in dyspepsia symptoms in people with non-ulcer dyspepsia when randomised to receive *H. pylori* eradication (95% CI 6% to 14%), compared to placebo. The NNT to cure 1 case of dyspepsia was 14 (95% CI 10 to 25).

5. Fischbach L, Evans EL. Meta-analysis: the effect of antibiotic resistance status on the efficacy of triple and quadruple first line therapies for *Helicobacter pylori. Aliment Pharmacol Ther*. 2007 Aug; 26(3):343-357. Available from: www.ncbi.nlm.nih.gov/pubmed/17635369.

RATIONALE: A systematic review and meta-analysis of 10 studies, including 10,178 participants, demonstrating pooled data that found that the efficacy of a PPI and clarithromycin and metronidazole was reduced more by resistance to clarithromycin, than it was by resistance to metronidazole. Metronidazole resistance reduced efficacy by 18%, whilst clarithromycin resistance was estimated to reduce efficacy by 35%. Clarithromycin resistance reduced the efficacy of PPI and clarithromycin and amoxicillin by 66%.

6. McNulty CA, Lasseter G, Shaw I, Nichols T, D'Arcy S, Lawson AJ et al. Is *Helicobacter pylori* antibiotic resistance surveillance needed and how can it be delivered? *Aliment Pharmacol Ther*. 2012 May; 35(10):1221-1230. Available from: www.ncbi.nlm.nih.gov/pubmed/22469191.

RATIONALE: A 2009/2010 study of *Helicobacter pylori* antibiotic resistance surveillance in 3 centres across England and Wales. Biopsy specimens were taken from endoscopy patients in Gloucester, England and Bangor, Wales. Of 1,153 biopsy specimens in Gloucester, 11% were tested positive for *H. pylori* on culture or biopsy urease test, and 9% were tested positive by serology. Antibiotic resistance to amoxicillin, rifabutin and tetracycline remained very low, whereas each course of clarithromycin, metronidazole and levofloxacin was related to a 50% increase in resistance.

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

RATIONALE: A systematic review and meta-analysis of 149 studies demonstrating an 80% mean eradication rate with levofloxacin 250mg BD containing regimens. 10 day regimens were more effective than 7 days, and side-effects were lower than with bismuth treatment. However, the authors conclude that this regimen should not be used if there has been previous use of a quinolone, as quinolone resistance develops easily.

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

RATIONALE: A randomised controlled trial, in which 339 patients across the UK, Germany, France, Ireland, Poland, and Spain were allocated to either 10 days

omeprazole 20mg BD plus 3 capsules containing bismuth 140mg, metronidazole 125mg, and tetracycline hydrochloride 125mg QDS after meals, or 7 days omeprazole 20mg BD plus 500mg amoxicillin and 500mg clarithromycin, all taken 4 times daily. According to intention to treat criteria, *H. pylori* eradication was successful in 92% of patients on quadruple therapy, and 69% of patients on triple therapy. In clarithromycin resistance, eradication was reduced to 8% of patients on triple therapy, but it did not influence quadruple therapy. Quadruple therapy is effective as a second line treatment, and should be considered if there is a past history of clarithromycin use.

9. O'Connor A, Fischbach W, Gisbert JP, O'Morain C. Treatment of *Helicobacter pylori* infection 2016. *Helicobacter*. 2016 Sep; 21(1):55-61. Available from: www.ncbi.nlm.nih.gov/pubmed/27531541.

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

10. Nocon M, Kuhlmann A, Leodolter A, Roll S, Vauth C, Willich SN et al. Efficacy and cost-effectiveness of the 13C-urea breath test as the primary diagnostic investigation for the detection of *Helicobacter pylori* infection compared to invasive and non-invasive diagnostic tests. *GMS Health Technol Assess*. 2009 Oct; 21(5):1-12. Available from: www.ncbi.nlm.nih.gov/pubmed/21289901.

    RATIONALE: A systematic review of 30 studies (3,415 patients) directly comparing the 13^C-UBT and other non-invasive tests to biopsy-based tests as the gold standard for *H. pylori* testing. The 13^C-UBT showed higher sensitivity and specificity than IgG serology in 18 studies, and showed higher sensitivity and specificity than SATs in 13 studies (a 100% sensitive test correctly identifies all patients with *H. pylori*, and a 100% specific test correctly identifies all patients without *H. pylori*). Sensitivity and specificity higher than 90% was found in 84% of the studies for the 13^C-urea breath test. Sensitivity and specificity higher than 90% was found in 62% of the studies for the stool antigen test, and 56% sensitivity and 44% specificity for the IgG test. Nine health economic evaluations were included in this Health Technology Assessment (HTA) report. Test and treat strategies using the 13^C-UBT were more cost-effective than serology-based strategies in 3 of the 9, and was dominated by a test and treat strategy using the SAT in 1 of those 3.

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

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

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(95% CI 89 to 96) and a specificity of 96% (95% CI 94 to 97), respectively. Pooled positive and negative LRs were 17 (12 to 23) and 0.1 (0.07 to 0.15).

12. Xin Y, Manson J, Govan L, Harbour R, Bennison J, Watson E, Wu O. Pharmacological regimens for eradication of Helicobacter pylori: an overview of systematic reviews and network meta-analysis. *BMC Gastroenterol*. 2016 Jul; 16(1):80-98. Available from: www.ncbi.nlm.nih.gov/pmc/articles/PMC4962503/.

    RATIONALE: A meta-analysis of 30 systematic reviews with pairwise meta-analysis, involving, 66,037 patients, which analyses the effectiveness of different pharmacological regimens to treat proven *H. pylori* infection. The results demonstrated the benefits of adding proton pump inhibitor (PPI) medication to an *H. pylori* eradication treatment regimen. Seven studies evaluated the impact of different PPIs within a triple therapy regimen on *H. pylori* eradication rate. The reported eradication rates ranged from 77% (data from 9 RCTs relating to rabeprazole-based triple therapy) to 94% (data from 1 RCT relating to esomeprazole-based triple therapy). Three studies also compared the effectiveness of PPI versus H_2RA within a triple therapy. One systematic review based on 20 RCTs with 2374 patients showed PPI was associated with greater effectiveness than H_2RA (OR 1.31; 95%CI 1.09 to 1.58).

13. Dore MP, Lu H, Graham DY. Role of bismuth in improving *Helicobacter pylori* eradication with triple therapy. *Gut*. 2016 Feb; 1:1-9. Available from: http://gut.bmj.com/content/early/2016/02/04/gutjnl-2015-311019.full.pdf.

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

14. O'Connor A, Gisbert JP, McNamara D, O'Morain C. Treatment of *Helicobacter pylori* infection 2011. *Helicobacter*. 2011 Sep; 16(1):53-58. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1523-5378.2011.00881.x/pdf.

    RATIONALE: A review of all previously published trials regarding the treatment of *H. pylori*. Seven studies were cited describing the successful use of levofloxacin 250mg to 500mg with amoxicillin or clarithromycin and a proton pump inhibitor as first line treatment for *H. pylori* (85% eradication). Rifabutin 150mg BD with amoxicillin 1g BD achieved 79 to 85% eradication in patients who had failed other treatment regimens. A study of a bismuth, omeprazole 20mg to 40mg, amoxicillin 1g BD and clarithromycin regimen showed superior eradication of 94% in a group treated for 14 days, compared with 80% for a group treated for 7 days. In a further study of patients unsuccessfully treated wit triple therapy, eradication rates of 77% were obtained for 1 week of bismuth-based quadruple therapy, and 94% for 2 weeks.

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

    RATIONALE: An ACOG guideline, providing details of first line regimens for *Helicobacter*

BSAC BRITISH SOCIETY FOR ANTIMICROBIAL CHEMOTHERAPY BIA British Infection Association RCGP Royal College of General Practitioners N100 Royal College of Nursing

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

16. Yuan Y, Ford AC, Khan KJ, Gisbert JP, Forman D, Leontiadis GI et al. Optimum duration of regimens for *Helicobacter pylori* eradication (Review). *Cochrane Database Syst Rev.* 2013 Dec; 12:1-421. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008337.pub2/epdf.
    RATIONALE: A systematic review and meta-analysis of 75 studies from around the world, suggesting that the optimal duration for *Helicobacter pylori* eradication therapy is controversial, with recommendations ranging from 7 to 14 days. The authors conclude that increasing the duration of PPI-based triple therapy increases *H. pylori* eradication rates (72.9% versus 81.9%; RR 0.66; 95% CI 0.60 to 0.74; NNT 11). For PPI, clarithromycin, and amoxicillin (PCA), prolonging treatment duration from 7 to 10, or from 10 to 14 days is associated with a significantly higher eradication rate (75.7% versus 79.9%; RR 0.80; 95% CI 0.72 to 0.89; NNT 21). The optimal duration of therapy for PCA and PAN (PPI, amoxicillin, and nitroimidazole) appears to be at least 14 days. The authors suggest that there was no statistically significant difference between regions. However, for conditions in which eradication is critical, as in MALToma, a longer eradication regimen of 14 days is recommended.

17. Buzas GM, Jozan J. Nitrofuran-based regimens for the eradication of *Helicobacter pylori* infection. *J Gastroenterol Hepatol.* 2007 Oct; 22(10):1571-1581. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1440-1746.2007.05082.x/epdf.
    RATIONALE: A systematic review and meta-analysis of 51 studies and 4,946 patients, examining furazolidone- and nitrofurantoin-based regimens in the eradication of infection. There have been some studies with small numbers of patients examining the effectiveness of furazolidone with amoxicillin (60% eradication) and furazolidone with levofloxacin (83% eradication) in patients on rescue treatment. The overall eradication rate of third-line rescue therapies was 65.5%, but side-effects of the regimens containing furazolidone were more frequent than in standard therapies. (p=0.02). The authors conclude that primary triple regimens containing furazolidone are slightly less efficient than the standard primary combinations, and that it is the duration of treatment, not the dose, which has the largest influence on the treatment outcome.

18. Test and treat for Helicobacter pylori (HP) in dyspepsia: quick reference guide for primary care: For consultation and local adaptation. Public Health England. July 2017. Available from: www.gov.uk/government/publications/helicobacter-pylori-diagnosis-and-treatment
    This evidence based quick reference tool gives advice on when and how to test for *Helicobacter pylori.* It advises the use of urea breath test or stool antigen test as first line diagnostic tests pre and post eradication treatment, as they are more accurate that serology which in the absence of previous historical tests cannot differentiate active from past infection.

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Clostridium difficile:

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

   RATIONALE: A European guideline, evaluating the available literature categorising *Clostridium difficile* infection severity. This guideline offers the following recommendations: antiperistaltic agents and opiates should be avoided; in general, strive to use antibiotics covering a spectrum no broader than necessary, and narrow the antibiotic spectrum of treatment after results of cultures and/or susceptibility tests become known; mild CDI (stool frequency <4 times daily; no signs of severe colitis), clearly induced by the use of antibiotics, may be treated by stopping the inducing antibiotic. Patients should be observed closely for any signs of clinical deterioration and placed on therapy immediately if this occurs. If oral therapy is possible, non-severe cases should be prescribed metronidazole 500mg 3 times daily orally for 10 days; severe cases should be prescribed vancomycin 125mg 4 times daily for 10 days. If oral therapy is not possible, non-severe cases should be prescribed metronidazole 500mg 3 times daily, intravenously, for 10 days. If severe cases unable to take oral treatment, metronidazole 500mg 3 times daily, intravenously, for 10 days, should be prescribed, plus intracolonic vancomycin 500mg in 100mL of normal saline every 4 to 12 hours (C-III) and/or vancomycin 500mg 4 times daily by nasogastric tube.

2. Public Health England (PHE). Updated guidance on the management and treatment of *Clostridium difficile* infection. 2013 May. Available from: www.gov.uk/government/publications/clostridium-difficile-infection-guidance-on-management-and-treatment.

   RATIONALE: A PHE guideline suggesting that supportive care should be given to patients with *Clostridium difficile*, including attention to hydration, electrolytes, and nutrition. Antiperistaltic agents should be avoided in acute infection, due to the theoretical risk of precipitating toxic megacolon by slowing the clearance of *C. difficile* toxin from the intestine. The precipitating antibiotic should be stopped wherever possible; agents with less risk of inducing CDI can be substituted if an underlying infection still requires treatment. Patients with mild disease may not require specific *C. difficile* antibiotic treatment. If treatment is required, oral metronidazole is recommended (400-500mg TDS for 10 to 14 days), as it has been shown to be as effective as oral vancomycin in mild to moderate CDI. For patients with moderate disease, a 10 to 14 day course of oral metronidazole is the recommended treatment (400-500mg TDS). This is because it is cheaper than oral vancomycin and there is concern that overuse of vancomycin may result in the selection of vancomycin-resistant enterococci. For patients with severe CDI oral vancomycin is preferred (125mg QDS for 10 to 14 days). This is because of relatively high failure rates of metronidazole and a slower clinical response to metronidazole, compared with oral vancomycin treatment. Two double-blind randomised studies reported that vancomycin is superior to metronidazole in severe cases of CDI. A pooled analysis of these 2 phase 3 studies has shown that metronidazole was overall inferior to vancomycin. The following symptoms should be used to indicate severe CDI: WCC >15x10^9/L; acutely rising blood creatinine (for example more than 50% increase above baseline);

temperature >38.5°C; evidence of severe colitis (abdominal signs; radiology). Recurrent disease may occur in up to 20% of patients, up to half of which may be reinfections, rather than relapse. The same antibiotic can be used for a second course of treatment. After a first recurrence, the risk of further recurrences is higher. For recurrent disease, a tapering course of vancomycin may be considered after the initial treatment course. There are various regimens for tapering off the dose of vancomycin including: 125mg QDS for 1 week; 125mg TDS for 1 week; 125mg BD for 1 week; 125mg OD for 1 week; 125mg on alternate days for 1 week; 125mg every third day for 1 week. Clearly, this may provide a considerable selective pressure for vancomycin resistance, for example 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. Fidaxomicin is very expensive and may not be of additional benefit for some strains of *C. difficile* (for example ribotype 0157). Its role in multiple recurrences is unclear. Local cost-effective decision making should determine its use.

3. Howell MD, Novack V, Grgurich P, Soulliard D, Novack L, Pencina M et al. Iatrogenic gastric acid suppression and risk of nosocomial *Clostridium difficile* infection. *Arch Intern Med*. 2010 May;170(9):784-789. Available from: www.ncbi.nlm.nih.gov/pubmed/20458086.

   RATIONALE: A pharmacoepidemiologic cohort study, presenting increasing evidence that acid-suppressing medications, in particular proton pump inhibitors, may be a risk factor for CDI. The authors report a correlation between the degree of acid suppression and risk of CDI (ie. a 'dose response' effect), which ranged from none (OR 1), to H_2 receptor antagonists (OR 1.53; 95% CI 1.12 to 2.10), to once daily PPI (OR 1.74; 95% CI 1.39 to 2.18), to more frequent PPI (OR 2.36; 95% CI 1.79 to 3.11). It remains possible that these associations are confounded by other CDI risk factors. However, given that acid suppression drugs, especially PPIs, may be over-prescribed and frequently not reviewed to determine if long-standing prescriptions are still justifiable, consideration should be given to stopping or reviewing the need for PPIs in patients with, or at high risk of, CDI.

4. Belmares J, Gerding DN, Parada JP, Miskevics S, Weaver F, Johnson S. Outcome of metronidazole therapy for *Clostridium difficile* disease and correlation with a scoring system. *J Infect*. 2007 Dec; 55(6):495-501. Available from: www.sciencedirect.com/science/article/pii/S0163445307007840.

   RATIONALE: A retrospective study of 102 patients given a 5 day course of metronidazole for *Clostridium difficile* infection. This study found that 70.6% responded to treatment by the end of the 5 day course. 21 of the remaining 30 patients eventually responded to metronidazole, but needed a longer course of treatment (14 days; overall response rate = 91%). The mean CDD score at presentation was higher among true failures (2.89 + 1.4) than among all metronidazole responders (0.77 + 1.0; p<0.0001). The CDD score (0-7) included variables previously suggested in the literature, to correlate with a higher disease severity: fever >38°C; ileus; hypotension (each scored 1); leucocytosis; specific CT abnormalities (weighted as 1 or 2 depending on WBC and CT findings.

5. National Institute for Health and Care Excellence (NICE). *Clostridium difficile* infection:

fidaxomicin. 2012 Jul. Available from: www.nice.org.uk/advice/esnm1/chapter/Introduction.
RATIONALE: A NICE guideline suggesting that, until recently, there were only 2 main
options for the treatment of CDI (metronidazole or vancomycin). Oral fidaxomicin was
approved for the treatment of CDI in Europe in 2012, and has been reviewed by both
NICE and the SMC. Two phase 3, multi-centred, randomised, double-blind studies with
almost identical designs compared oral fidaxomicin (200mg BD for 10 to 14 days) with oral
vancomycin (125mg QDS for 10 to 14 days). Fidaxomicin was non-inferior to
vancomycin in the initial clinical cure of CDI (RR 0.88; 12% difference; 95% CI 0.64 to
1.19; p=0.396), but was superior in reducing recurrence (RR 0.54; 46% superiority; 95%
CI 0.42 to 0.71; p<0.001), and sustained clinical cure (RR 0.68; 32% difference; 95% CI
0.56 to 0.81; p<0.001). The side-effect profile of fidaxomicin appears similar to that of oral
vancomycin. The acquisition cost of fidaxomicin is considerable higher than vancomycin,
which is more expensive than metronidazole. Decision makers need to take into account
the benefits versus increased costs.

Traveller's diarrhoea:

1. Bradley AC. Travelers' Diarrhea: Centers for Disease Control and Prevention; 2017.
   Available from: wwwnc.cdc.gov/travel/yellowbook/2018/the-pre-travel-consultation/travelers-
   diarrhea [Accessed: Sept 2018].
   Guidance from CDC on the treatment of travellers' diarrhoea. This review indicates that
   the primary agent studied for treatment of TD, other than antimicrobial drugs, is bismuth
   subsalicylate (BSS), which is the active ingredient in adult formulations of Pepto-Bismol
   and Kaopectate. Studies from Mexico have shown that this agent (taken daily
   prophylactically as either 2 oz. of liquid or 2 chewable tablets 4 times per day) reduces the
   incidence of TD by approximately 50%. BSS commonly causes blackening of the tongue
   and stool and should be avoided by travellers with aspirin allergy, renal insufficiency, and
   gout, and by those taking anticoagulants, probenecid, or methotrexate. BSS is not
   generally recommended for children aged <12 years. Although prophylactic antibiotics can
   prevent some TD, the emergence of antimicrobial resistance has made the decision of
   how and when to use antibiotic prophylaxis for TD difficult. **At this time, prophylactic
   antibiotics should not be recommended for most travellers.** Travellers may become
   colonized with extended-spectrum β-lactamase (ESBL)–producing bacteria, and this risk
   is increased by exposure to antibiotics while abroad. The risks associated with the use of
   prophylactic antibiotics should be weighed against the benefit of using prompt, early self-
   treatment with antibiotics when moderate to severe TD occurs, shortening the duration of
   illness to 6–24 hours in most cases. Prophylactic antibiotics may be considered for short-
   term travellers who are high-risk hosts (such as those who are immunosuppressed) or
   who are taking critical trips (such as engaging in a sporting event) without the opportunity
   for time off in the event of sickness. **Treatment:** Antibiotics are effective in reducing the
   duration of diarrhoea by about a day in cases caused by bacterial pathogens that are
   susceptible to the particular antibiotic prescribed. However, risk versus benefits will need
   to be considered by the clinician and patient as travellers who take antibiotics may acquire
   resistant organisms such as ESBL- producing organisms, or Clostridium difficile infection.
   The effectiveness of a particular antimicrobial drug depends on the etiologic agent and its
   antibiotic sensitivity. First-line antibiotics have traditionally been the fluoroquinolones,
   such as ciprofloxacin but increasing microbial resistance to the fluoroquinolones,

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especially among Campylobacter isolates, may limit their usefulness in many destinations, particularly South and Southeast Asia, where both Campylobacter infection and fluoroquinolone resistance is prevalent. A potential alternative to fluoroquinolones is azithromycin. Single-dose regimens are equivalent to multi-dose regimens and may be more convenient for the traveller. The best regimen for azithromycin treatment may be a single dose of 1,000 mg, but side effects (mainly nausea) may limit the acceptability of this large dose. Giving azithromycin 500mg for 1 to 3 days may limit this adverse event.

2. Clinical Knowledge Summaries (CKS). Diarrhoea – prevention and advice for travellers. 2018 June. Available from: https://cks.nice.org.uk/diarrhoea-prevention-and-advice-for-travellers#!topicsummary.

   RATIONALE: A CKS guideline, listing high risk zones for traveller's diarrhoea as: Africa; Latin America; the Middle East; most parts of Asia. This guideline also lists groups of people who are at higher risk of developing traveller's diarrhoea, including: young children and babies, and elderly or frail people; people with reduced immunity (such as those with HIV infection or AIDS); people with severe cardiac or renal disease; people with inflammatory bowel disease; people with reduced acidity in the stomach, which is a risk factor for infection with acid-sensitive organisms, such as *Salmonella* and *Campylobacter*. **For 'stand-by' treatment of travellers' diarrhoea they suggest to p**rescribe ciprofloxacin 500 mg twice daily for 3 days (licensed indication, requiring private prescription). They advise the person to evaluate their response after 24 hours of taking the antibiotic and to complete the 3-day course if they are still unwell, or stop sooner if they are improved. They advise azithromycin (500 mg daily for 3 days (off-label use) for adults and children of more than 45 kg body weight), instead of ciprofloxacin for the following groups: children and adolescents, people travelling to countries where quinolone resistance is prevalent (for example Thailand and the Far East), pregnant women, and people for whom quinolones are contraindicated. A short 2-day course of bismuth subsalicylate (Pepto Bismol— 2 tablets twice a day) can be considered as 'stand-by' treatment if the person is travelling to an area where quinolone resistance is high (for example south Asia). Bismuth subsalicylate is not available to prescribe on the NHS. It should not be prescribed for: children under the age of 16 years old; pregnant or breastfeeding women; people who are hypersensitive to aspirin or other salicylates.

3. de Bruyn G, Hahn S, Borwick A. Antibiotic treatment for travellers' diarrhoea (Review). *Cochrane Database Syst Rev.* 2000 Jul; 20(3):1-29. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002242/epdf.

   RATIONALE: A systematic review of 20 randomised controlled trials, 10 of which evaluated short-courses of quinolones, 3 of which evaluated stat doses of quinolones, and 1 of which evaluated azithromycin for traveller's diarrhoea. The authors conclude that antibiotic treatment is effective in reducing the duration of post-treatment diarrhoea, and severity of diarrhoea. However, this is at the price of an increased chance of side-effects from antibiotic treatment.

4. Committee to Advise on Tropical Medicine and Travel (CATMAT). Statement on travellers' diarrhoea. An advisory committee statement (ACS). 2015 Apr. Available from: www.phac- aspc.gc.ca/tmp-pmv/catmat-ccmtmv/diarrhea-diarrhee-eng.php.

RATIONALE: A CATMAT statement, in which the authors recommend that bismuth subsalicylate 2.1g to 4.2g per day be considered as an option for preventing traveller's diarrhoea for adults at significant risk, and who are willing to accept multiple doses per day. The authors also suggest that a lower dosage of bismuth subsalicylate (1.05g per day) could be used to prevent traveller's diarrhoea in situations where a higher dose is not feasible. These recommendations are based on 4 randomised controlled trials investigating the use of bismuth subsalicylate versus placebo. The authors found that, overall, a strong protective effect is found after 3 to 4 weeks' follow-up (RR 0.50; 50% effectiveness; 95% CI 0.44 to 0.67), resulting in 250 fewer cases of traveller's diarrhoea per 100 travellers treated. This strong effect was similarly found when restricted to those receiving a high (4.2g per day) or low (1.05g per day) dosage of bismuth subsalicylate (RR 0.51; 49% effectiveness; 95% CI 0.39 to 0.65, and RR 0.65; 35% effectiveness; 95% CI 0.50 to 0.86, respectively). Similarly, there was no difference in effect found when comparing high to low dosage (RR 0.87; 13% difference; 95% CI 0.63 to 1.22). The authors state that the use of bismuth subsalicylate is permitted in the case of certain children aged 2 years and older, based on an individual assessment of risks and benefits. Bismuth subsalicylate is not recommended in children younger than 2 years.

Threadworm:

1. Clinical Knowledge Summaries (CKS). Threadworm. 2011 Dec. Available from: http://cks.nice.org.uk/threadworm#!topicsummary.

    RATIONALE: A CKS guideline, suggesting that all household members should be treated at the same time if threadworm is present. This guideline states that there is no good trial evidence regarding the efficacy of anthelmintics in the treatment of threadworm, and the limited data available is from relatively old, small studies, comparing mebendazole with either placebo, or with drugs that are not available in the UK. Mebendazole does not kill eggs, which survive for 3 weeks; therefore, adequate personal and environmental hygiene is essential to prevent reinfestation from recently swallowed eggs, or eggs already in the environment. Hygiene measures include: washing the perianal area first thing in the morning; washing or wet-wiping at 3 hourly intervals during the day; changing underwear every morning; bathing or showering immediately on rising each morning, and washing around the anus to remove any eggs laid by the worms during the night; hand hygiene; washing sleepwear, bed linen, towels, and cuddly toys at normal temperatures, and rinsing well; thoroughly vacuuming and dusting, paying particular attention to the bedrooms, including vacuuming mattresses. Thorough hygiene measures should be continued for 2 weeks in people who have taken an anthelmintic, and for 6 weeks in people who are using hygiene measures alone, as adults survive for 6 weeks. A one-off dose of mebendazole can be prescribed in children over 6 months, but hygiene measures alone should be used in children under 6 months for at least 6 weeks. Mebendazole should be avoided in the first trimester of pregnancy and hygiene is the preferred method of treatment for this group.

2. Ibarra J. Threadworms: a starting point for family hygiene. *Br J Community Nurs*. 2001 Aug; 6(8):414-420. Available from: www.ncbi.nlm.nih.gov/pubmed/11865209.

    RATIONALE: A review article, emphasising the importance of thorough hygiene measures in cases of threadworm infestation. The most important of these is good hand hygiene,

which is also key to preventing the spread of many other more serious infections.

3. Lohiya G-S, Tan-Figueroa L, Crinella FM, Lohiya S. Epidemiology and control of enterobiasis in a developmental center. *West J Med*. 2000 May; 172(5):305-308. Available from: www.ncbi.nlm.nih.gov/pmc/articles/PMC1070873/pdf/wjm17200305.pdf.

    RATIONALE: A population-based study in a USA long-term care facility for 1,000 residents with developmental disabilities, and high rates of threadworm (*Enterobius vermicularis*). All cases of Enterobius and all 30 residents living in the same unit were treated with a single dose of mebendazole 100mg, which was repeated at 14 days. Prevalence of Enterobius fell from 31% to 1% over 3 years in ambulatory patients. The authors state that mebendazole only kills the adult worm, not the eggs or larvae, by inhibiting its microtubule formation and glucose synthesis. The surviving eggs and larvae in a hosts intestines can mature to new adults within 14 days. A second dose, 14 days after the first, is crucial to kill these new adults. A second dose sooner than 14 days would leave the later-maturing adults unaffected and, after 14 days, the new adults would already have produced eggs. Contacts can be infected with larvae or adult worms without visible perianal eggs, which is the mainstay of diagnosis by sellotape slides and strips.

Genital tract infections

STI screening:

1. British Association for Sexual Health and HIV (BASHH). Standards for the management of sexually transmitted infections (STIs). 2014 Jan. Available from: www.medfash.org.uk/uploads/files/p18dtqli8116261rv19i61rh9n2k4.pdf.

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

2. Public Health England (PHE). Sexually transmitted infections and chlamydia screening in England, 2017. 2018 June. Available from: www.gov.uk/government/statistics/national-chlamydia-screening-programme-ncsp-data-tables.

    RATIONALE: A PHE report stating that, in 2017, there were approximately 422,147 diagnoses of sexually transmitted infections (STIs) made in England, about the same as o 2016. The impact of STIs remains greatest in young heterosexuals 15 to 24 years, black ethnic minorities and gay, bisexual and other men who have sex with men. Local and national prevention activities need to focus on groups at highest risk. Consistent and correct use of condoms can significantly reduce risk of STIs. Rapid, open access to treatment and partner notification can reduce the risk of complications and infection spread. Regular testing for HIV and STIs is essential for good sexual health: anyone

under 25 who is sexually active should be screened for chlamydia annually, and on change of sexual partner. Men who have sex with men should test annually for HIV and STIs and every 3 months if having condomless sex with new or casual partners. Black ethnic minority men and women should have a regular STI screen, including an HIV test, if having condomless sex with new or casual partners.

Chlamydia trachomatis/urethritis:

1. Public Health England (PHE). Monitoring rates of chlamydia re-testing within the English National Screening Programme, Jan. 2013 to June 2017 Health Protection Report Volume 12 Number 20. 2018 June. Available from:https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/713564/hpr2018_chlmd-retest.pdf

    RATIONALE: A PHE report providing an update for monitoring rates of chlamydia re-testing using 2 national STI surveillance systems. The report states the English National Chlamydia Screening Programme policy recommends that sexually active 15-24 year olds are tested for chlamydia annually and on change of sexual partner. Young adults who test positive for chlamydia are at high risk of repeat infection(s) and since August 2013 it is recommended that those testing positive are routinely offered a re-test around 3 months after completing treatment. Findings from the report suggest that in 2017, as few as 1 in 8 chlamydia diagnoses among young adults were followed by a re-test within 7 to 14 weeks. The rationale discussed for retesting at 3 months is that positivity at re-test is higher than the positivity seen overall in both specialist and non-specialist sexual health services: 14.3% vs. 8.1% in non-specialist sexual health services and 17.4% vs 11.8% in 2017 in specialist sexual health services. The proportion of patients who re-tested positive in specialist sexual health services was consistently higher than those re-tested in non-specialist sexual health services. These findings support the inclusion of offer of re-test at around 3 months within the English National Chlamydia Screening Programme case management guidance. The report also covers tools and methods for improving re-testing.

2. Scottish Intercollegiate Guidelines Network (SIGN). Management of genital *Chlamydia trachomatis* infection: a national clinical guideline. 2009 Mar. Available from: www.sign.ac.uk/assets/sign109.pdf.

    RATIONALE: A SIGN guideline advising that the treatment of partners prior to resuming sexual intercourse is the strongest predictor for preventing re-infection with *Chlamydia trachomatis*. Sexual partners of chlamydia-positive individuals are at risk of infection and subsequent morbidity; treating them will also reduce the risk of re-infection of the index case. The prevalence of infection in sexual partners of chlamydia-positive cases has been shown to be 60 to 75%. Sexual partners of those with conditions for which chlamydia is a frequent cause, such as PID or epididymo-orchitis, are also at risk of infection. This guideline recommends either doxycycline 100mg BD for 7 days, or azithromycin 1g stat as first line treatment for *Chlamydia trachomatis* in pregnant women, as cure rates for both treatments are over 90%. However, the authors advise that, taking compliance with therapy into account, uncomplicated genital chlamydial infection should be treated with azithromycin 1g as a single oral dose.

3. Nwokolo NC, Dragovic B, Patel S, Tong CYW, Barker G, Radcliffe K. 2015 UK national guideline for the management of infection with *Chlamydia trachomatis. Int J STD AIDS.* 2015 Oct; 27(4):251-267. Available from: www.bashh.org/documents/UK%20Chlamydia%20Guidelines%202015.pdf.

   RATIONALE: A UK national guideline stating that partners should also be treated for *Chlamydia trachomatis* infection, as there is a concordance rate of up to 75%. A test of cure is not routinely recommended, but should be performed in pregnancy, or where non-compliance or re-exposure is suspected. The higher rate of positive tests after treatment during pregnancy is attributed to either: a less efficacious treatment regimen; non-compliance; re-infection. A test of cure should be repeated no earlier than 3 weeks after the end of treatment, as treatment failure with azithromycin has been reported at 8%, questioning its effectiveness. This is recommended especially where poor compliance is suspected, or if symptoms persist after the end of treatment. This guideline recommends the following treatment regimens: for uncomplicated urogenital infection, doxycycline 100mg BD for 7 days (contraindicated in pregnancy); azithromycin 1g orally as a single dose. Alternative regimens (if either of the above is contraindicated) include erythromycin 500mg BD for 10 to 14 days, or ofloxacin 200mg BD/400mg OD for 7 days. Following an extensive review of the evidence and a professional and public consultation, in August 2013, the National Chlamydia Screening Programme (NCSP) in England issued a recommendation that young people under the age of 25 who test positive for chlamydia should be offered a repeat test around 3 months after treatment of the initial infection. This is based on evidence that young adults who test positive for chlamydia are 2 to 6 times more likely to have a subsequent positive test, and that repeated chlamydia infection is associated with an increased risk of complications, such as PID and tubal infertility.

4. Rose SB, Garrett SM, Stanley J, Pullon SRH. Retesting and repeat positivity following diagnosis of *Chlamydia trachomatis* and *Neisseria gonorrhoea* in New Zealand: a retrospective cohort study. *BMC Infect Dis.* 2017 Jul; 17(1):526. Available from: www.ncbi.nlm.nih.gov/pubmed/28754106.

   RATIONALE: A retrospective cohort study in Wellington, New Zealand, involving the analysis of laboratory data for chlamydia and gonorrhoea tests performed in primary care and sexual health clinics between July 2012 and July 2015. Overall, 29.4% (1,919/6,530) were retested between 6 weeks and 6 months, with 18% (347/1,919) of those retested returning positive results. Lower odds of retesting were observed for males (OR 0.4; 95% CI 0.34 to 0.48). Factors associated with higher odds of repeat positivity on retesting included those aged between 15 and 19 years (OR 1.78; 95% CI 1.32 to 2.41), and those with chlamydia/gonorrhoea co-infection (OR 1.6; 95% CI 1.32 to 4.35). The authors conclude that greater priority needs to be placed on increasing retesting, and reducing rates of reinfection. Therefore, repeat test of cures should be repeat 3 to 6 months after completing a course of treatment for chlamydial or gonococcal infection.

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

   RATIONALE: A meta-analysis of 12 randomised controlled trials (n=1,543), reporting that microbiological cure was achieved in 97% of people taking azithromycin 1g once, and 98% of those taking doxycycline 100mg BD for 7 days (p=0.296; no significant difference).

The authors conclude that azithromycin and doxycycline are equally efficacious in achieving microbial cure and have similar tolerability, with azithromycin being the most effective antimicrobial in pregnancy. Further trials comparing these antibiotics are unnecessary.

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

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

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

   RATIONALE: A systematic review and meta-analysis of 8 RCTs, involving 587 pregnant women, aiming to compare data regarding the effectiveness and safety of azithromycin with alternative regimens in the treatment of pregnant women with *Chlamydia trachomatis* infection. In all included studies, 1g azithromycin stat was compared with erythromycin 500mg OD 3 or 4 times daily for 7 days, or amoxicillin 500mg 3 times daily for 7 days. Results indicated that there was no difference between azithromycin and erythromycin regarding treatment success (OR 2.66; 95% CI 0.69 to 10.29), but azithromycin was associated with fewer adverse events (OR 0.11; 95% CI 0.07 to 0.18). The authors conclude that azithromycin is associated with similar effectiveness, but less adverse events, when compared with erythromycin or amoxicillin in the treatment of pregnant women with *C. trachomatis* infection, so should be considered as a first line agent.

8. Brocklehurst P, Rooney G. Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy (Review). *Cochrane Database Syst Rev*. 1998(4). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000054/epdf.

   RATIONALE: A systematic review and meta-analysis of 11 randomised controlled trials. Pooled data from 4 RCTs reported that 8% of women taking azithromycin 1g stat (11/145) failed to achieve microbiological cure, compared with 19% of women taking erythromycin 500mg 4 times daily for 7 days (27/145; OR 0.38; 62% difference; 95% CI 0.19 to 0.74). Pooled data from 3 RCTs found that 9% of women taking amoxicillin 500mg 3 times daily for 7 days (17/199) failed to achieve microbiological cure, compared with 15% of women taking erythromycin (28/191; OR 0.54; 46% difference; 95% CI 0.28 to 1.02). The authors conclude that amoxicillin is an acceptable alternative therapy for the treatment of genital

chlamydial infections in pregnancy when compared with azithromycin or erythromycin. Clindamycin 450mg 4 times daily for 14 days may be considered if azithromycin, erythromycin and amoxicillin are contraindicated or not tolerated.

9. British Association for Sexual Health and HIV (BASHH). The use of antibiotics to treat genital infections in pregnant women. 2017 Aug. Available from: www.bashhguidelines.org/media/1151/ceg-statement-antibiotics-in-pregnancy.pdf.

    RATIONALE: A BASHH statement on the release of a paper by Muanda et al, which found an association between the use of a number of antibiotics in pregnancy and spontaneous abortion. This paper is a retrospective, case-control study, and an association does not prove causation. In the case of chlamydial infection in pregnant women, it may be considered that amoxicillin or erythromycin may be preferable to azithromycin, given that Muanda et al did not find an association with those 2 antibiotics. However, azithromycin is better tolerated, and more effective than erythromycin in treating chlamydial infection in pregnancy. Therefore, avoiding azithromycin means using a less effective treatment, which may result in a greater change of pregnancy loss due to inadequately treated infection. BASHH see no reason at the present time to change the recommendations in its current guidelines for treating genital infections in pregnancy. Good clinical practice remains to discuss the uncertainties, and the potential risks and benefits of the treatment options, with the patient, and to document the discussion in the clinical notes. This is especially important, given that the use of these antibiotics in pregnancy is 'off-label'.

Epididymitis:

1. Street E, Joyce A, Wilson J. 2010 United Kingdom national guideline for the management of epididymo-orchitis. 2011 Jun. Available from: www.bashh.org/documents/3546.pdf.

    RATIONALE: A UK national guideline stating that, in men over 35 years, the cause is most often non-sexually transmitted Gram-negative enteric organisms. Particular risks include recent instrumentation and catheterisation. In men under 35 years, epididymo-orchitis is most often caused by a sexually transmitted pathogen, such as *Chlamydia trachomatis* or *Neisseria gonorrhoeae*. These men should be referred to a GUM clinic for definitive diagnosis and treatment. There is crossover between these groups, and complete sexual history is imperative. If clinicians decide that the infection is likely to be due to chlamydia or other non-gonococcal organisms (ie. where gonorrhoea is considered unlikely, as microscopy is negative for Gram-negative intracellular diplococci and there are no risk factors for gonorrhoea identified), the authors advise that doxycycline 100mg BD for 10 to 14 days, ofloxacin 200mg BD for 14 days, or ciprofloxacin 500mg BD for 10 days should be prescribed.

2. Public Health England Expert Panel. In a conversation with the British Infection Association Expert Panel (oral communication, May 2016).

    RATIONALE: Expert consensus, noting that most of the studies of epididymitis have concerned ofloxacin, with very few that have studied ciprofloxacin, and none that have directly compared the 2. In men over 35 years old, ofloxacin 200mg BD for 14 days or ciprofloxacin 500mg BD for 10 days should be used. In men under 35 years old or STI risk, consider non-gonococcal chlamydia and refer to GUM, or consider treatment with doxycycline 100mg BD for 10 to 14 days, or ofloxacin 200mg BD for 14 days. If thought to

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be due to an enteric organism, ciprofloxacin 500mg BD for 10 days, or ofloxacin 200mg BD for 14 days should be used.

Vaginal candidiasis:

1. British Association for Sexual Health and HIV (BASHH). United Kingdom national guideline on the management of vulvovaginal candidiasis (2007). 2007 Aug. Available from: www.bashhguidelines.org/media/1155/united-kingdom-national-guideline-on-the-management-of-vulvovaginal-candidiasis.pdf

   RATIONALE: A BASHH guideline suggesting that, since all topical and oral azole therapies give a clinical and mycological cure rate of over 80% in uncomplicated acute vulvovaginal candidiasis, choice should be a matter of personal preference, availability, and affordability/cost. Nystatin preparations give a 70 to 90% cure rate in patients with vulvovaginal candidiasis. Topical azole therapies give higher mycological cure of 80% or above but can cause vulvovaginal irritation, so this should be considered if symptoms persist or worsen, or in pregnancy. This guideline lists the potential dosing regimens of both oral azoles and nystatin. For uncomplicated vulvovaginal candidiasis, the following options are included: clotrimazole 500mg pessary stat, or 10% cream 5g stat or 100mg pessary for 6 nights (200mg pessary for 3 nights); econazole 150mg pessary stat; fenticonazole 600mg pessary stat; oral fluconazole 150mg stat; miconazole pessary 100mg for 14 nights. For recurrent vulvovaginal candidiasis (more than 4 attacks per year), oral fluconazole 150mg every 72 hours for 3 doses induction, followed by 150mg once a week for 6 months maintenance is recommended.

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

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

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

   RATIONALE: A UKTIS webpage stating that fluconazole is a triazole antifungal commonly used in the treatment of candidiasis. Standard fluconazole therapy generally comprises a single 150mg oral dose, and is not recommended during pregnancy. However, vaginal candidiasis is common in pregnancy, and as fluconazole is sometimes prescribed to treat candidiasis that has not responded to topical clotrimazole treatment, exposure during pregnancy is not uncommon. Where fluconazole use is considered necessary in

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pregnancy, the risks and benefits of treatment should be discussed with the patient, to support evidence-based shared decision making. Data on the outcomes of over 8,000 fluconazole-exposed pregnancies, the majority of which were exposed to a 150mg single oral dose, showed no increase in the incidence of overall malformation rate. One case-control and 1 large cohort study reported a significant association between conotruncal defects and in utero exposure to standard doses of fluconazole during the first trimester; however, the absolute risk to the foetus is still likely to be very small (<0.1%). An increased risk of spontaneous abortion following maternal exposure to fluconazole has been reported in a recent large study, but a causal association remains to be confirmed. Rates of stillbirth, prematurity, and low birth weight have not been shown to be elevated in standard dose fluconazole-exposed pregnancies. No studies have evaluated whether neurodevelopmental outcomes are altered in infants exposed to fluconazole in utero.

4. Young GL, Jewell D. Topical treatment for vaginal candidiasis (thrush) in pregnancy (Review). *Cochrane Database Syst Rev*. 2001 Oct; 4:1-21. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000225/epdf.

    RATIONALE: A systematic review and meta-analysis of 10 studies, aiming to assess the effects of different methods for treating vaginal candidiasis in pregnancy. Ten trials were included. Based on 5 trials, imidazole drugs were more effective than nystatin when treating vaginal candidiasis in pregnancy (odds ratio 0.21, 95% confidence interval 0.16 to 0.29). A trial of clotrimazole was more effective than placebo (odds ratio 0.14, 95% confidence interval 0.06 to 0.31). Single dose treatment was no more or less effective than 3 or 4 day's treatment. However, 2 trials involving 81 women, showed that treatment lasting for 4 days was less effective than treatment for 7 days (odds ratio 11.7, 95% confidence interval 4.21 to 29.15). Based on 2 trials, treatment for 7 days was no more or less effective than treatment for 14 days (odds ratio 0.41, 95% confidence interval 0.16 to 1.05). Terconazole was as effective as clotrimazole (odds ratio 1.41, 95% confidence interval 0.28- 7.10). The authors conclude that topical imidazoles and not nystatin should be used if possible for treatment of symptomatic vaginal candidiasis in pregnancy. There is no evidence to suggest that asymptomatic women need to be treated. Treatments for 7 days may be necessary in pregnancy rather than the shorter courses more commonly used in non-pregnant women.

Bacterial vaginosis:

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

    RATIONALE: A meta-analysis of 6 randomised controlled trials in 1,698 non-pregnant and pregnant women, reviewing the data on the treatment of bacterial vaginosis, published from 1993 to 1996. For non-pregnant women, the authors suggest the use of metronidazole (500mg orally, twice daily, for 7 days), clindamycin vaginal cream (2%, once daily, for 7 days), or metronidazole vaginal gel (0.75%, twice daily, for 5 days), as the preferred treatment for bacterial vaginosis. For pregnant, high-risk women (women with a prior preterm birth), the objective of the treatment is to prevent adverse outcomes in pregnancy, in addition to the relief of symptoms. Thus, systemic therapy for possible subclinical upper genital tract infection, as well as medication that has been studied in

pregnant women, are preferable. For pregnant, low-risk women (women without a prior preterm birth) with symptomatic disease, the main objective of the treatment is to relieve symptoms. Data does not support the routine treatment of male sexual partners. Pooled data found no significant difference between cumulative cure rates 5 to 10 days after finishing treatment for oral 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%). One study reported on the use of a single 2g dose of metronidazole, and found that a higher cumulative cure rate was recorded with the 7 day metronidazole regimen than with the single dose regimen (88% versus 54%, respectively). The authors therefore recommend metronidazole 250mg orally 3 times daily for 7 days, when treating pregnant, low-risk women with bacterial vaginosis.

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

    RATIONALE: A review article, stating that metronidazole can be prescribed in women with bacterial vaginosis as 500mg twice daily for 7 days, or as a 2g stat dose, with the 7 day course resulting in less relapses. The costs of the recommended antimicrobials are listed, and it is demonstrated that oral treatment is cheaper than topical treatment. The author recommends the following topical treatment: clindamycin 2% vaginal cream, 5g at bedtime for 7 days; metronidazole vaginal gel, 5g at bedtime for 5 days. Although this article recommends metronidazole 500mg 4 times daily, the authors do state that this can be reduced and still result in a high cure rate (84 to 96%).

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

    RATIONALE: A systematic review and meta-analysis of 21 trials, involving 7,847 pregnant women diagnosed with bacterial vaginosis or intermediate vaginal flora. The antibiotics included were: oral metronidazole 400mg BD for 2 days; erythromycin 300mg TDS for 14 days; clindamycin 300mg BD for 5 days; amoxicillin 500mg TDS for 14 days; vaginal metronidazole 0.75% gel at night for 5 nights; intravaginal clindamycin 5g for 7 nights. Antibiotic therapy was shown to be effective in eradicating bacterial vaginosis during pregnancy (RR 0.42; 58% effectiveness; 95% CI 0.31 to 0.56; 10 trials, n=4,403; random- effect T^2=0.19; I^2=91%). Antibiotic treatment also reduced the risk of late miscarriage (RR 0.20; 80% reduction; 95% CI 0.05 to 0.76; 2 trials, n=1,270; fixed-effect I^2=0%). The overall risk of pre-term birth was not significantly reduced. The authors conclude that antibiotic treatment can eradicate bacterial vaginosis in pregnancy; however, this review provides little evidence that screening and treating all pregnant women with bacterial vaginosis will prevent pre-term birth and its consequences. When screening criteria were broadened to include women with abnormal flora, there was a 47% reduction in pre-term birth.

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

    RATIONALE: A UKTIS webpage stating that, where oral treatment is deemed appropriate,

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

5. British Association for Sexual Health and HIV (BASHH). UK national guideline for the management of bacterial vaginosis 2012. 2012 Jan. Available from: www.bashh.org/documents/4413.pdf.

> RATIONALE: A BASHH guideline offering recommendations on diagnosis, treatment regimens, and health promotion principles needed for the effective management of bacterial vaginosis, covering both the management of the initial presentation, and recurrence. This guideline discusses findings from 2 studies, in which it was found that no reduction in relapse rates were reported when male partners of women with bacterial vaginosis were treated with metronidazole 400mg twice daily for 5 to 7 days, tinidazole 2g single dose, or clindamycin 300mg twice daily for 7 days.

Genital herpes:

1. British Association for Sexual Health and HIV (BASHH). 2014 UK national guideline for the management of anogenital herpes. 2014 Aug. Available from: www.bashh.org/documents/HSV%20Final%20guidelines%20with%20ref%20sorted.pdf.

> RATIONALE: A BASHH guideline, advising that all patients with a first episode of genital herpes are given general advise about saline bathing, analgesia, and anaesthetic agents, for example lidocaine ointment). These may be useful to apply, especially prior to micturition. Although the sensitisation exists in the use of topical anaesthetic agents, lidocaine is a rare sensitiser and can be used safely in genital herpes in the form of gel or ointment. Oral antiviral drugs are indicated within 5 days of the start of the episode, while new lesions are still forming, or if systemic symptoms persist. Aciclovir 400mg 3 times daily, valaciclovir 500mg twice daily, and famciclovir 250mg 3 times daily, for 5 days, all reduce the severity and duration of episodes. Antiviral therapy does not alter the natural history of the disease in that frequency or severity of subsequent recurrences remains unaltered. Topical agents are less effective than oral agents. Combining oral and topical treatment is of no additional benefit over oral treatment alone. Intravenous therapy is indicated only when the patient cannot swallow or tolerate oral medication because of vomiting. There are no comparative studies to show benefit from therapy longer than 5

days. However, it may still be prudent to review the patient after 5 days and continue therapy if new lesions are still appearing at this time, or if systemic symptoms are still present, or if complications have occurred. For recurrent genital herpes, this guideline advises that recurrences are self-limiting and generally cause minor symptoms. Management decisions should be made in partnership with the patient. Strategies include: supportive therapy only; episodic antiviral treatments; suppressive antiviral therapy. The best strategy for managing an individual patient may change over time, according to recurrence frequency, symptom severity, and relationship status. Patients should again be given general advice about using saline bathing, Vaseline, analgesia, and 5% lidocaine ointment. For episodic antiviral treatment, short-course therapies offer more convenient and cost-effective strategies for managing genital herpes episodically, and should be regarded as first line options. Oral aciclovir 800mg 3 times daily for 2 days, valaciclovir 500mg twice daily for 3 days, and famciclovir 1g twice daily for 1 day are recommended. The reduction in duration is a median of 1 to 2 days. Head-to-head studies show no advantage of 1 therapy over another, or the advantage of extended 5 day treatment over short-course therapy. Prodrugs (such as valaciclovir and famciclovir) offer simplified twice a day dosing. Aborted lesions have been documented in up to a third of patients with early treatment. Patient initiated treatment started early in an episode is most likely to be effective, as treatment prior to the development of papules is of greatest benefit. Patients who have taken part in trials of suppressive therapy have had to have at least 6 recurrences per annum. Such patients have fewer or no episodes on suppressive therapy. Patients with lower rates of recurrence will probably also have fewer recurrences with treatment. Patients should be given full information on the advantages and disadvantages of suppressive therapy. The decision to start suppressive therapy is a subjective 1, balancing the frequency of recurrence with the cost and inconvenience of treatment.

Patients suffering from psychological morbidity for which the diagnosis causes significant anxiety may benefit from suppressive therapy. Patient safety and resistance data for long- term suppressive therapy with aciclovir now extends to over 20 years of continuous surveillance. This confirms that aciclovir is an extremely safe compound requiring no monitoring in previously well patients, and only a dose adjustment in those with severe renal disease. Recommended suppressive regimens for treatment include: aciclovir 400mg twice daily; famciclovir 250mg twice daily; valaciclovir 500mg once daily, all for 1 year. These doses can be increased if breakthrough recurrences occur.

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

   RATIONALE: A CKS guideline stating that all people with suspected genital herpes should be referred to a GUM specialist for diagnosis, treatment, screening for sexually transmitted infections, counselling, and follow-up. This guideline recommends that treatment with oral aciclovir (200mg 5 times a day for 5 days) should be started within 5 days of the start of the episode, or while new lesions are forming. Management of recurrent episodes is included, and recommends self-care measures, including topical anaesthesia and increasing fluid intake to produce dilute urine, episodic antiviral treatment for infrequent attacks (oral aciclovir 200mg 5 times a day for 5 days), and suppressive antiviral treatment for frequent attacks (oral aciclovir 400mg twice daily for 6 to 12 months). Suppressive antiviral treatment should particularly be considered if the condition

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is causing psychological distress, or is affecting the individual's social life.

3. Heslop R, Roberts H, Flower D, Jordan V. Interventions for men and women with their first episode of genital herpes (Review). *Cochrane Database Syst Rev.* 2016 Aug; 30(8):1-171. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010684.pub2/epdf.
RATIONALE: A systematic review and meta-analysis of 26 trials and 2,084 participants, aiming to determine the effectiveness and safety of the different existing treatments for first-episode genital herpes on the duration of symptoms and time to recurrence. Aciclovir, valaciclovir, and famciclovir are competitive inhibitors of viral DNA polymerase, resulting in inhibition of viral DNA synthesis. The drugs have an excellent margin of safety because they are converted by viral thymidine kinase to the active drug only inside virally infected cells. The results from this review demonstrated that aciclovir does reduce the duration of symptoms in individuals undergoing their first episode of genital herpes (mean days reduction -3.22 days; 95% CI -5.91 to -0.54). Oral valaciclovir also showed a similar length of symptom duration when compared to aciclovir. There was however no evidence found to demonstrate that topical aciclovir reduces symptoms (mean days reduction -0.61 days; 95% CI -2.16 to 0.95; 3 RCTs; n=195); I^2=56%), suggesting that topical antivirals do not reduce symptom duration for patients undergoing their first episode of genital herpes.

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

   RATIONALE: A systematic review and meta-analysis of 26 randomised controlled trials, aiming to compare the effectiveness and safety of 3 oral antiviral drugs (aciclovir, famciclovir, and valaciclovir) prescribed to suppress genital herpes outbreaks in non-pregnant parties. In placebo-controlled trials, there was low quality evidence that the risk of having at least 1 clinical recurrence was reduced with aciclovir (RR 0.48; 52% reduction; 95% CI 0.39 to 0.58; 9 trials; n=2,049), valaciclovir (RR 0.41; 59% reduction; 95% CI 0.24 to 0.69; 4 trials; n=1,788), or famciclovir (RR 0.57; 43% reduction; 95% CI 0.50 to 0.64; 2 trials; n=732). The authors conclude that aciclovir, valaciclovir, and famciclovir are strong antimicrobials for the treatment of genital herpes, but there is no superiority of 1 drug over another when used as suppressive antiviral therapy in patients experiencing at least 4 recurrences of genital herpes per year.

Gonorrhoea:

1. Public Health England (PHE) GRASP Steering Committee and the British Association for Sexual Health and HIV (BASHH). CEG position statement on the treatment of gonorrhoea. 2015 Dec. Available from: www.bashh.org/documents/GRASP%20statement%20letter%20HF.docx.
RATIONALE: A PHE and BASHH position statement on the treatment of gonorrhoea in the United Kingdom. This statement states that antibiotic resistance is now very high, and recommends that dual treatment with ceftriaxone 500mg intramuscularly plus azithromycin 1g orally is advised for the treatment of all gonorrhoea cases, irrespective of the results of chlamydia testing, in order to mitigate against the selection of gonococci with reduced

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susceptibility to cephalosporins. It is difficult for an organism to develop simultaneous resistance to 2 different antimicrobial classes, meaning that dual treatment creates a pharmacological barrier to the emergence of isolates exhibiting resistance to 1 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 for easier selection of ceftriaxone resistance. For co-infection with rectal chlamydia, this statement recommends specific treatment of each infection, ie. ceftriaxone combined with azithromycin for gonorrhoea, with the addition of doxycycline for concurrent rectal chlamydia. Of 15,758 reported cases of pelvic inflammatory disease in 2013, only 323 (2%) involved gonococci. Therefore, it is reasonable to continue the use of ceftriaxone and doxycycline in this patient group, as it is unlikely to impact on measures to delay the development of widespread ceftriaxone resistance. This statement stresses the importance of test of cure for all patients, but particularly for those not treated with dual gonococcal therapy.

2. Public Health England (PHE). Surveillance of antimicrobial resistance to *Neisseria gonorrhoeae*: Key findings from the 'Gonococcal resistance to antimicrobials surveillance programme' (GRASP) and related surveillance data. 2017 June. Available from: www.gov.uk/government/publications/gonococcal-resistance-to-antimicrobials-surveillance-programme-grasp-report.

    RATIONALE: A PHE report describing trends in, and epidemiology of, antimicrobial resistance and decreased susceptibility in gonococcal infection in England and Wales. Key points from the report highlight that current first-line treatment for gonorrhoea in the UK is dual therapy with ceftriaxone (500mg IM) and azithromycin (1g oral). Effectiveness is threatened by antimicrobial resistance. Between 2015 and 2016, gonococcal isolates collected through PHE's sentinel surveillance system showed: no resistance to ceftriaxone, a decline in azithromycin resistance, an increase in cefixime resistance for the second consecutive year, a decline in resistance to ciprofloxacin, and to penicillin. It recommends that laboratories should test for susceptibility and refer suspected azithromycin/ceftriaxone resistant isolates to PHE's national reference laboratory. Clinicians should ensure all patients are treated according to national guidelines and be alert to changes in antibiotics recommended for front line use. Patients having sex with new/multiple partners should be advised on consistent condom use/regular STI testing.

3. Bignell C, Fitzgerald M, Guideline Development Group, British Association for Sexual Health and HIV UK. UK national guideline for the management of gonorrhoea in adults, 2011. *Int J STD AIDS*. 2011 Oct; 22(10):541-547. Available from: www.ncbi.nlm.nih.gov/pubmed/21998172.

    RATIONALE: A guideline offering advice on diagnosis, treatment, and health promotion for anogenital and pharyngeal gonorrhoea. Nucleic acid amplification tests (NAATs) are being used more for diagnosis, and are increasing detection rates in the pharynx and rectum. First line treatment using ceftriaxone with azithromycin is advised, along with routine test of cure. The aim is to slow the spread of resistant gonorrhoea, now that fewer antibiotics remain effective. This guideline recommends that: all patients treated for gonorrhoea should be recommended to have a TOC; all patients with gonorrhoea should

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be screened for genital infection with *Chlamydia trachomatis*, or receive presumptive treatment for this infection; all patients identified with gonorrhoea should have partner notification carried out; all patients identified with gonorrhoea should be offered written information about STIs and their prevention; all patients with gonorrhoea should receive first line treatment, or the reasons for not doing so should be documented.

4. Wetten S, Mohammed H, Yung M, Mercer CH, Cassell JA, Hughes G. Diagnosis and treatment of chlamydia and gonorrhoea in general practice in England 2000-2011: a population-based study using data from the UK Clinical Practice Research Datalink. *BMJ Open*. 2015 Apr; 5(5):1-9. Available from:
www.ncbi.nlm.nih.gov/pmc/articles/PMC4452740/pdf/bmjopen-2015-007776.pdf.
RATIONALE: A retrospective, population-based study, demonstrating the relative contribution of GPs to the diagnosis of chlamydia and gonorrhoea in England. GPs make an important contribution to the diagnosis and treatment of bacterial STIs in England. While most patients diagnosed with chlamydia were managed appropriately, many of those treated for gonorrhoea received antimicrobials no longer recommended for use. The authors recommend that confirmed cases of gonorrhoea should be referred to GUM, and that stat doses of ceftriaxone and azithromycin are the antimicrobials of choice. The authors conclude that, given the global threat of antimicrobial resistance, GPs should remain aware of national guidelines, and remain alert to treatment failure in their patients.

Trichomoniasis:

1. Sherrard J, Ison C, Moody J, Wainwright E, Wilson J, Sullivan A. United Kingdom national guideline on the management of *Trichomonas vaginalis* 2014. *Int J STD AIDS*. 2014 Feb; 25(8):541-549. Available from: www.bashh.org/documents/TV_2014%20IJSTDA.pdf.
RATIONALE: A BASHH guideline suggesting that current partners, and any partners within the 4 weeks prior to presentation, should be screened for the full range of STIs and treated for TV irrespective of the results of investigations. This guideline suggests that systemic antibiotic therapy is required to affect a permanent cure of *Trichomonas vaginalis*, due to the high frequency of infection of the urethra and paraurethral glands in females. A systematic review of 54 trials found that almost any nitroimidazole drug given as a single dose, or over a longer period, results in parasitological cure in >90% of cases. Oral single-dose treatment with any nitroimidazole drug seems to be effective in achieving short-term parasitological cure, but is associated with more frequent side-effects than either longer oral, or intravaginal treatment. Intravaginal treatment showed parasitological cure rates around 50%, which is unacceptably low. There is a spontaneous cure rate in the order of 20 to 25%. This guideline recommends metronidazole 2g orally in a single dose, or metronidazole 400 to 500mg twice daily for 5 to 7 days.

2. Gulmezoglu AM, Azhar M. Interventions for trichomoniasis in pregnancy (Review). *Cochrane Database Syst Rev*. 2011 May; 11(5):1-18. Available from:
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000220.pub2/epdf.
RATIONALE: A systematic review and meta-analysis of 2 trials, including 842 pregnant women. In both trials, around 90% of women were cleared of trichomonas in the vagina

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

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

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

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

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

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

RATIONALE: A review article, stating that treatment of trichomoniasis is commonly with metronidazole, with alternative treatments including vaginal clotrimazole, and arsenical pessaries. These preparations provide local symptom relief, but documentation on their effectiveness as cures has been inconsistent. If clotrimazole is prescribed, a daily intravaginal pessary at a dose of 100mg for 6 days can be given to provide temporary relief. However, limited information about the effects of these drugs makes it questionable whether these regimens are curative or merely palliative.

6. Forna F, Gulmezoglu AM. Interventions for treating trichomoniasis in women. *Cochrane Database Syst Rev.* 2003 Apr; 2:1-96. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000218/epdf.

RATIONALE: A systematic review and meta-analysis of 54 studies, in which study populations were heterogeneous. Women attending emergency departments, venereal disease clinics, gynaecology outpatient clinics, cancer screening clinics, prisons, and private practices were recruited into different trials. In most trials, single dose treatment with any nitroimidazole drug resulted in parasitological cure rates above 90%. The authors conclude that oral single dose treatment with any nitroimidazole seems to be effective in achieving short-term parasitological cure, in comparison with longer 5 to 7 day courses (12% less effective, but not significant; RR 1.12; 95% CI 0.58 to 2.16). However, although rarely severe, side-effects seem to be relatively common and dose-related, and mainly of a gastrointestinal nature.

Pelvic inflammatory disease:

1. British Association for Sexual Health and HIV (BASHH). United Kingdom National Guideline for the Management of Pelvic Inflammatory Disease. 2018. Available from: www.bashhguidelines.org/media/1170/pid-2018.pdf

RATIONALE: A BASHH guideline that offers recommendations on the management of pelvic inflammatory disease (PID). It is aimed primarily at women aged 16 years or older presenting to health care professionals working in departments offering **specialist care in STI management within the United Kingdom** but should be adopted across all providers as they may need to develop local care pathways where appropriate. Testing for gonorrhoea and chlamydia in the lower genital tract is recommended since a positive result supports the diagnosis of PID. The absence of infection at this site does not exclude PID. Local availability of *M. genitalium* testing currently varies but implementation of testing is strongly recommended to guide the choice of appropriate therapy. An elevated ESR or C reactive protein, or high blood white cell count, also supports the diagnosis but is non-specific and usually only abnormal in moderate or severe PID. The absence of endocervical or vaginal pus cells has a good negative predictive value (95%) against a diagnosis of PID, but their presence is non-specific (poor positive predictive value of 17%). Differential diagnosis includes: ectopic pregnancy, appendicitis, endometriosis, complications of an ovarian cyst, urinary tract infection, irritable bowel syndrome/acute bowel infection or diverticular disease, lower abdominal pain usually in association with other gastrointestinal symptoms, and long term functional pain (pain of unknown aetiology). The guidance recommends for **Outpatient Regimens: 1) i.m. ceftriaxone 500mg single dose followed by oral doxycycline 100mg twice daily *plus* metronidazole 400mg twice daily for 14 days.** (Clinical trial data support the use of

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cefoxitin for the treatment of PID but this agent is not easily available in the UK so ceftriaxone, which has a similar spectrum of activity, is recommended); **2) *OR* oral ofloxacin 400mg twice daily *plus* oral metronidazole 400mg twice daily for 14 days; 3) *OR* oral moxifloxacin 400mg once daily for 14 days.** Metronidazole is included in some regimens to improve coverage for anaerobic bacteria. Anaerobes are of relatively greater importance in patients with severe PID and metronidazole may be discontinued in those patients with mild or moderate PID who are unable to tolerate it. Ofloxacin and moxifloxacin should be avoided in patients who are at high risk of gonococcal PID (for example when the patient's partner has gonorrhoea, in clinically severe disease, following sexual contact abroad) because of high levels of quinolone resistance. Three large RCTs support the efficacy of moxifloxacin for PID. There is a potential risk of serious liver reactions occurring with this agent but they are uncommon (12 cases reported in the UK from 2003-16 with no deaths) and moxifloxacin is generally well tolerated. Of the 3 recommended PID treatment regimens, moxifloxacin provides the highest microbiological activity against *M. genitalium*. Doxycycline is now suggested as empirical treatment for male partners of women with PID to reduce exposure to macrolide antibiotics which has been associated with increased resistance in *M. genitalium.*

2. Ross JDC, Cronje HS, Paszowski T, Rakoczi I, Vildaite D, Kureishi A et al. Moxifloxacin versus ofloxacin plus metronidazole in uncomplicated pelvic inflammatory disease: results of a multicentre, double blind, randomised trial. *Sex Transm Infect*. 2006 Dec; 82(6):446-451. Available from: www.ncbi.nlm.nih.gov/pmc/articles/PMC2563874/.

   RATIONALE: A randomised controlled trial of 564 patients with uncomplicated PID in hospitals from 13 countries, comparing oral metronidazole 500mg twice daily with either oral ofloxacin 400mg twice daily, or moxifloxacin 400mg once daily. Clinical resolution with 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 (for example when the patient's partner has gonorrhoea; in clinically severe disease; following sexual contact abroad). Quinolones should also be avoided as first line empirical treatment for PID in areas where >5% of PID is caused by quinolone resistant *Neisseria gonorrhoeae*.

3. Public Health England (PHE). Surveillance of antimicrobial resistance to *Neisseria gonorrhoeae*: Key findings from the 'Gonococcal resistance to antimicrobials surveillance programme' (GRASP) and related surveillance data. 2015 Nov. Available from: www.gov.uk/government/publications/gonococcal-resistance-to-antimicrobials-surveillance-programme-grasp-report.
   RATIONALE: A PHE report describing trends in, and epidemiology of, antimicrobial resistance and decreased susceptibility in gonococcal infection in England and Wales. In 2014, in England, the number of new gonorrhoea diagnoses increased by 21.4% (especially among men who have sex with men, and young adults). Ciprofloxacin resistance is now endemic in England and Wales, accounting for 25% of all gonorrhoea isolates tested in 2014. 5.6% of isolates exhibited decreased susceptibility to cefixime; only 3 isolates showed decreased susceptibility to ceftriaxone (MIC >0.125mg/L). If

gonorrhoea is suspected, a stat dose of 500mg IM ceftriaxone should be given.

4. Ison CA, Mouton JW, Jones K, Fenton KA, Livermore DM. Which cephalosporin for gonorrhoea? *Sex Transm Infect*. 2004 Aug; 80:386-388. Available from: http://sti.bmj.com/content/80/5/386.full.pdf+html.

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

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

   RATIONALE: A systematic review, identifying 34 trials of antibiotic treatment for PID. Most studies were small, open-label, and of poor methodological design. One small trial compared oral ofloxacin plus metronidazole, with clindamycin plus gentamicin. The cure rate was 15/15 for ofloxacin plus metronidazole, and was 17/18 for clindamycin plus gentamicin. This review found 1 trial of ceftriaxone plus doxycycline, 2 trials of cefoxitin plus probenecid and doxycycline, and 3 trials of cefoxitin plus doxycycline, compared to other antibiotics. Meta-analyses of these 6 studies found no difference in cure rates between IM cephalosporin plus doxycycline and the comparator antibiotics.

Skin and soft tissue infections

General references:

1. Royal College of General Practitioners (RCGP). *Skin Infections*. Available from: http://elearning.rcgp.org.uk/course/info.php?popup=0&id=161 [Accessed: 5 Oct 2018].

   RATIONALE: AN RCGP webpage hosting a free 2-hour training module on diagnosing and managing skin infections for continued professional development. This series of training modules includes information on: staphylococcal and streptococcal skin infections; other bacterial skin infections; antibiotics; leg ulcers; pressure sores; acne; viral skin infections, including herpes zoster, warts, and molluscum; fungal and parasitic infections; brief overview of tropical skin conditions. This module equals 2 hours towards CPD, and can be imported into the RCGP Revalidation portfolio.

Impetigo:

1. Denton M, O'Connell B, Bernard P, Jarlier V, Williams Z, Henriksen AS. The EPISA study: antimicrobial susceptibility of *Staphylococcus aureus* causing primary or secondary skin and soft tissue infections in the community in France, the UK and Ireland. *J Antimicrob Chemother*. 2008 Mar; 61(3):586-588. Available from: www.ncbi.nlm.nih.gov/pubmed/18222949.

RATIONALE: A prospective study stating that, of *Staphylococcus aureus* isolates from the UK, only 75.6% were susceptible to fusidic acid. A diagnosis of impetigo was associated with reduced fusidic acid susceptibility. The authors conclude that differences in the prevalence of certain diagnoses, particularly impetigo, rather than differences in antibiotic consumption may explain some of the observed differences in the susceptibility seen between the 3 countries included in the study.

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

   RATIONALE: Expert consensus, recommending that oral antibiotics should be used for extensive, severe, or bullous impetigo, and that topical antibiotics should be reserved only for the treatment of very localised lesions. There are concerns that widespread use of topical fusidic acid will lead to increased resistance, rendering its use for severe staphylococcal infections, such as osteomyelitis, or MRSA, ineffective. If a topical antibiotic is used, a short 5 day course reduces exposure and the risk of resistance. Since few agents are effective against MRSA, mupirocin should be reserved for MRSA, and not used for other topical treatment of impetigo. For empirical treatment of impetigo, flucloxacillin should be used first line, because it is a narrow-spectrum antibiotic that is effective against Gram-positive organisms, including *Staphylococcus aureus*, unless MRSA. It also demonstrates suitable pharmacokinetics, with good diffusion into skin and soft tissue. Clarithromycin is recommended for people with penicillin allergy, as it is also active against most staphylococcal and streptococcal species.

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

   RATIONALE: A systematic review and meta-analysis of 68 trials and 5,578 participants, reporting on 50 different treatments, including placebo. Most trials were in primary impetigo, or did not specify. Topical antibiotic treatment showed better cure rates than placebo (RR 2.24; 95% CI 1.61 to 3.13) in 6 studies with 575 participants. In 4 studies with 440 participants, when topical antibiotics were compared (mupirocin ointment 2%, 3 times daily for 5 to 10 days, and fusidic acid cream gel 2%, 2 to 3 times daily for a maximum of 21 days) none were more effective than the others (RR 1.03; 95% CI 0.95 to 1.11). In 10 studies with 581 participants, topical mupirocin ointment 2%, 3 times daily for 5 to 10 days, was shown to be slightly superior to oral erythromycin 40mg/kg/day, across 3 doses for 7 days (RR 1.07; 95% CI 1.01 to 1.13). There were no significant differences in cure rates from treatment with topical versus other oral antibiotics. There were, however, differences in the outcome from treatment with different oral antibiotics: penicillin V 50mg/kg/day, across 4 doses for 10 days, was inferior to erythromycin 40mg/kg/day, across 4 doses for 10 days, in 2 studies with 79
   participants (RR 1.29; 95% CI 1.07 to 1.56), and cloxacillin 250-500mg, 4 times daily for 7 days, in 2 studies with 166 participants (RR 1.59; 95% CI 1.21 to 2.08). There was a lack of evidence for the benefit of using disinfectant solutions. When 2 studies with 292 participants were pooled, topical antibiotics were significantly better than disinfecting treatments (RR 1.15; 95% CI 1.01 to 1.32). The reported number of side-effects was low, and most of these were mild. Side-effects were more common for oral antibiotic treatment, compared to topical treatment. Gastrointestinal side-effects accounted for most of the

difference. Expert opinion is that, as topical mupirocin is the only topical antibiotic suitable for MRSA, this should be reserved for MRSA-associated infections. The authors conclude that there is good evidence that topical mupirocin and topical fusidic acid are equally, or more, effective than oral treatment. Due to the lack of studies in people with extensive impetigo, it is unclear if oral antibiotics are superior to topical antibiotics in this group. Fusidic acid and mupirocin are of similar efficacy; penicillin is not as effective as most other antibiotics. There is a lack of evidence to support disinfection measures to manage impetigo.

4. Clinical Knowledge Summaries (CKS). Impetigo. 2015 Jul. Available from:
    https://cks.nice.org.uk/impetigo#!topicsummary.
    RATIONALE: A CKS guideline, recommending oral flucloxacillin, 4 times daily for 7 days, as first line systemic treatment of impetigo. Oral clarithromycin 250-500mg twice daily for 7 days can be used if the patient is allergic to penicillins. This guideline states that, for topical antibiotic treatment, topical fusidic acid can be used alone, or in combination with systemic treatment, and should be applied thinly 3 to 4 times daily to uncovered lesions. Less frequent applications may be adequate for covered lesions. The summary states that extensive, severe or bullous infections usually require treatment with an oral antibiotic.

Cold sores:

1. Spurance SL, Nett R, Marbury T, Wolff R, Johnson J, Spaulding T. Acyclovir cream for the treatment of herpes simplex labialis: results of 2 randomized, double-blind, vehicle-controlled, multicenter clinical trials. *Antimicrob Agents Chemother*. 2002 Jul; 46(7):2238-2243. Available from: www.ncbi.nlm.nih.gov/pmc/articles/PMC127288/pdf/0797.pdf.
    RATIONALE: Two randomised controlled trials (n=1,385), in which healthy adults with a history of frequent herpes labialis were recruited from the general population, randomised equally to 5% aciclovir cream or vehicle control, given study medication, and told to self-initiate treatment 5 times daily for 4 days, beginning within 1 hour of the onset of a recurrent episode. In study 1, the mean duration of episodes was 4.3 days for patients treated with aciclovir cream, and 4.8 days for those treated with the vehicle control (HR 1.23; 95% CI 1.06 to 1.44; p=0.007). In study 2, the mean duration of episodes was 4.6 days for patients treated with aciclovir cream, and 5.2 days for those treated with the vehicle control (HR 1.24; 95% CI 1.06 to 1.44; p=0.006). Efficacy was apparent whether therapy was initiated early (prodrome or erythema lesion stage), or late (papule or vesicle stage). The authors conclude that there was a statistically significant reduction in the duration of lesion pain in both studies, and that aciclovir 5% cream reduces the mean duration and pain of an episode by about half a day.

2. Spurance SL, Rea TL, Thoming C, Tucker R, Saltzman R, Boon R. Penciclovir cream for the treatment of herpes simplex labialis. A randomized, multicenter, double-blind, placebo-controlled trial. Topical Penciclovir Collaborative Study Group. *JAMA*. 1997 May; 277(17):1374-1379. Available from: www.ncbi.nlm.nih.gov/pubmed/9134943.
    RATIONALE: A randomised controlled study, comparing the safety and efficacy of topical 1% penciclovir cream with vehicle control cream for the treatment of a recurrent episode of herpes simplex labialis in immunocompetent patients. Findings indicated that healing of

classical lesions was 0.7 days faster for penciclovir-treated patients, compared with those who received vehicle control cream (median 4.8 days penciclovir versus 5.5 days control; HR 1.33; 95% CI 1.18 to 1.49; p<0.001). Pain (median 3.5 days penciclovir versus 4.1 days control; HR 1.22; 95% CI 1.09 to 1.36; p<.001) and lesion virus shredding (median 3 days versus 3 days; HR 1.35; 95% CI 1.10 to 1.64; p=.003) also resolved more quickly for penciclovir-treated patients compared with patients who applied the vehicle control.

3. Raborn GW, Martel AY, Lassonde M, Lewis MA, Boon R, Spurance SL et al. Effective treatment of herpes simplex labialis with penciclovir cream: combined results of 2 trials. *J Am Dent Assoc.* 2002 Mar; 133(3):303-309. Available from: www.ncbi.nlm.nih.gov/pubmed/11934185.

   RATIONALE: Two randomised controlled trials (n=4,573), in which the efficacy and safety of topical 1% penciclovir cream and a placebo cream was compared. Time to loss of a classical lesion and the percentage of patients who had lost a classical lesion by days 6 and 8 were evaluated. Combined data revealed that penciclovir recipients lost classical lesions 31% faster than did placebo recipients (4.9 versus 5.5 days, respectively; HR 1.31; 95% CI 1.20 to 2.42; p=0.0001), and experienced 28% faster resolution of lesion pain (3.8 versus 4.3 days, respectively; HR 1.28; 95% CI 1.17 to 1.39; p=0.0001). Significant benefits were achieved with penciclovir use when treatment was initiated in the early stages (p=0.001) and later stages (p=0.0055). The authors conclude that penciclovir cream positively affects recurrent herpes simplex labialis, and dose frequency is vital to topical treatment. Even when penciclovir was applied late, it was effective in favourably altering the course of recurrent of herpes simplex labialis by a mean duration of 1 day.

4. Clinical Knowledge Summaries (CKS). Herpes simplex – oral. 2016 Oct. Available from: https://cks.nice.org.uk/herpes-simplex-oral#!topicsummary.

   RATIONALE: A CKS guideline, stating that oral herpes simplex virus is usually a mild, self-limiting infection that resolves within approximately 10 to 14 days, with HSV-1 being the cause in more than 90% of cases. Oral herpes simplex virus can, however, cause severe or life-threatening complications in some cases, particularly in immunocompromised people. This guideline recommends that oral prophylaxis can be prescribed if herpes simplex is frequent, severe or has predictable triggers. In this case, oral aciclovir 500mg 5 times daily for 5 days can be prescribed.

5. Arduino PG, Porter SR. Oral and perioral herpes simplex virus type 1 (HSV-1) infection: review of its management. *Oral Dis.* 2006 May; 12(3):254-270. Available from: www.ncbi.nlm.nih.gov/pubmed/16700734.

   RATIONALE: A review article in which it is stated that prophylaxis with oral antivirals may be of use for those with frequent, severe episodes, or predictable triggers, for example sunlight, or for immunocompromised individuals, as they are at higher risk of complications. Specialist advice should be sought if long-term prophylaxis is being considered. The authors conclude that systemic aciclovir may be effective in reducing the duration of symptoms of recurrent HSV-1 infection, but the optimal timing and dose of the treatment are uncertain. There is also evidence that prophylactic oral aciclovir may reduce the frequency and severity of recurrent attack of herpetic infection in immunocompromised patients, but the optimal timing and duration of treatment is uncertain and can vary in

different situations.

6. Chi C-C, Wang S-H, Delamere FM, Wojnarowska F, Peters MC, Kanjirath PP. Interventions for prevention of herpes simplex labialis (cold sores on the lips). *Cochrane Database Syst Rev.* 2015 Aug; 8:1-173. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010095.pub2/epdf.
    RATIONALE: A systematic review and meta-analysis of 32 randomised controlled trials, and a total of 2,640 immunocompetent participants. The evidence for short-term (less than 1 month) use of oral acyclovir in preventing recurrent herpes simplex labialis was inconsistent across the doses used in the studies, but was most effective when a 400mg twice daily dose, for 5 to 7 days was used (RR 0.36; 95% CI 0.13 to 0.51; n=177). The authors conclude that the current evidence demonstrates that long-term use of oral antiviral agents can prevent HSL, but the clinical benefit is small. There was no evidence demonstrating an increased risk of adverse events.

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

1. Holmes A, Ganner M, McGuane S, Pitt TL, Cookson BD, Kearns AM. *Staphylococcus aureus* isolates carrying Panton-Valentine leucocidin genes in England and Wales: frequency, characterization, and association with clinical disease. *J Clin Microbiol.* 2005 May; 43(5):2384-2390. Available from: www.ncbi.nlm.nih.gov/pmc/articles/PMC1153723/.
    RATIONALE: A prospective study in which the Staphylococcus Reference Unit tested 515 UK isolates of *Staphylococcus aureus* for PVL, of which only 8 (1.6%) were positive for the PVL locus. However, of 470 *S. aureus* isolates associated with clinical disease, 23 (4.9%) were PVL-positive. In abscesses, 7 of 16 (44%) were positive. The PVL genes were also detected in isolates responsible for community-acquired pneumonia, burn infections, bacteraemia, and scalded skin syndrome. This PVL is relatively rare overall, but much more common in patients with abscesses (20.8 to 46%).

2. Shallcross LJ, Williams K, Hopkins S, Aldridge RW, Johnson AM, Hayward AC. Panton- Valentine leukocidin associated staphylococcal disease: a cross-sectional study at a London hospital, England. *Clin Microbiol Infect.* 2010 Nov; 16(11):1644-1648. Available from: www.ncbi.nlm.nih.gov/pubmed/20969671.
    RATIONALE: A prospective, cross-sectional study, stating that there has been a rapid emergence of highly pathogenic strains of *Staphylococcus aureus*, associated with the toxin Panton-Valentine leukocidin (PVL). The strains are considered to be rare among healthy people, but mainly severe. In this study, 390 clinical *Staphylococcus aureus* isolates were collected from hospital and community specimens, and were investigated for the presence of the PVL genes. Results indicated that MRSA with PVL was rare (0.8% of all isolates), but MSSA with PVL was common (9% of all specimens). Results also suggested that PVL infection was more frequent in males (OR 3; 95% CI 1.3 to 7), and in young adults aged between 20 and 39 years (OR 3.7; 95% CI 1.3 to 10.4). The authors conclude that community-onset PVL-associated disease mainly causes skin and soft tissue infections.

3. Ellington MJ, Ganner M, Smith IM, Perry C, Cookson BD, Kearns AM. Panton-Valentine

leucocidin-related disease in England and Wales. *Clin Microbiol Infect.* 2010 Jan; 16(1):86-88. Available from: www.ncbi.nlm.nih.gov/pubmed/19681948.

> RATIONALE: A retrospective study, in which 720 PVL-SA isolates were identified during 2005 (n=224) and 2006 (n=496), demonstrating an almost 2-fold increase. PVL-SA was identified in individuals in previously recognised at risk groups, including: school children; nursing home residents; military service personnel; household contacts of individuals with PVL-SA disease; injecting drug users; men who have sex with men. The authors conclude that the data supports an increasing trend in PVL-SA, but this data is likely to reflect an underestimate of PVL-related disease, due to factors influencing case ascertainment.

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

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

Eczema:

1. Birnie AJ, Bath-Hextall FJ, Ravenscroft JC, Williams HC. Interventions to reduce *Staphylococcus aureus* in the management of atopic eczema (Review). *Cochrane Database Syst Rev.* 2008 Jul; 16(3):1-60. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003871.pub2/epdf.

> RATIONALE: A systematic review and meta-analysis, in which most randomised controlled trials identified were small, of poor quality, and heterogeneous. Oral antibiotics were not associated with benefit in 2 small trials of people with eczema without visible signs of infection (n=66). Adding antibiotics to topical steroids reduced the numbers of *Staphylococcus aureus* in 4 trials (n=302), but not in a further 9 trials (n=677).

2. National Institute for Health and Care Excellence (NICE). Atopic eczema in under 12s: diagnosis and management. 2016 Jul. Available from: www.nice.org.uk/Guidance/cg57.

> RATIONALE: A NICE guideline, covering the diagnosis and assessment of the impact of eczema, the management during and between flares, and information and education for children and their parents or carers about the condition. This guideline states that flucloxacillin should normally be the first line treatment for active *Staphylococcus aureus* and streptococcal infections, because it is active against both. Erythromycin or clarithromycin should be used when there is local resistance to flucloxacillin, and in children with penicillin allergy, as it is as effective as cephalosporins, less costly, and less likely to encourage resistance. Topical antibiotics, including those combined with topical corticosteroids, should be used to treat localised overt infection only, and for no longer than 2 weeks.

Leg ulcer:

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

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

2. O'Meara S, Al-Kurdi D, Ologun Y, Ovington LG, Martyn-St James M, Richardson R. Antibiotics and antiseptics for venous leg ulcers (Review). *Cochrane Database Syst Rev*. 2014 Jan; 1:1-156. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003557.pub5/pdf/standard.

   RATIONALE: An updated Cochrane review of 45 randomised controlled trials, established to determine the effects of systemic, topical antibiotics and antiseptics on the healing of venous leg ulcers. The authors state that the evidence does not currently support the routine use of systemic antibiotics in venous leg ulcers, especially with the increasing problem of bacterial resistance in the community. There is, however, some evidence in support of cadexomer iodine as a topical preparation. This review suggests that all wounds are colonised by bacteria and, at a certain level, some bacteria can cause significant infection and delay healing. The authors conclude that antibacterial preparations should only be used in cases of clinical infection, as bacterial colonisation alone is not considered adverse to healing.

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

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

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

   RATIONALE: A detailed guideline providing evidence-based recommendations on the management of venous leg ulcers. The guideline provides advice on the assessment of the leg, the importance of Doppler studies, and the use of dressings and compression in treating venous leg ulcers. SIGN recommend that ulcerated legs should be washed normally in tap water and carefully dried. This guideline clearly states that routine

bacteriological samples should not be taken in the absence of clinical infection (cellulitis; pyrexia; increased pain; rapid extension of area of ulceration; malodour; increased exudate). It is also advised that only patients with a non-healing or atypical venous leg ulcer should be referred for consideration of biopsy, and that colonisation of wounds does not necessarily mean that a wound is infected. Finally, this guideline states that antibiotics should not be started unless there is clear sign of clinical infection.

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

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

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

   RATIONALE: An editorial, stating that many chronic, poorly healing lesions get treated with antibiotics, despite the lack of evidence for long-term antimicrobial treatment. One of the only novel agents to reach clinical use is 1 using reactive oxygen species (ROS), oxygen radicals, as an antimicrobial mechanism. This editorial outlines the following 5 key points: reactive oxygen species is highly active against Gram-positive and negative organisms, with some viral and fungal activity; ROS can prevent biofilm formation and reduce existing biofilm activity; ROS has significant therapeutic implications for topical treatment of wounds, surgical cavities, respiratory tract and urinary mucosa; ROS is delivered by topical and local application; ROS can support infection prevention and antimicrobial stewardship. The author concludes that early clinical data supports ROS treatment in skin and soft tissue lesions to reduce bacterial bioburden and biofilm in critical colonisation, and in preventing surgical site infection. The approach is that the use of ROS in leg ulceration can reduce unnecessary antimicrobial prescribing for colonisation, and reduce the amount of time community nurses currently spend dressing and treating non-healing leg ulcers.

7. Dryden M, Cooke J, Salib R, Holding R, Pender SLF, Brooks J. Hot topics in reactive oxygen therapy: Antimicrobial and immunological mechanisms, safety and clinical applications. *J Glob Antimicrob Resist*. 2017 Mar; 8:194-198. Available from: www.ncbi.nlm.nih.gov/pubmed/28219826.

   RATIONALE: An editorial, stating that reactive oxygen species, when combined with various delivery mechanisms, has the potential to become a powerful novel therapeutic agent against difficult-to-treat infections, especially in those involving biofilm. ROS is rapidly active in vitro against all Gram-positive and Gram-negative bacteria tested, and also has antifungal and antiviral properties. ROS has successfully been used in infection prevention, eradication of multiresistant organisms, prevention of surgical site infection, and intravascular line care. For skin and soft tissue infections, 1 large observational study and 5 in vitro studies have recorded a reduction in bacterial load and biofilm, and healing has been promoted with the use of ROS. The authors conclude that this antimicrobial mechanism has great potential for the control of bioburden and biofilm at many sites. However, well-designed randomised controlled studies are needed to clearly demonstrate the effectiveness of its use.

Acne:

1. Clinical Knowledge Summaries (CKS). Acne vulgaris. 2014 Sep. Available from: http://cks.nice.org.uk/acne-vulgaris#!topicsummary.

   RATIONALE: A CKS guideline, recommending that people with acne should: not wash more than twice daily; use a mild soap or cleanser and lukewarm water; not use vigorous scrubbing when washing acne-affected skin; not attempt to 'clean' blackheads; avoid excessive use of makeup and cosmetics; use fragrance-free, water-based emollient if dry skin is a problem. This guideline states that topical retinoids normalise follicular keratinisation, promote drainage of comedones, and inhibit new comedone formation. Benzoyl peroxide is a potent bactericide and significantly reduces the population of Propionibacterium acnes in the sebaceous follicle. There is good evidence from placebo-controlled trials that benzoyl peroxide reduces both inflammatory and non-inflammatory lesions. Due to its bactericidal properties, benzoyl peroxide produces rapid improvement in inflammatory lesions and prevents the development of antibiotic resistance. Topical antibiotics are recommended as they are especially effective in reducing the number of inflammatory lesions. There is a lack of evidence from comparative randomised controlled trials to show that any particular topical antibiotic has an advantage over another. It is thought that monotherapy with antibiotics can lead to resistance, not only in Propionibacterium acnes, but also in other potentially pathogenic bacteria, especially certain strains of *Staphylococcus aureus*, coagulase-negative staphylococci, and Group A streptococci, which can lead to both therapeutic failure of acne and bacterial resistance. Monotherapy with antibiotics should be strongly discouraged; antibiotics should be combined with retinoids and/or benzoyl peroxide. Treatment with a topical antibiotic should be limited to 12 weeks' duration where possible, to reduce the risk of resistance developing. Oral antibiotics are universally recommended by experts for the treatment of severe acne, or extensive acne that would be difficult to treat with a topical drug. Oral tetracyclines are recommended first line as it is effective at reducing lesion counts and severity. Oral erythromycin should be reserved for use when tetracyclines

are contraindicated. There is a lack of evidence from placebo-controlled trials to verify the efficacy of erythromycin, although evidence from comparative trials indicate that it is probably as effective as tetracyclines. This guideline indicates that anyone presenting with severe acne should be referred to a specialist, and that treatment with topical retinoids and benzoyl peroxide should be continued for at least 6 weeks.

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

   RATIONALE: A PCDS guideline outlining the aetiology, diagnosis, classification, and treatment regimens for acne vulgaris. This guideline suggests that anyone with severe acne should be referred immediately, and that topical preparations containing benzoyl peroxide and/or topical retinoids are an essential part of treatment. This guideline states that there is little additional benefit in using antibiotics for more than 3 months, as prolonged use increases the resistance of Propionibacterium acnes. It is therefore recommended that antibiotics should be stopped after 3 months; however, the patient should remain on their topical agent. If the patient does not respond to 2 types of antibiotics, especially if they are starting to scar, the patient should be referred for consideration of isotretinoin.

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

   RATIONALE: A systematic review and meta-analysis of 5 systematic reviews and 64 randomised controlled trials. The authors advise that topical benzoyl peroxide 5% twice to 4 times daily or a topical retinoid once daily should be considered as first line treatment in mild acne. Topical benzoyl peroxide 5% and topical azelaic acid 20% reduce inflammatory and non-inflammatory lesions compared with placebo, but can cause itching, burning, stinging, and redness of the skin. Topical antibiotics such as clindamycin 1% and erythromycin 2% (alone or with zinc) reduce inflammatory lesions compared with placebo, but have not been shown to reduce non-inflammatory lesions. This review references several studies indicating development of antibiotic resistance to *Propionibacterium acnes* when using topical application or oral antibiotics for acne treatment. *(Cooper AJ. Systematic review of Propionibacterium acnes resistance to systemic antibiotics. Med J Aust 1998;169:259–261. Search date 1998. [PubMed] and Simonart T, Dramaix M. Treatment of acne with topical antibiotics: lessons from clinical studies. Br J Dermatol 2005;153:395–403.[PubMed])*. Tetracycline may reduce overall acne severity, but may cause skin discoloration, and should be avoided in pregnant or breastfeeding women. Antimicrobial resistance can develop with the use of topical or oral antibiotics, and their efficacy may decrease over time. Topical preparations of tretinoin 0.025%, adapalene 0.1% daily, and isotretinoin 0.05% may reduce inflammatory and non-inflammatory lesions, but can also cause redness, burning, dryness, and soreness of the skin. Oral antibiotics, including doxycycline 100mg daily, erythromycin 500mg twice daily, minocycline 1, 2, or 3/mg/kg/day, oxytetracycline 500mg twice daily, and tetracycline 500mg twice daily for a maximum of 3 months are considered useful for people with more severe acne. Adverse effects in the RCTs involving oral doxycycline, tetracycline, and erythromycin reported no or few withdrawals and adverse events were low and usually gastrointestinal. The review reported side effects with minocycline in 13.6%, with increased risk of pigmentation and SLE; the review suggests that people taking

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minocycline for more than 6 months should be monitored for hepatotoxicity, pigmentation, and SLE. All these oral antibiotics can cause contraceptive failure. The systematic review showed evidence that erythromycin was effective, but stated some concerns about bacterial resistance. *PHE prefers that a tetracycline is used before a macrolide, as resistance of staphylococci, pneumococci and streptococci to macrolides is more of a problem in countries with high macrolide use.*

4. Tan J, Humphrey S, Vender R, Barankin B, Gooderham M, Kerrouche N et al. A treatment for severe nodular acne: a randomized investigator-blinded, controlled, noninferiority trial comparing fixed-dose adapalene/benzoyl peroxide plus doxycycline vs. oral isotretinoin. *BJD*. 2014 Oct; 171(6):1508-1516. Available from: http://onlinelibrary.wiley.com/doi/10.1111/bjd.13191/abstract.

 RATIONALE: A multicentre, randomised controlled trial involving 266 subjects, aiming to compare the efficacy and safety of oral isotretinoin versus doxycycline 200mg plus benzoyl peroxide 2.5% gel in severe nodular acne over 20 weeks. Doxycycline plus benzoyl peroxide showed a significantly earlier onset of action in reducing nodules, pustules, and total lesions at week 2, whereas oral isotretinoin was superior at week 20. Doxycycline plus benzoyl peroxide was noninferior to oral isotretinoin in the intent-to-treat population (95% CI 2.7 to 20.8; p=0.13) and per-protocol population (95% CI 3.9 to 28.6; p=0.01), based on the composite efficacy/safety end point. The authors conclude that doxycycline plus benzoyl peroxide showed a favourable composite efficacy/safety profile compared with oral isotretinoin, and can be used as an alternative in patients intolerant to oral isotretinoin as an option for treatment of severe nodular acne.

Cellulitis and erysipelas:

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

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

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suspected following river or sea water exposure, management and treatment advice should be sought from a specialist.

2. British Lymphology Society. Consensus document on the management of cellulitis in lymphoedema. 2015 Apr. Available from:
www.lymphoedema.org/images/pdf/CellulitisConsensus.pdf.

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

3. Ferreira A, Bolland MJ, Thomas MG. Meta-analysis of randomised trials comparing a penicillin or cephalosporin with a macrolide or lincosamide in the treatment of cellulitis or erysipelas. *Infection*. 2016 Oct; 44(5):607-615. Available from:
www.ncbi.nlm.nih.gov/pubmed/27085865.

RATIONALE: A systematic review of 15 studies: 9 in patients with cellulitis or erysipelas; 6 in patients with various skin and soft tissue infections. The efficacy of treatment of cellulitis or erysipelas was similar with a beta-lactam and a macrolide or lincosamide (RR 1.24; 95% CI 0.72 to 2.41; p=0.44). Treatment efficacy was also similar for skin or soft tissue infections, including cellulitis and erysipelas (RR 1.28; 95% CI 0.96 to 1.69; p=0.09). Risk of adverse effects were also similar for beta-lactams and macrolides or lincosamides (RR 0.86; 14% difference; 95% CI 0.64 to 1.16; p=0.31).

4. Brindle R, Williams OM, Davies P, Harris T, Jarman H, Hay AD, et al. Adjunctive clindamycin for cellulitis: a clinical trial comparing flucloxacillin with or without clindamycin for the treatment of limb cellulitis. BMJ Open. 2017;7(3):e013260. Available from:
https://bmjopen.bmj.com/content/bmjopen/7/3/e013260.full.pdf

This parallel, double-blinded, randomized controlled trial compared flucloxacillin at a minimum of 500 mg 4 times per day for 5 days, with clindamycin 300 mg 4 times per day for 2 days given orally versus flucloxacillin given alone, in 410 emergency department attendances and general practice referrals within 20 hospitals in England. This study was designed to test the hypothesis that a toxin-inhibiting antibiotic, of which clindamycin is the exemplar, is effective in streptococcal infections. The primary outcome was improvement at day 5. No significant difference was seen in improvement (defined as being afebrile with either a reduction in affected skin surface temperature or a reduction in the circumference of the affected area) at day 5 for flucloxacillin with clindamycin (136/156, 87%) versus flucloxacillin alone (140/172, 81%)-OR 1.55 (95% CI 0.81 to 3.01), p=0.174. Diarrhoea is significantly higher at day 5 in the flucloxacillin with clindamycin allocation (34/160, 22%) versus flucloxacillin alone (16/176, 9%)-OR 2.7 (95% CI 1.41 to 5.07), p=0.002. There was no clinically significant difference in any secondary outcome measures including resolution of systemic features, resolution of inflammatory markers, recovery of renal function, reduction in the affected area, decrease in pain, return to work or normal

activities and the absence of increased side effects. The addition of a short course of clindamycin to flucloxacillin early on in limb cellulitis does not improve outcome. The addition of clindamycin doubles the likelihood of diarrhoea within the first few days. Therefore we no longer recommend the addition of clindamycin in severe or un-resolving cases.

5. Bruun T, Oppegaard O, Kittang BR, Mylvaganam H, Langeland N, Skrede S. Etiology of cellulitis and clinical prediction of streptococcal disease: a prospective study. *Open Forum Infect Dis*. 2015 Nov; 3(1):181-189. Available from: www.ncbi.nlm.nih.gov/pubmed/26734653.

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

6. Kilburn SA, Featherstone P, Higgins B, Brindle R. Interventions for cellulitis and erysipelas (Review). *Cochrane Database Syst Rev*. 2010 Jun; 16(6):1-72. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004299.pub2/epdf.

    RATIONALE: A systematic review and meta-analysis of 25 studies, with a total of 2,488 participants. It was commonly reported that symptoms were rated by the participant or medical practitioner as symptom-free. No 2 trials examined the same antibiotics; therefore the review grouped similar types of drugs together. Three studies (n=88) comparing a penicillin for 7 days with a cephalosporin for ten days showed no difference in treatment effect (RR 0.99; 1% reduction; 95% CI 0.68 to 1.43). Macrolides (azithromycin or erythromycin 250-500mg for 5 to 7 days)/streptogramins (oral pristinamycin 1g three times daily for 14 days) were found to be more effective than penicillins for 7 days (RR 0.84; 16% reduction; 95% CI 0.73 to 0.97). In 2 trials (n=419), an oral macrolide for 5 to 7 days was compared with intravenous penicillin, which demonstrated that oral therapies can be more effective than IV therapies (RR 0.85; 15% reduction; 95% CI 0.73 to 0.98). However, the authors conclude that this warrants further study.

7. Fisher RG, Benjamin DK Jr. Facial cellulitis in childhood: a changing spectrum. *South Med J*. 2002 Jul; 95(7):672-674. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12144069.
    RATIONALE: A retrospective study stating that buccal cellulitis is commonly due to infection with *Haemophilus influenzae*, although rates are decreasing. Trauma was the most common antecedent to facial cellulitis. Co-amoxiclav is recommended for empirical treatment of facial cellulitis, as it is broader spectrum than flucloxacillin, and also covers anaerobes and other less common causes of facial cellulitis.
    NB See dental section for advice around dental-associated swelling.

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Bites:

1. Medeiros I, Saconato H. Antibiotic prophylaxis for mammalian bites (Review). *Cochrane Database Syst Rev.* 2001 Apr; 2:1-20. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001738/epdf

   RATIONALE: A systematic review and meta-analysis, in which only 1 trial (n=48) analysed human bites. The infection rate in the antibiotic group, who received either cefaclor 250mg 3 times daily, cefazolin 1g 4 times daily intravenously, or benzylpenicillin 1.2 million units 4 times daily intravenously, (0%) was significantly lower than the infection rate in the control group (47%; OR 0.02; 98% lower; 95% CI 0.00 to 0.33). For dog bites, pooled results from 6 randomised controlled trials (n=463) found that the infection rate was not reduced after the use of prophylactic antibiotics (phenoxymethylpenicillin 250mg 4 times daily for 5 days, erythromycin 500mg 4 times daily for 7 days, oxacillin 500mg 4 times daily for 5 days, or dicloxacillin 250mg 4 times daily; 4%) compared with the control group (5.5%; OR 0.74; 26% difference; 95% CI 0.30 to 1.8). For cat bites, 1 very small study (n=11) reported a lower infection rate in the treatment group who received prophylactic antibiotics (0%) compared with the control group (67%). The authors conclude that there is evidence that the use of antibiotic prophylaxis after bites of the hand reduces infection. Prevention of tetanus and rabies where appropriate, together with adequate cleansing of such wounds, are also universally accepted measures of managing bite wounds.

2. Clinical Knowledge Summaries (CKS). Bites – human and animal. 2015 Jul. Available from: http://cks.nice.org.uk/bites-human-and-animal#!topicsummary

   RATIONALE: A CKS guideline stating that thorough irrigation with warm, running water is vital for the management of a human or animal bite. Antibiotic prophylaxis should be given for all human bite wounds under 72 hours old, even if there are no signs of clinical infection. Prophylaxis for animal bites is not required unless: it is a bite to the hand, foot, or face; puncture wounds; all cat bites; wounds requiring surgical debridement; wounds involving joints, tendons, ligaments, or suspected fractures; wounds that have undergone primary closure; wounds to people who are at risk of serious wound infection (for example those who are diabetic, cirrhotic, asplenic, immunosuppressed, or people with a prosthetic valve or prosthetic joint). This guideline also provides treatment and dosing regimens for human and animal bites. Co-amoxiclav is recommended for both prophylaxis and treatment of all bites, as it is a broad-spectrum antibiotic, and effective against most bacteria isolated from human and domestic animal bites. For human bites in those with penicillin allergy, metronidazole 400mg 3 times daily plus clarithromycin 250-500mg twice daily for 7 days is recommended. For animal bites, metronidazole 400mg 3 times daily plus doxycycline 100mg twice daily for 7 days is recommended.

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

   RATIONALE: Expert consensus, recommending that the risk of tetanus, rabies, HIV and hepatitis B and C should be assessed in all human bites. Co-amoxiclav 375-625mg 3 times daily, for 7 days, is recommended for the 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 bite wounds. For those with human bites and penicillin

allergy, metronidazole plus either doxycycline or clarithromycin are recommended. Metronidazole is included to cover anaerobes, and both doxycycline and clarithromycin are active against both staphylococci and streptococci. Doxycycline is also active against Eikenella species: another common pathogen isolated from human mouths. For those with animal bites and penicillin allergy, metronidazole plus doxycycline is recommended, as these cover anaerobes, Pasteurella species, staphylococci and streptococci. Macrolides are not recommended for animal bites, as they do not adequately cover Pasteurella species. Specialist advice should be sought for children under the age of 12 years. People with penicillin allergy should be reassessed at 24 and 48 hours after starting a course of antimicrobial treatment, as the recommended regimen covers the majority, but not all, of the likely pathogens from human and animal bites.

4. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014 Jun; 59(2):10-52. Available from: http://cid.oxfordjournals.org/content/early/2014/06/14/cid.ciu296.

RATIONALE: An IDSA guideline, providing detailed advice on the treatment of human and animal bites, and emphasising the important of promptly diagnosing SSTIs, identifying the pathogen, and administering effective treatments. Where pre-emptive treatment of animal and human bite wounds is concerned, the author's recommendations include pre-emptive early antimicrobial therapy for 3 to 5 days for patients who: are immunocompromised; are asplenic; have advanced liver disease; have pre-existing or resultant oedema of the affected area; have moderate to severe injuries, especially to the hands or face; have injuries that may have penetrated the periosteum or joint capsule. Prophylactic or early pre-emptive therapy seems to provide only marginal benefit to wound care for patients with dog bites who present within 12 to 24 hours after injury, particularly in those: with low-risk wounds; that are not associated with puncture wounds; with no history of an immunocompromising disorder or use of immunosuppressive drugs; with wounds not involving the face, hand, or foot. The authors conclude that antibiotics reduce the risk of infection in dog bite wounds but suggest limiting this to 'high risk' wounds. For infected wounds, the authors recommend antimicrobial agents active against both aerobic and anaerobic bacteria, such as amoxicillin-clavulanate. Purulent bite wounds and abscesses are more likely to be polymicrobial, whereas nonpurulent wounds commonly yield staphylococci and streptococci. Pasteurella species are commonly isolated from both nonpurulent wounds, with or without lymphangitis, and from abscesses. Unless no alternative agents are available, macrolides should be avoided for prophylaxis and treatment of animal bites, due to variable activity against *Pasteurella multocida* and fusobacteria. Human bites may occur from accidental injuries, purposeful biting, or closed- fist injuries. The bacteriologic characteristics of these wounds are complex, but include aerobic bacteria, such as streptococci, *Staphylococcus aureus*, and *Eikenella corrodens*, as well as with multiple anaerobic organisms, including Fusobacterium, Peptostreptococcus, Prevotella, and Porphyromonas species. *Eikenella corrodens* is resistant to first-generation cephalosporins, macrolides, clindamycin, and aminoglycosides; therefore, treatment with amoxicillin-clavulanate is recommended. If there is history of hypersensitivity to beta-lactams, a fluoroquinolone, such as ciprofloxacin plus metronidazole is recommended.

5. Morgan M, Palmer J. Dog bites. *BMJ.* 2007;334(7590):413-417. Available from: www.bmj.com/content/334/7590/413

> RATIONALE: This useful overview of the treatment of dog bites includes reference to a meta-analysis undertaken in 1994. The article summarises the key points: wound management is as important as use of antimicrobials; for patients considered to be at higher risk of infection (alcoholism, immunosuppression especially <u>cirrhosis</u>, <u>asplenia</u>, or post mastectomy, oral steroids, rheumatoid arthritis, diabetes, lymphoeodema after radiotherapy) or those with wound factors (wound over 6 hours old, devitalised tissue, previously sutured wounds, full thickness wounds involving tendons, ligaments and joints, bites on limbs especially hands) the prophylaxis of choice is co-amoxiclav. Erythromycin or flucloxacillin should never be used alone prophylactically as *Pasteurella* infection is usually resistant; infected wounds presenting within 12 hours of injury are usually due to *Pasteurella multocida*. This review recommends that pregnant women with a history of rash after penicillin should be offered ceftriaxone. *PHE recommends 1-2 grams daily dependent on the severity of the infection (BNF 2018).*

Scabies:

1. Sashidharan PN, Basavaraj S, Bates CM. UK National Guideline on the management of scabies. Clinical Effectiveness Group British Association for Sexual Health and HIV. 2016. Available from: www.bashhguidelines.org/media/1137/scabies-2016.pdf

> RATIONALE: This guidance gives extensive evidence based advice on the recommended management of scabies and its treatment, although it notes that there are no trials on the treatment of Malathion. Patients should not use permethrin if they are allergic to chrysanthemums. The guidance gives advice on application of permethrin: apply to the whole body from the chin and ears downwards paying special attention to the areas between the fingers and toes and under the nails. In immunosuppressed the very young and elderly people permethrin should be applied to the whole body including the scalp and face. Apply treatment to cool dry skin, not after a hot bath. Allow the cream to dry before dressing, and put on clean clothing after treatment. Wash cream off after 8 to 12 hours, and reapply 1 week later. If hands are washed with soap within 8 hours of application, they should be treated again with cream. Larger patients may need up to 2 30g packs for adequate treatment. Current sexual partners and members of the same household with close contact should be examined and treated at the same time. Contact close partners for previous month. New burrows at any stage post treatment indicate the need for repeat treatment. Pruritus more than 2 weeks after treatment may reflect treatment failure, reinfection or drug allergy to the anti-scabetic.

2. Medicines.org. *Lyclear Dermal Cream*. Available from: www.medicines.org.uk/EMC/medicine/10439/SPC/Lyclear+Dermal+Cream/ [Accessed: 20 September, 2016].

> RATIONALE: An EMC webpage stating that Lyclear 5% Dermal Cream is indicated for the treatment of scabies in adults and children over 2 months of age. Adults and adolescents over 12 years of age should apply up to 30g of cream; children aged from 6 to 12 years should apply up to 15g of cream; children aged from 2 months to 5 years should apply up

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to 7.5g of cream. Cream should be applied uniformly to the whole body, including the neck, palms of the hands, and soles of the feet. The head and face can be spared, unless scabies efflorescences are present in this region. On application, the areas between the fingers and toes (also under the finger and toenails), the wrists, elbows, armpits, external genitalia, and the buttocks, should be especially carefully treated.

3. Strong M, Johnstone P. Interventions for treating scabies (Review). *Cochrane Database Syst Rev*. 2007 Jul; 18(3):1-74. Available from:
   http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000320.pub2/epdf.
   RATIONALE: A systematic review and meta-analysis of 20 studies, involving 2,392 children and adults undergoing drug treatment for scabies. One trial was placebo controlled, 18 compared 2 or more drug treatments, 3 compared treatment regimens, and 1 compared different drug vehicles. 19 of the 22 studies included were conducted in resource-poor countries, although 1 was a large multicentre trial involving 8 centres in Mexico and the USA (4 sexually transmitted disease clinics, 2 dermatology clinics, and 2 family practice clinics). Results indicated that fewer treatment failures occurred by day 7 with oral ivermectin, compared with placebo (n=55); topical permethrin (5% cream) appeared more effective than oral ivermectin 200 µg/kg bodyweight single dose (n=140), topical crotamiton (n=194), and topical lindane (n=753); permethrin appeared more effective in reducing itch persistence than crotamiton (n=94), and lindane (n=490); no significant differences were detected between permethrin and a natural pyrethrin-based topical treatment (n=40), or between permethrin and benzyl benzoate (n=53). The authors conclude that topical permethrin is significantly more effective than oral ivermectin, topical crotamiton, and topical lindane (RR 0.32; 68% reduction; 95% CI 0.13 to 0.75; n=735). There were no studies on the effectiveness of malathion. More research is required on the effectiveness of malathion, particularly when compared with permethrin, as no trials were identified.

Mastitis:

1. Spencer JP. Management of mastitis in breastfeeding women. *Am Fam Phys*. 2008 Sep; 78(6):727-731. Available from: www.aafp.org/afp/2008/0915/p727.pdf.
   RATIONALE: A review article defining mastitis as localised, painful inflammation of the breast, occurring in conjunction with flu-like symptoms. When antibiotics are needed, those effective against *Staphylococcus aureus* are preferred, as this organism is responsible for most cases of mastitis. This article states that, in breastfeeding women, continued breastfeeding should be encouraged in the presence of mastitis, and generally does not pose a risk to the infant. As the mother and infant are usually colonised with the same organisms at the time mastitis develops, breastfeeding can continue during an episode of mastitis without worry of the bacterial infection being transmitted to the infant.

2. Clinical Knowledge Summaries (CKS). Mastitis and breast abscess. 2015 Aug. Available from: http://cks.nice.org.uk/mastitis-and-breast-abscess#!topicsummary.
   RATIONALE: A CKS guideline defining mastitis as a painful inflammatory condition of the breast, which may or may not be accompanied by infection. This guideline recommends that mastitis should be suspected if a woman has: a painful breast; fever and/or general

malaise; a tender, red, swollen, and hard area of the breast, usually in a wedge-shaped distribution. Finally, this guideline recommends the following for first line management of a woman with mastitis not requiring urgent admission or referral: offering reassurance that the breast should return to normal following appropriate treatment; advising on measures to relieve pain and discomfort, such as the use of simple analgesics and applying a warm compress to the breast; encouraging breastfeeding women to continue feeding if possible, including from the affected breast; identifying and managing predisposing factors for mastitis, where possible, including poor infant attachment to the breast, nipple damage, smoking, and/or an underlying breast abnormality; prescribing oral antibiotics if indicated; offering appropriate advice on measures to prevent recurrence, such as encouraging good breastfeeding technique and maintaining good hygiene. The first line treatment regimens suggested for lactating women are: flucloxacillin 500mg 4 times daily for 10 to 14 days, or in penicillin allergy, erythromycin 250-500mg 4 times daily, or clarithromycin 500mg twice daily for 10 to 14 days.

3. Jahanfar S, Ng CJ, Teng CL. Antibiotics for mastitis in breastfeeding women (Review). *Cochrane Database Syst Rev*. 2013 Feb; 28(2):1-29. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005458.pub3/epdf.
   RATIONALE: A small systematic review and meta-analysis of 2 trials, aiming to examine the effectiveness of antibiotic therapies in relieving symptoms for breastfeeding women with mastitis. One trial (n=25) compared amoxicillin 500mg 3 times daily for 7 days with cephradine 500mg 3 times daily for 7 days and found no significant difference between the 2 antibiotics in terms of symptom relief and abscess formation. Another study (n=213) compared breast emptying versus antibiotic therapy plus supportive therapy, and no therapy. The findings suggest faster clearance of symptoms for women using antibiotics, compared to the other treatment arms.

Dermatophyte infection – skin:

1. Public Health England (PHE). Fungal skin and nail infections: quick reference guide. 2017 Jun. Available from: www.gov.uk/government/publications/fungal-skin-and-nail-infections-diagnosis-and-laboratory-investigation.
   RATIONALE: A PHE guideline emphasising the importance of sending skin scrapings to confirm diagnosis of fungal infections before starting oral antibiotics. The authors recommend terbinafine, as it is fungicidal and has a shorter treatment time, instead of azole, which is fungistatic and takes longer to treat. This guideline also states that scalp infections should be discussed with a specialist.

2. Crawford F, Hollis S. Topical treatments for fungal infections of the skin and nails of the foot (Review). *Cochrane Database Syst Rev*. 2007 Jul; 18(3):1-11. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001434/full.
   RATIONALE: A systematic review and meta-analysis, in which pooled data from 11 randomised controlled trials specifically focussed on fungal skin, not nail, infection (n=962). This review covered 3 azoles: bifonazole; clotrimazole; miconazole, and two allylamines: naftifine; 1% terbinafine. Where stated, the concentration was 1%, and the frequency of treatment was once or twice daily, for 4 or more weeks. The pooled relative risk of failure to cure was 0.88 (12% risk; 95% CI 0.78 to 0.99), significantly favouring the

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allylamines naftifine or terbinafine (12% lower). The authors conclude that, in placebo-controlled trials, allylamines, azoles, and undecenoic acid are efficacious in treating dermatophyte skin infections. At 6 weeks, in 5 trials, 1% terbinafine for 1 week had similar outcomes to 1% clotrimazole and miconazole used for 4 weeks (RR treatment failure 0.75; 25% difference; 95% CI 0.33 to 1.72). Two trials followed patients for more than 12 weeks, and found that, when measuring treatment failure, terbinafine
was favoured (RR 0.47; 53% increase; 95% CI 0.22 to 1.02), but this did not quite reach statistical significance. When 1% terbinafine for 4 to 6 weeks was compared with 1% azoles for 4 to 6 weeks (8 trials; n=962), there was 37% less treatment failure from terbinafine (RR 0.63; 95% CI 0.42 to 0.94). Longer 4 week courses of clotrimazole were definitely more effective than 1 week, but 4 and 1 week terbinafine had similar efficacy; the trials were, however, small. All antifungal compounds demonstrated some success in curing athlete's foot. The best results were observed with the use of allylamines (terbinafine), which are now available over the counter. There is a small amount of evidence that butenafine may be similarly good. Azoles are also very effective, and participants should be advised that although all azoles appear to be similarly effective, using an azole cream for 4 weeks is likely to produce better results than using it for 1 week. Azoles may also be more efficacious than tolnaftate, but they seem no more efficacious than undecenoic acid.

3. Bell-Syer SE, Hart R, Crawford F, Torgerson DJ, Tyrell W, Russell I. Oral treatments for fungal infections of the skin of the foot (Review). *Cochrane Database Syst Rev*. 2012 Apr; 2:1-41. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003584/epdf.
RATIONALE: A systematic review and meta-analysis of 15 trials, involving 1,438 participants. One RCT (n=41) found that oral terbinafine 250mg daily for 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 (RR of cure with terbinafine 25; 95% CI 2 to 384). One RCT (n=77) found that oral itraconazole 400mg daily 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). Pooled data from 3 RCTs (n=222) found no difference in cure rates between oral terbinafine 250mg daily for 2 weeks (76% cured), and itraconazole 100mg daily for 4 weeks (71% cured; RD 5%; 95% CI -6 to 27).

4. Medicines.org. *Lamisil AT 1% Cream*. Available from:
www.medicines.org.uk/emc/medicine/21036 [Accessed: 20 September, 2016].
RATIONALE: An EMC webpage recommending Lamisil AT 1% Cream for the treatment of tinea pedis (athlete's foot) and tinea cruris (dhobie itch/jock itch), caused by Trichophyton (for example *T. rubrum*; *T. mentagrophytes*; *T. verrucosum*; *T. violaceum*) and *Epidermophyton floccosum*. Terbinafine cream is not licensed for the treatment of candida infection.

5. Primary Care Dermatology Society (PCDS). Tinea manuum (hands), pedis (feet), and unguium (nails). 2015 Oct. Available from: www.pcds.org.uk/clinical-guidance/tinea-pedis-feet-manuum-hands-and-unguium-nails.
RATIONALE: A PCDS guideline on the diagnosis and management of tinea. For tinea manuum, treatment is with a topical antifungal agent, for example terbinafine cream, for 1

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to 2 weeks, or 1 of the imidazole creams, such as miconazole, for 2 to 4 weeks. Terbinafine is more expensive but slightly more effective. Systemic/oral treatment should be used if there is co-existent nail involvement; in which case, treat as per tinea unguium. For tinea pedis with interdigital involvement or fine scaling, treatment should be the same as for tinea manuum. Topical treatments need to involve the soles of the feet as well as the interdigital spaces. Systemic treatment should be used if there is co-existent nail involvement; in which case, treat as per tinea unguium. Recurrence is common, and patients need to be advised to keep feet well aerated by wearing breathable footwear and leaving shoes off around the home. Prophylactic treatment with topical antifungals used once to twice a week can help.

6. Fuller LC, Barton RC, Mohd Mustapa MF, Proudfoot LE, Punjabi SP, Higgins EM. British Association of Dermatologists' guidelines for the management of tinea capitis 2014. *Br J Dermatol*. 2014 Sep; 171(3):454-463. Available from: http://onlinelibrary.wiley.com/doi/10.1111/bjd.13196/epdf.

   RATIONALE: A British Association of Dermatologists' guideline recommending that oral therapy is generally required to eradicate tinea capitis. The authors suggest that it is reasonable to begin treatment on the basis of 1 or more cardinal signs, whilst awaiting confirmatory mycology. Clear evidence has now emerged to show that the optimal treatment regimen varies according to the dermatophyte involved. Treatment protocols should therefore reflect local epidemiology, and be based on the most likely culprit organism. A prolonged course, or a change of agent, may be required in cases of treatment failure, or if an unexpected fungus is identified on culture. The definitive end point for adequate treatment must be mycological cure, rather than clinical response.

Dermatophyte infection – nail:

1. Roberts DT, Taylor WD, Boyle J, British Association of Dermatologists. Guidelines for treatment of onychomycosis. *Br J Dermatol*. 2003 Mar; 148(3):402-410. Available from: www.ncbi.nlm.nih.gov/pubmed/12653730.

   RATIONALE: A British Association of Dermatologists guideline stating that only 50% of cases of nail dystrophy are fungal, and it is not easy to identify these clinically. The length of treatment needed (6 to 12 months) is too long for a trial of therapy. Treatment should not be commenced before mycological confirmation of infection, through taking nail clippings. Dermatophytes are by far the commonest causal organisms. Culture of yeasts and non-dermatophyte moulds should be interpreted carefully in each individual case. In the majority of cases, yeasts are likely to be a secondary infection, and non-dermatophyte moulds to be saprophytic in previously damaged nails. Topical nail lacquer treatment is inferior to oral treatment in all but a small number of cases of very distal nail infection. Terbinafine is superior to itraconazole, both in vitro and in vivo, for dermatophyte onychomycosis, and should be considered as first line treatment, with itraconazole as the next best alternative. Terbinafine is licensed at a dose of 250 mg daily for 6 weeks and 12 weeks in fingernail and toenail infection, respectively. Itraconazole is licensed at a dose of 200 mg daily for 12 weeks continuously, or alternatively at a dose of 400 mg daily for 1 week per month. It is recommended that 2 of these weekly courses, 21 days apart, are given for fingernail infections and 3 courses for toenail disease. Cure rates of 80 to 90% for fingernail infection and 70 to 80% for toenail infection can be expected. In cases

of treatment failure, the reasons for such failure should be carefully considered. In such cases, either an alternative drug, or nail removal, in combination with a further course of therapy to cover the period of regrowth, should be considered.

2. Ferrari J. Fungal toenail infections. *BMJ Clin Evid*. 2011 Aug;17(15):1-24. Available from: www.ncbi.nlm.nih.gov/pmc/articles/PMC3275109/pdf/2011-1715.pdf.

    RATIONALE: A systematic review and meta-analysis comparing antifungal treatment for toenail infections. One systematic review pooled data from 2 randomised 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 daily for 12 weeks (69%), compared with oral itraconazole 200mg daily for 12 weeks (48%) (RR 21% reduction; 95% CI 13% to 29%). Four small RCTs were identified that found no statistically significant difference between continuous and pulsed itraconazole for dermatophyte onychomycosis.

3. Chang CH, Young-Xu Y, Kurth T, Orav JE, Chan AK. The safety of oral antifungal treatments for superficial dermatophytosis and onychomycosis: a meta-analysis. *Am J Med.* 2007 Sep; 120(9):791-798. Available from: www.ncbi.nlm.nih.gov/pubmed/17765049.

    RATIONALE: A systematic review and meta-analysis pooling data from about 20,000 participants, which found that both continuous and pulse therapy with terbinafine, itraconazole, or fluconazole were well tolerated. The risk of having asymptomatic raised liver transaminases was less than 2% for all treatments. The risk of having raised liver transaminases that required treatment discontinuation with continuous treatment ranged from 0.11% (itraconazole 100mg/day) to 1.22% (fluconazole 50mg/day). The risk with pulse treatment ranged from 0.39% (itraconazole 400mg/day) to 0.85% (fluconazole 300-450mg/week).

4. Clinical Knowledge Summaries (CKS). Fungal nail infection. 2014 Sep. Available from: http://cks.nice.org.uk/fungal-nail-infection#!topicsummary.

    RATIONALE: A CKS guideline recommending oral terbinafine as first line treatment. 250mg once a day should be prescribed for between 6 weeks and 3 months for fingernails, and for 3 to 6 months for toenails. Visible improvement can be expected after the end of 2 months of treatment for fingernails, and after 3 months of treatment for toenails. Oral itraconazole can be used as an alternative treatment. This should be prescribed as pulsed therapy of 200mg twice a day for 1 week, with subsequent courses repeated after a further 21 days. Fingernail infections require 2 pulsed courses, and toenail infections require at least 3 pulsed courses. Specialist advice should be sought for children, as fungal nail infection is rare, and the preferred treatments are not licensed for use in children.

5. Crawford F, Hollis S. Topical treatments for fungal infections of the skin and nails of the foot (Review). *Cochrane Database Syst Rev*. 2007 Jul; 18(3):1-11. Available from: www.ncbi.nlm.nih.gov/pubmed/17636672.

    RATIONALE: A systematic review and meta-analysis, concluding that there is little evidence that topical antifungals are effective in the management of onychomycosis, or fungally infected toenails. The majority of available data demonstrates low cure rates after

long treatment times with ciclopiroxolamine. Amorolfine and butenafine regimens may be much more effective than ciclopiroxolamine and tea tree oil, but only a few observations are available. Large randomised controlled trials comparing the effectiveness of topical amorolfine and butenafine are needed to establish an alternative to oral treatments.

6. Primary Care Dermatology Society (PCDS). Tinea manuum (hands), pedis (feet), and unguium (nails). 2015 Oct. Available from: www.pcds.org.uk/clinical-guidance/tinea-pedis-feet-manuum-hands-and-unguium-nails.

    RATIONALE: A PCDS guideline on the diagnosis and management of tinea. For tinea unguium, a patient information leaflet should be provided. Topical treatments have a low cure rate, but may be suitable for treating distal nail infection (as opposed to involvement of the nail matrix), or superficial white infections. Nails should be filed or cut back as much as possible prior to applying the treatment. For adults, oral terbinafine is the most effective systemic treatment, with eradication rates of 69%, compared with 48% for itraconazole. Terbinafine 250mg OD should be given for 6 weeks for fingernails, and 3 to 4 months for toenails. If the patient is unable to take terbinafine, or the tinea appears resistant to treatment, then itraconazole can be used as pulse therapy. Treatment success is denoted by the continued growth of new, healthy, proximal nail. Once treatment is complete it can still take a number of months for any previously affected nail to fully grow out. Recurrent episodes may be due to tinea pedis, in which case, once the infection has been eradicated, it is worth considering the application of a topical antifungal cream once to twice a week, including interdigital spaces.

Varicella zoster/chickenpox; herpes zoster/shingles:

1. Public Health England (PHE). Varicella: the green book, chapter 34. 2015 Aug. Available from: www.gov.uk/government/publications/varicella-the-green-book-chapter-34.

    RATIONALE: A PHE guideline stating that pregnant women are at greater risk of varicella pneumonia, and there is a risk to the foetus of congenital varicella syndrome if exposure occurs during the first 20 weeks of pregnancy, and severe disease in the neonate if varicella is contracted a week before delivery. Following infection in the second and third trimesters, herpes zoster may present in otherwise healthy infants. Occasional cases of foetal damage comprising chorioretinal damage, microcephaly, and skin scarring have been reported following maternal varicella infection between 20 and 28 weeks' gestation, but the risk is lower than for the first trimester. Neonates and immunocompromised individuals are at greater risk of disseminated or haemorrhagic varicella. Urgent specialist assessment is needed for all neonates, pregnant women, or immunocompromised individuals with varicella, in order to assess the need for varicella immunoglobulin and antiviral treatment.

2. Klassen TP, Hartling L, Wiebe N, Belseck EM. Acyclovir for treating varicella in otherwise healthy children and adolescents (Review). *Cochrane Database Syst Rev*. 2005 Oct; 19(4):1-24. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002980.pub3/epdf.

    RATIONALE: A systematic review and meta-analysis, pooling data from 3 studies with participants from 2 to 18 years of age within 24 hours of rash onset. Findings indicated that aciclovir was associated with a small reduction in the number of days with fever (-1.1; 95% CI -1.3 to -0.9), and in reducing the maximum number of lesions. Results were less

supportive of a reduction in the number of days of itching. There were no differences in complication rates between those treated with aciclovir or placebo.

3. Swingler G. Chickenpox. *Clin Evid.* 2005 Dec; 14:875-881. Available from: www.ncbi.nlm.nih.gov/pmc/articles/PMC2943770/.

   RATIONALE: A literature review, identifying 1 systematic review that cited 1 randomised controlled trial (n=148), comparing early versus late administration of aciclovir 800mg 5 times daily with placebo. Findings indicated that aciclovir given within 24 hours of the onset of rash significantly reduced the maximum number of lesions (p<0.01), and the time to full crusting of lesions (p=0.001), compared with placebo. No significant differences were found in time to full crusting of lesions if aciclovir was given 24-72 hours after onset of rash (p>0.2).

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

   RATIONALE: Expert consensus, recommending that treatment with aciclovir should be considered if it can be started within 24 hours of rash, and if they are at increased risk of complications. This includes those: over 14 years of age; in severe pain; with dense/oral rash; taking steroids; smokers. For shingles, treatment should be considered if patient has Ramsey Hunt syndrome, or eczema, and can be considered up to a week after rash onset if continued vesicle formation or immunocompromised.

5. Mohsen AH, Peck RJ, Mason Z, Mattock L, McKendrick MW. Lung function tests and risk factors for pneumonia in adults with chickenpox. *Thorax.* 2001 Oct; 56(10):796-799. Available from: www.ncbi.nlm.nih.gov/pubmed/11562520.

   RATIONALE: A prospective study, including 38 patients admitted to a university hospital. 19 patients had pneumonia, and 19 did not. Epidemiological data and density of rash were recorded, spirometric tests were performed, and carbon monoxide transfer factor was measured. Results indicated that varicella pneumonia was associated with the presence of respiratory symptoms (p=0.006), current smoking (p=0.003), and a history of close contact (p=0.009). There was also a trend towards patients with pneumonia having a more severe rash. Current smokers had a higher mean number of spots than non-smokers (p=0.005).

6. de Martino M, Chiarugi A, Boner A, Montini G, De' Angelis GL. Working Towards an Appropriate Use of Ibuprofen in Children: An Evidence-Based Appraisal. Drugs. 2017;77(12):1295-311. Available from: www.ncbi.nlm.nih.gov/pubmed/28597358

   RATIONALE: A critical review of the paediatric literature over the last 15 years on side effects and adverse events associated with ibuprofen, in order to highlight circumstances associated with higher risks and to promote safe and appropriate use of this drug. The literature from 2000 to the articles publication indicates that particular circumstances, such as viral infections and fever, seem to be associated with a higher rate of adverse events in people being treated with an NSAID. The authors discuss how the risk of developing complications (most commonly - bronchitis, pneumonia and superinfections of the skin) during a varicella infection seems to be linked with NSAID use. The go through 5 papers (Lesko 2001, Byington 2002, Mikaeloff 2008, Souyri 2008, and Durand 2015) that

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have linked NSAID use during varicella infections to complications. They conclude that ibuprofen should not be used as an antipyretic, except in rare cases. Ibuprofen remains the drug of first choice in the treatment of inflammatory pain in children but should not be used when a child has varicella.

7. Wood MJ, Kay R, Dworkin RH, Soong SJ, Whitley RY. Oral acyclovir therapy accelerates pain resolution in patients with herpes zoster: a meta-analysis of placebo-controlled trials. *Clin Infect Dis*. 1996 Feb; 22(2):341-347. Available from: www.ncbi.nlm.nih.gov/pubmed/8838194.

    RATIONALE: A systematic review and meta-analysis of 4 randomised controlled trials (n=691), which found greatest benefit in those aged over 50 years, in whom pain resolved twice as fast with aciclovir compared with placebo. Statistical significance was only recorded in 1 study in those comparing all patients, to patients over the age of 50 (HR 2.13; 95% CI 1.42, 3.19; p<.001). Oral aciclovir 800mg 5 times daily for 7 to 10 days also reduced the incidence of post-herpetic neuralgia at 3 (21% with aciclovir; 43% with placebo) and 6 months (12% with aciclovir; 25% with placebo). The authors conclude that, overall, the reductions of pain duration and prevalence with aciclovir were approximately twofold, in comparison with placebo.

8. Dworkin RH, Johnson RW, Breuer J, Gnann JW, Levin MJ, Backonja M et al. Recommendations for the management of herpes zoster. *Clin Infect Dis*. 2007 Jan; 44(1):1-26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17143845.

    RATIONALE: A review article stating that the treatment of shingles should be considered for non-truncal involvement, people with moderate or severe pain, or those with moderate or severe rash. Evidence from randomised controlled trials supports treatment for all those over 50 years of age, to prevent the incidence of post-herpetic neuralgia. The results of further trials support the use of aciclovir, brivudin, famciclovir, and valaciclovir as first line antiviral therapy for the treatment of patients with herpes zoster.

9. Hope-Simpson RE. Postherpetic neuralgia. *J R Coll Gen Pract*. 1975 Aug; 25(157):571-575. Available from: www.ncbi.nlm.nih.gov/pmc/articles/PMC2157719/.

    RATIONALE: A prospective study, showing that the incidence of post-herpetic neuralgia (PHN) in a general practice population increases with age, with a third of cases being among those over 80 (34.4%). Women, especially those between 50 and 69 years old, suffered more zoster than men, and women with zoster suffered more post-herpetic neuralgia. Results indicated that there is a demonstrable change in the rate of post-herpetic neuralgia after the age of 50, with 7.4% of people between the ages of 50 and 59 developing PHN; 21.2% of those between 60 and 69; 28.6% of those between 70 and 79; 34.4% in those over the age of 80. No post-herpetic neuralgia occurred after zoster in those under 30 years of age, and the incidence of neuralgia was not affected by the anatomical location of the zoster. The duration of post-herpetic neuralgia was unrelated to the age of the patient, but cranial neuralgias lasted much longer on average than neuralgia in other sites.

10. Wood MJ, Shukla S, Fiddian AP, Crooks RJ. Treatment of acute herpes zoster: effect of early (< 48 h) versus late (48-72 h) therapy with acyclovir and valaciclovir on prolonged pain. *J*

Infect Dis. 1998 Nov; 178(1):81-84. Available from: www.ncbi.nlm.nih.gov/pubmed/9852981.
RATIONALE: A systematic review of 2 databases (n=1,076), which found no difference in time to complete resolution of zoster-associated pain, whether treatment was started within 48 hours, or between 48 and 72 hours after the onset of cutaneous herpes zoster. Median times to complete resolution of zoster-associated pain were 26 and 62 days, respectively, for patients treated with aciclovir and placebo within 48 hours (HR 1.68; 95% CL 1.19, 2.38), and 28 and 58 days, respectively, for those treated later (HR 2.20; 95% CL 1.03, 4.71). In the valaciclovir versus aciclovir study, the corresponding figures were 44 and 51 days for patients treated early (HR 1.28; 95% CL 1.03, 1.60), and 36 and 48 days for those treated later (HR 1.40; 95% CL 1.04, 1.87). The authors conclude that aciclovir significantly shortened the time to complete resolution of zoster-associated pain compared with placebo, even when therapy was delayed up to 72 hours after rash onset.

11. Primary Care Dermatology Society (PCDS). Herpes zoster (syn. shingles). 2016 Jul. Available from: www.pcds.org.uk/clinical-guidance/herpes-zoster.
    RATIONALE: A PCDS guideline, recommending that all patients with ophthalmic zoster, irrespective of age or severity of symptoms, should be prescribed oral antiviral drugs at the first sign of disease. First line oral antiviral treatment for adults should be aciclovir 800mg 5 times daily for 7 days. For children, the condition is often mild and may not require treatment. Patients with a red eye or visual complaints must be referred to an ophthalmologist urgently. Those not needing referral must be reviewed after 1 week.

12. Kurokawa I, Kumano K, Murakawa K, Hyogo Prefectural PHN Study Group. Clinical correlates of prolonged pain in Japanese patients with acute herpes zoster. *J Int Med Res*. 2002 Feb; 30(1):56-65. Available from: http://journals.sagepub.com/doi/pdf/10.1177/147323000203000109.
    RATIONALE: A prospective study involving 263 adult patients presenting within 10 days of the onset of shingles across 17 institutions in Japan. All patients in whom pain persisted for more than 3 months were over 60 years of age. Decreased pain persistence was observed in patients in whom aciclovir therapy was initiated within 72 hours of the onset of symptoms, in comparison with those in whom therapy was initiated after this time. The difference between the 2 groups of patients was not, however, statistically significant. Treatment should still be initiated up to 1 week after rash onset, particularly if the patient is at high risk of complications or severe shingles.

13. Rasi A, Heshmatzade Behzadi A, Rabet M, Hassanloo J, Honarbakhsh Y, Dehghan N et al. The efficacy of time-based short-course acyclovir therapy in treatment of post-herpetic pain. *J Infect Dev Ctries*. 2010 Nov; 4(11):754-760. Available from: www.ncbi.nlm.nih.gov/pubmed/21252455.
    RATIONALE: A prospective clinical trial involving 152 patients diagnosed with acute herpes zoster, aiming to determine whether short-course aciclovir therapy (800mg 5 times daily for 4 days) can alleviate HZ-associated pain and prevent post-herpetic neuralgia. Patients were divided into 2 groups: group 1 had a rash with a duration of less than 72 hours; group 2 had a rash with a duration of more than 72 hours. To assess PHN, that patients categorised and assessed the severity of their symptoms using a 4-point verbal rating scale. Results indicated that, by the 4th week, 134 out of 152 patients (88.2%) had complete pain response. Of these, 68 patients (89.5%) were from group 1, and 66 patients

(86.8%) were from group 2. After 4 weeks, the mean verbal rating scale scores had changed significantly in both groups, compared to the scores at the beginning of the study (p=0.001), but there was no statistical difference
between the 2 groups (0.88 + 0.66; 0.94 + 0.72; p=0.66). After 3 months, no differences were observed in the treatment results between the 2 groups (0.51 + 0.13; 0.54 + 0.19; p=0.77).

14. Beutner KR, Friedman DJ, Forszpaniak C, Anderson PL, Wood MJ. Valaciclovir compared with aciclovir for improved therapy for herpes zoster in immunocompetent adults. *Antimicrob Agents Chemother*. 1995 Jul; 39(7):1546-1553. Available from:
www.ncbi.nlm.nih.gov/pmc/articles/PMC162779/pdf/391546.pdf.

    RATIONALE: A randomised double-blind controlled trial (n=1,141) including people aged 50 years and older, within 72 hours of onset of herpes zoster. Findings indicated that valaciclovir 1g 3 times daily for 7 or 14 days reduced the time to resolution of pain, compared with aciclovir 800mg 5 times daily 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 (p=0.03).

15. Chen N, Li Q, Yang J, Zhou M, Zhou D, He L. Antiviral treatment for preventing postherpetic neuralgia. *Cochrane Database Syst Rev*. 2014 Feb; 6(2):1-68. Available from:
www.ncbi.nlm.nih.gov/pubmed/24500927.

    RATIONALE: A systematic review and meta-analysis of 6 randomised controlled trials (n=1,211), aiming to assess the effectiveness of antiviral agents in preventing PHN. The randomised controlled trials included examined antiviral treatment given within 72 hours after the onset of herpes zoster for preventing PHN. Results indicated that there were no significant differences between aciclovir and placebo in the incidence of PHN 4 months after the onset of acute herpetic rash (RR 0.75; 25% difference; 95% CI 0.51 to 1.11), or at 6 months (RR 1.05; 95% CI 0.87 to 1.27; 2 trials; n=476). In 4 of the trials analysed (n=692), there was some evidence for a reduction in the incidence of pain 4 weeks after the onset of rash. In the trial of famciclovir versus placebo, neither 500mg nor 750mg doses of famciclovir reduced the incidence of herpetic neuralgia significantly. The authors conclude that there is high quality evidence suggesting that oral aciclovir does not reduce the incidence of PHN significantly. However, further well-designed trials are needed to investigate famciclovir and other antiviral treatments in preventing PHN. The authors suggest that further trials should pay more attention to the severity of pain and quality of life of participants, and should be conducted among different groups of people, such as people who are immunocompromised.

16. Shen MC, Lin HH, Lee SS, Chen YS, Chiang PC, Liu YC. Double-blind, randomized, acyclovir-controlled, parallel-group trial comparing the safety and efficacy of famciclovir and acyclovir in patients with uncomplicated herpes zoster. *J Microbiol Immunol Infect*. 2004 Apr; 37(2):75-81. Available from: www.ncbi.nlm.nih.gov/pubmed/15181487.

    RATIONALE: A small randomised controlled trial (n=55), in which the efficacy and safety of famciclovir (administered at 250mg 3 times daily) and aciclovir (800mg 5 times daily, both for 7 days), for the treatment of acute uncomplicated herpes zoster in immunocompetent adults was compared. Results indicated that both famciclovir and

aciclovir were comparable in healing lesions, and in the cessation of acute-phase pain. The authors conclude that famciclovir, administered less frequently and at lower unit doses than aciclovir, is an effective treatment for uncomplicated herpes zoster.

Tick bites (Lyme disease):

1. Warshafsky S, Lee DH, Francois LK, Nowakowski J, Nadelman RB, Wormser GP. Efficacy of antibiotic prophylaxis for the prevention of Lyme disease: an updated systematic review and meta-analysis. *J Antimicrob Chemother*. 2010 Apr; 65(6):1137-1144. Available from: http://jac.oxfordjournals.org/content/65/6/1137.long.

    RATIONALE: A systematic review and meta-analysis of the evidence, aiming to explore the efficacy of antibiotic prophylaxis for the prevention of Lyme disease. Four placebo-controlled clinical trials were included, involving 1,082 subjects. The risk of Lyme disease in the placebo group was 2.2% (95% CI 1.2% to 3.9%), compared with 0.2% (95% CI 0% to 1%) in the antibiotic prophylaxis group. These findings suggest that antibiotic prophylaxis significantly reduces the odds of developing Lyme disease compared with placebo (POR 0.084; 95% CI 0.002 to 0.57; p=0.0037). The authors conclude that the available evidence to date supports the use of antibiotic prophylaxis for the prevention of Lyme disease following an *Ixodes scapularis* tick bite. Pooled data suggests that 1 case of Lyme disease is prevented for about every 50 patients who are treated with antibiotics.

2. British Infection Association (BIA). The epidemiology, prevention, investigation and treatment of Lyme borreliosis in United Kingdom patients: a position statement by the British Infection Association. *J Infect*. 2011 May; 62(5):329-338. Available from: www.aldf.com/pdf/BIA%202011statement%20on%20Lyme%20disease.pdf.

    RATIONALE: A BIA position statement on the investigation, diagnosis, treatment, and prevention of Lyme borreliosis in United Kingdom patients. The authors state that antimicrobial prophylaxis is not routinely recommended by European authorities but may be used in immunocompromised individuals following a tick bite. In such situations, a single dose of doxycycline 200mg orally can be given. For treatment, doxycycline 100mg twice daily is recommended, unless pregnancy or breastfeeding, in which case amoxicillin 500mg 3 times daily should be considered first-line, all for 14 to 21 days. This statement suggests that prophylaxis should only be given within 72 hours of tick removal. The authors also state that individuals who have had ticks removed should check for possible development of erythema migrans or other early symptoms for the following 4 to 6 weeks and be aware that an erythema migrans rash might occur at another site following an unapparent tick bite.

3. National Institute for Health and Care Excellence (NICE). Lyme disease. 2018 April. Available from: www.nice.org.uk/guidance/ng95/resources/lyme-disease-pdf- 1837756839877.

    RATIONALE: A national guideline covering the diagnosis and management of Lymes disease. The guidance states that the bacteria that causes Lyme disease is transmitted by bites of infected ticks found in grassy and wooded areas. Infected ticks are found throughout the UK and Ireland. Though prevalence data is incomplete, particularly high-risk areas include the south of England and Scottish Highlands. Lyme disease may be more prevalent in parts of central, eastern and northern Europe (including Scandinavia)

and parts of Asia, the US and Canada. Most bites do not transmit Lyme disease and prompt correct removal can reduce the risk of disease transmission. Diagnosis is based on clinical assessment and laboratory testing. For adults and young people (aged 12 and over) diagnosed with Lyme disease, antibiotics should be offered according to their symptoms. Women should be asked (including young women under 18) if they might be pregnant before offering antibiotic treatment and allergic reaction to the antibiotic assessed for if symptoms worsen. Be aware that a Jarisch–Herxheimer reaction may cause an exacerbation of symptoms but does not usually warrant stopping treatment. Treatment recommendations are provided for a number of different scenarios. For Lyme disease without focal symptoms including erythema margins and/or non-focal symptoms the guidelines recommends oral doxycycline 100mg twice per day or 200mg once per day for 21 days. An alternative of amoxicillin 1,000g 3 times per day for 21 days is also offered, as is a second alternative of azithromycin 500mg daily for 17 days. If there are focal symptoms (affecting the cranial nerves or peripheral nervous system) doxycycline or amoxicillin are recommended. A clinical review during/after treatment should be considered to assess for possible side effects and response to treatment.

4. Nadelman RB, Nowakowski J, Fish D, Falco RC, Freeman K, McKenna D et al. Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an *Ixodes scapularis* tick bite. *N Engl J Med*. 2001 Jul; 345(2):79-84. Available from: www.nejm.org/doi/pdf/10.1056/NEJM200107123450201.

RATIONALE: A randomised, double-blind, placebo-controlled trial involving 482 subjects treated with a single 200mg dose of doxycycline after removing an attached *I. scapularis* tick from their bodies within the previous 72 hours. At base line, 3 weeks, and 6 weeks, subjects were interviewed and examined, and serum antibody tests were performed, along with blood cultures. Erythema migrans developed at the site of the tick bite in a significantly smaller proportion of the subjects in the doxycycline group than of those in the placebo group (1 of 235 subjects, and 8 of 247 subjects, respectively. The efficacy of treatment was recorded at 87%, and objective extra-cutaneous signs of Lyme disease did not develop in any subject. The authors conclude that a single 200mg dose of doxycycline given within 72 hours after an *I. scapularis* tick bite can prevent the development of Lyme disease.

5. Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2006 Nov; 43(9):1089-1134. Available from: www.ncbi.nlm.nih.gov/pubmed/17029130.

RATIONALE: A clinical practice guideline, prepared by an expert panel of the Infectious Diseases Society of America. Information is provided about prevention, epidemiology, clinical manifestations, diagnosis, and treatment of many Ixode tickborne infections. Doses and durations of antimicrobial therapy are recommended for the treatment and prevention of Lyme disease, and a list is provided of therapies to be avoided. This guideline states that doxycycline (100mg BD for 10 to 21 days), amoxicillin (500mg TDS for 14 to 21 days), or cefuroxime axetil (500mg BD for 14 days) is recommended for the treatment of adult patients with early localised or early disseminated Lyme disease associated with erythema migrans, in the absence of specific neurologic manifestations or

advanced atrioventricular heart block. Antibiotics recommended for children under 8 years of age are amoxicillin (50mg/kg per day in 3 divided doses; maximum of 500mg per dose), cefuroxime axetil (30mg/kg per day in 2 divided doses; maximum of 500mg per dose), or, if the patient is 8 years or older, doxycycline (4mg/kg per day in 2 divided doses; maximum of 100mg per dose). For prophylaxis, a single dose of doxycycline may be offered to adults (200mg dose) and to children 8 years or older (4mg/kg, up to a maximum dose of 200mg).

Eye infections

Conjunctivitis:

1. The College of Optometrists. Conjunctivitis (bacterial). 2016 Jan. Available from: www.college-optometrists.org/guidance/clinical-management-guidelines/conjunctivitis-bacterial-.html.

    RATIONALE: A college of Optometrists guideline, providing clear step-by-step descriptions of the aetiology, predisposing factors, symptoms, signs, differential diagnoses, and management of conjunctivitis. This guideline states that conjunctivitis often resolves in 5 to 7 days without treatment, and suggests that patients can bathe/clean the eyelids with lint or cotton wool dipped in sterile saline or boiled (cooled) water to remove crusting. The patient should be advised that the condition is contagious, so towels should not be shared. Treatment with topical antibiotics for bacterial cases may improve short-term outcomes, and render the patient less infectious to others.

2. Jefferis J, Perera R, Everitt H, van Weert H, Rietveld R, Glasziou P et al. Acute infective conjunctivitis in primary care: who needs antibiotics? An individual patient data meta-analysis. *Br J Gen Pract.* 2011 Sep; 61(590):542-548. Available from: www.ncbi.nlm.nih.gov/pmc/articles/PMC3162176/pdf/bjgp61-e542.pdf.

    RATIONALE: A systematic review and meta-analysis of 3 trials and 622 patients with both viral and bacterial acute conjunctivitis. 80% (246/308) of patients who received antibiotics, and 74% (233/314) of controls were cured at day 7. Overall, 6 of 100 experienced clinical benefit (8% difference; 95% CI 1% to 14%) at 7 days. Subgroups that showed a significant benefit from antibiotics were patients with purulent discharge, which is more indicative of bacterial infection (RD 0.09; 91% difference; 95% CI 0.01 to 0.17), and patients with mild severity of red eye (RD 0.10; 90% difference; 95% CI 0.02 to 0.18). The authors conclude that acute conjunctivitis seen in primary care can be thought of as a self-limiting condition, with most patients getting better regardless of antibiotic
    therapy. Patients with purulent discharge or a mild severity of red eye may have a small benefit from antibiotic treatment, such as chloramphenicol 0.5% eye drops, and fusidic acid 1% gel.

3. American Academy of Ophthalmology (AAO). Conjunctivitis PPP – 2013. 2013 Oct. Available from: www.aao.org/preferred-practice-pattern/conjunctivitis-ppp--2013.

    RATIONALE: An AAO guideline outlining the signs and symptoms of both viral and bacterial conjunctivitis, and stating that conjunctivitis infrequently causes permanent visual loss or structural damage. Treatment of conjunctivitis is ideally directed at the root cause. Indiscriminate use of topical antibiotics or corticosteroids should be avoided, as antibiotics

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can induce toxicity and corticosteroids can potentially prolong adenoviral infections, and worsen herpes simplex virus infections. Most cases of conjunctivitis are viral and will not respond to anti-bacterial agents, and mild bacterial conjunctivitis is likely to be self-limiting.

4. Rose PW, Harnden A, Brueggemann AB, Perera R, Sheikh A, Crook D et al. Chloramphenicol treatment for acute infective conjunctivitis in children in primary care: a randomised double-blind placebo-controlled trial. *Lancet*. 2005 Jul; 366(9479):37-43. Available from: www.ncbi.nlm.nih.gov/pubmed/15993231.

    RATIONALE: A randomised controlled trial including 326 school children with a clinical diagnosis of conjunctivitis, which found that most children presenting with acute infective conjunctivitis in primary care get better by themselves, and there is no statistically significant difference between using placebo or chloramphenicol (0.5% eye drops every 2 hours for the first 24 hours, and then 4 times daily until 48 hours after the infection had resolved). Clinical cure by day 7 occurred in 83% of children given placebo, compared to 86% of children given chloramphenicol (RD 3.8%; 95% CI -4.1% to 11%). The authors conclude that most children presenting with acute infective conjunctivitis in primary care will get better by themselves, and do not need treatment with an antibiotic.

5. Sheikh A, Hurwitz B. Antibiotics versus placebo for acute bacterial conjunctivitis (Review). *Cochrane Database Syst Rev.* 2006 Apr; 19(2):1-21. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001211.pub2/epdf.

    RATIONALE: A systematic review and meta-analysis of 11 randomised controlled trials (n=3,673), looking specifically at clinical and microbiological remission rates, in patients with acute bacterial conjunctivitis, aged greater than 1 month. The diagnosis may have been on clinical or microbiological grounds, and acute was defined as symptoms of less than 4 weeks duration. Findings indicated that topical antibiotics (ciprofloxacin 0.3% 1 to 2 drops every 2 hours whilst awake on the first day, and every 4 hours whilst awake on day 2; fusidic acid gel 1% 4 times daily over a week; chloramphenicol 0.5% eye drops) were of benefit in improving early (days 2 to 5) clinical (RR 1.36; 95% CI 1.15 to 1.61), and microbiological (RR 1.55; 95% CI 1.37 to 1.76) remission rates. At the late time point (days 6 to 10), antibiotics were found to still confer modest benefits in clinical remission (RR 1.21; 95% CI 1.10 to 1.33), and microbiological cure rates (RR 1.37; 95% CI 1.24 to 1.52). By days 6 to 10, 41% (95% CI 38 to 43) of cases had resolved in those receiving placebo. No data was found on the cost-effectiveness of antibiotics. No serious outcomes were reported in either the active or placebo arms of these trials, suggesting that important sight-threatening complications are an infrequent occurrence. The authors conclude that, although acute bacterial conjunctivitis is frequently self-limiting, the findings from this review suggest that the use of antibiotic eye drops is associated with modestly improved rates of clinical and microbiological remission, in comparison to the use of placebo. Use of antibiotic eye drops should therefore be considered in order to speed the resolution of infection.

6. Rietveld RP, ter Riet G, Bindels PJE, Bink D, Sloos JH, van Weert HCPM. The treatment of acute infectious conjunctivitis with fusidic acid: a randomised controlled trial. *Br J Gen Pract*. 2005 Dec; 55(521):924-930. Available from: www.ncbi.nlm.nih.gov/pmc/articles/PMC1570507/pdf/bjpg55-924.pdf.

    RATIONALE: A randomised controlled trial including 163 patients in the Netherlands,

which found no statistically significant difference in clinical cure rates at 7 days in people using fusidic acid 1% gel 4 times daily for 7 days (62%), compared with people taking a placebo (59%) (RD 5.3%; 95% CI -11% to 18%). The authors conclude that, at 7 days, cure rates in the fusidic acid 1% gel and placebo group were similar, but the confidence interval was too wide to clearly demonstrate their equivalence (ARD 5.3%; 95% CI -11 to 18). These findings do not support the current prescription practices of fusidic acid by general practitioners.

7. Medicines.org. *Fucithalmic/Fusidic Acid 1% Viscous Eye Drops*. Available from: www.medicines.org.uk/emc/medicine/28430 [Accessed: 22 September, 2016].

   RATIONALE: An EMC webpage stating that fucithalmic/fusidic acid 1% viscous eye drops is active against a wide range of Gram-positive organisms, particularly *Staphylococcus aureus*. Other species against which fucithalmic has been shown to have in vitro activity against include: Streptococcus; Neisseria; Haemophilus; Moraxella; Corynebacteria. This website states that fucithalmic/fusidic acid 1% viscous eye drops can be used as treatment for bacterial conjunctivitis, where the organism is known to be susceptible. One drop should be administered into each eye twice daily, and treatment should be continued for at least 48 hours after the eye returns to normal.

Blepharitis:

1. The College of Optometrists. Blepharitis (inflammation of the lid margins). 2016 Feb. Available from: www.college-optometrists.org/en/utilities/document-summary.cfm/docid/91502CC4-6126-47D9-A707F0E015D55230.

   RATIONALE: A College of Optometrists guideline, providing clear step-by-step descriptions of the assessment, aetiology, and treatment of blepharitis. This guideline states that blepharitis is typically bilateral, and chronic or relapsing, and is bacterial and usually staphylococcal, caused by: direct infection; reaction to staphylococcal exotoxin; allergic response to staphylococcal antigen. This guideline recommends lid hygiene as first line measures for symptom control, including: gentle washing; warm compresses; lid massage; lid scrubs; avoidance of cosmetic products. If infection is still present after 2 weeks of trying simple measures, antibiotic ointment, such as chloramphenicol, can be placed in the eyes twice daily. If lid hygiene and topical treatment fail, a systemic tetracycline, such as doxycycline or oxytetracycline, can be prescribed as maintenance for several weeks or months.

2. Lindsley K, Matsumura S, Hatef E, Akpek EK. Interventions for chronic blepharitis. *Cochrane Database Syst Rev*. 2014 Dec; 5:1-117. Available from: www.ncbi.nlm.nih.gov/pmc/articles/PMC4270370/pdf/nihms396402.pdf.

   RATIONALE: A systematic review and meta-analysis of 34 studies, involving 2,169 adults with clinically diagnosed blepharitis. With regard to anterior/mixed staphylococcal and seborrheic blepharitis, the results of treatment interventions are mixed, but these may be due to the fact that most studies included participants with blepharitis from various aetiologies. When only cases of anterior blepharitis and blepharoconjunctivitis were included, there was some suggestion that clinical outcomes were better with topical antibiotics, compared with placebo. Studies measuring microbiological outcomes

demonstrated that topical antibiotics (chloramphenicol 0.5% eye drops; norfloxacin 0.3% ophthalmic solution; ciprofloxacin ophthalmic solution) were effective in obtaining negative cultures from the ocular surface, but clinical significance was not clear. There were no significant differences between different kinds of antibiotics when compared directly, or with placebo. Studies that evaluated both topical antibiotics and topical steroids did not show clinically significant improvements from baseline individually, or when compared with 1 another. Although these studies showed that antibiotic therapy significantly decreases bacteriological cultures compared with steroid therapy, bacteriological improvement was not associated with clinical improvement. Mechanical measures, using lid hygiene and/or detergents, demonstrated improvements of signs and symptoms in the majority of participants, with no side-effects. However, the 2 studies assessing these measures used different types of detergents and comparison groups. Compliance to lid hygiene and lid scrubs may also be an issue in long-term use. Many therapies were studied for the treatment of posterior blepharitis, but due to the variation in medical and mechanical interventions, most comparisons were evaluated only by a single study. Oral doxycycline was observed to have clinical improvements at high (200mg BD) and low (20mg BD) doses, with adverse events occurring more frequently in the high-dose group. Topical cyclosporine was studied long-term (3 months) and showed mixed results for clinical tests, when compared with placebo, or topical antibiotics plus steroids. Castor-oil-containing eyedrops were more efficacious than saline eyedrops, in terms of improving tear function, especially stability. The explanation may be that posterior blepharitis is associated with poor mebum secretion, and adding oily substances may help with improving tear film stability. Finally, heat application showed some benefit in terms of patient symptoms, and some effectiveness regarding tear function.

3. Clinical Knowledge Summaries (CKS). Blepharitis. 2015 Oct. Available from: http://cks.nice.org.uk/blepharitis#!topicsummary.

   RATIONALE: A CKS guideline, which found no significant evidence from randomised placebo-controlled trials on topical or oral antibiotics for the treatment of blepharitis. One systematic review (n=2,169), concluded that, although topical antibiotics were shown to provide some symptomatic relief in anterior blepharitis, there is no strong evidence to support their use. The effectiveness of oral antibiotics was further inconclusive. Although randomised controlled trials to support the effectiveness of chloramphenicol in the treatment of blepharitis are lacking, it is a broad spectrum topical antibiotic which is the drug of choice for superficial eye infections. If chloramphenicol is prescribed, 1% eye ointment should be administered twice daily for a 6 week trial. Oral antibiotics can be prescribed if lid hygiene and topical antibiotics are ineffective. Oxytetracycline and doxycycline are both licensed for the treatment of acne rosacea, which often accompanies blepharitis, so these tetracyclines can be considered suitable options for treatment. These antibiotics should also be prescribed in the presence of Meibomian gland dysfunction. Oxytetracycline should be prescribed at 500mg twice daily for 4 weeks, followed by 250mg twice daily for a further 8 weeks, if required. Doxycycline should be prescribed at 100mg once a day for the first 4 weeks, followed by 50mg once a day for a further 8 weeks, if required. Eyelid hygiene should be also be maintained.

Suspected dental infections in primary care (outside dental setting)

General references:

1. Scottish Dental Clinical Effectiveness Programme (SDCEP). Drug prescribing for dentistry: Dental clinical guidance. 2016 Jan. Available from: www.sdcep.org.uk/wp-content/uploads/2016/03/SDCEP-Drug-Prescribing-for-Dentistry-3rd-edition.pdf.

   RATIONALE: An SDCEP guideline, stating that antibiotics do not cure toothache or odontogenic pain. Severe throbbing toothache without swelling of the soft tissues or pyrexia is usually caused by pulpitis. As an inflammatory condition, temporary relief of the symptoms of pulpitis is best achieved with regular analgesics, whilst the patient accesses definitive dental treatment (often a root canal treatment, or extraction). Irreversible pulpitis is characterised by throbbing toothache, which keeps the patient awake at night, and the tooth responds to hot and cold temperatures. Untreated, this type of toothache will initially resolve for a few days, weeks, or even months. However, the untreated condition may turn into a dental abscess, the symptoms of which are more dangerous than the initial pulpitis. Patients should be strongly advised to seek definitive dental treatment as soon as possible. Analgesics for the temporary relief of toothache include ibuprofen and/or paracetamol. Opioid analgesics, such as codeine, are relatively ineffective against dental pain. In adults, the dose of ibuprofen can be increased, if necessary, to a maximum dose of 2.4g daily. Avoid use in those with hypersensitivity to aspirin, or any other NSAID, including those in whom attacks of asthma, angioedema, urticaria, or rhinitis have been precipitated by aspirin or any other NSAID. Do not prescribe for patients taking a low dose of aspirin daily. Avoid use in pregnant women, and avoid in those with previous or active peptic ulcer disease, unless a proton pump inhibitor is co-prescribed. Use with caution in the elderly, patients with allergic disorders, nursing mothers, those taking oral anticoagulants (such as warfarin), those with coagulation defects, those with an inherited bleeding disorder, and those with renal, cardiac, or hepatic impairment. Restrict ibuprofen use to 5 days or less in those patients taking antihypertensive drugs.

Mucosal ulceration and inflammation (simple gingivitis):

1. Scottish Dental Clinical Effectiveness Programme (SDCEP). Management of acute dental problems: guidance for healthcare professionals. 2013 Mar. Available from: www.sdcep.org.uk/wp-content/uploads/2013/03/SDCEP+MADP+Guidance+March+2013.pdf.

   RATIONALE: An SDCEP guideline stating that mucosal ulcers are caused by a number of conditions, such as: recurrent aphthous stomatitis; herpes viruses; hand, foot and mouth disease; adverse reactions to drugs; nutritional deficiencies; some gastrointestinal diseases; oral lichen planus; oral cancer. These causes should be evaluated and treated. This guideline recommends that salt solution (half a teaspoon of salt dissolved in warm water) or compound sodium chloride mouthwash (300mL diluted with an equal volume of water) should be used to treat simple gingivitis, if more severe, or if pain limits oral hygiene to treat or prevent secondary infection. Both chlorhexidine 0.2% mouthwash and chlorhexidine oromucosal solution, alcohol-free 0.2% (300mL) are recommended for patients (rinse with 10mL for 1 minute, twice daily). Patients should spit out mouthwash after use. This guideline recommends leaving a 30-minute interval between using chlorhexidine mouthwash and toothpaste, due to staining of teeth and dilution of

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chlorhexidine. Mouthwash should be used until lesions resolve, or until less pain allows for good oral hygiene.

2. Lang NP, Hase JC, Grassi M, Hammerle CH, Weigel C, Kelty E et al. Plaque formation and gingivitis after supervised mouth rinsing with 0.2% delmopinol hydrochloride, 0.2% chlorhexidine digluconate and placebo for 6 months. *Oral Dis*. 1998 Jun; 4(2):105-113. Available from: www.ncbi.nlm.nih.gov/pubmed/9680899.

     RATIONALE: A double-blind, randomised 6-month clinical trial of 162 patients with gingivitis, comparing the effects of 0.2% chlorhexidine mouthwash or 0.2% delmopinol mouthwash to placebo, on plaque formation and gingivitis. Both mouthwashes were more effective than placebo; however, chlorhexidine mouthwash was statistically significantly more effective in relation to the clinical outcome parameters measured to quantify gingivitis and plaque formation. Findings also indicated that the long-term use of chlorhexidine mouthwash was less tolerated by subjects.

3. Gunsolley JC. A meta-analysis of 6-month studies of antiplaque and antigingivitis agents. *J Am Dent Assoc.* 2006 Dec; 137(12):1649-1657. Available from: www.sciencedirect.com/science/article/pii/S0002817714647942.

     RATIONALE: A meta-analysis of 7 studies conducted between 1989 and 2005, looking at chlorhexidine 0.12% mouthwash, and evaluating its efficacy at reducing gingival inflammation. Chlorhexidine had the most consistent results, according to the Modified Gingival Index scoring system (a statistically sensitive scoring system that allows for the non-invasive assessment of the severity and extent of gingival inflammation).

4. Berchier CE, Slot DE, Van der Weijden GA. The efficacy of 0.12% chlorhexidine mouth rinse compared with 0.2% on plaque accumulation and periodontal parameters: a systematic review. *J Clin Periodontol*. 2010 Sep; 37(9):829-839. Available from: www.ncbi.nlm.nih.gov/pubmed/20618550.

     RATIONALE: A systematic review from the Netherlands, aiming to evaluate the effects of 0.12% chlorhexidine versus 0.2% chlorhexidine in the management of gingival inflammation and plaque control. Medline, PubMed and the Cochrane Database were searched for randomised controlled trials and cohort studies. 409 titles and abstracts identified 8 eligible publications. Overall, there was no evidence for the benefit of 0.2% over 0.12% in the reduction of gingivitis; however, there was some evidence in favour of 0.2% chlorhexidine regarding the reduction of plaque.

5. Hasturk H, Nunn M, Warbington M, Van Dyke TE. Efficacy of a fluoridated hydrogen peroxide-based mouth rinse for the treatment of gingivitis: a randomized clinical trial. *J Periodontol*. 2004 Jan; 75(1):57-65. Available from: www.ncbi.nlm.nih.gov/pubmed/15025217.

     RATIONALE: An American placebo controlled trial of 99 patients, looking at the effects of fluoridated hydrogen peroxide-based mouth rinse 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 mouth rinse group compared with the placebo group (p=0.004).

Acute necrotising ulcerative gingivitis:

1. Clinical Knowledge Summaries (CKS). Gingivitis and periodontitis. 2016 Dec. Available from: https://cks.nice.org.uk/gingivitis-and-periodontitis#!topicsummary.
    RATIONALE: A CKS guideline, recommending that acute necrotising ulcerative gingivitis should be referred to a dentist for urgent assessment and management. During the acute phase, the person should, if possible, use a soft toothbrush to clean their teeth. Once pain subsides, good oral hygiene should be commenced by brushing teeth for 2 minutes twice a day (in the morning, and last thing at night), preferably with a powered toothbrush. Paracetamol or ibuprofen can be prescribed for pain relief, or chlorhexidine (0.12% or 0.2%) mouthwash, or hydrogen peroxide 6% mouthwash. Metronidazole 400mg 3 times a day for 3 days can be prescribed in the presence of systemic signs or symptoms of infection.

2. Preshaw PM. Antibiotics in the treatment of periodontitis. *Dent Update*. 2004 Oct; 31(8):448-450. Available from: www.ncbi.nlm.nih.gov/pubmed/15554049.
    RATIONALE: A review article recommending root surface instrumentation, chemical plaque control (chlorhexidine mouthwash), and oral hygiene advice as the gold standard treatment for acute necrotising ulcerative gingivitis. This review also states that metronidazole (400mg 3 times daily, for 3 days) can be added in acute stages, however systemic antibiotics are not usually indicated in the vast majority of periodontal conditions encountered in general dental practice.

3. Loesche WJ, Syed SA, Laughon BE, Stoll J. The bacteriology of acute necrotizing ulcerative gingivitis. *J Periodontol*. 1982 Apr; 53(4):223-230. Available from: www.ncbi.nlm.nih.gov/pubmed/6122728.
    RATIONALE: A small longitudinal study, in which a total of 8 patients with acute necrotising ulcerative gingivitis were included. Those systemically ill (n=3) were treated with metronidazole (200mg TDS), and those with localised symptoms only received standard periodontal therapy. Those systemically ill initially had more microbiological findings. Metronidazole treatment reduced the number of anaerobes, but at a two to 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 acute necrotising ulcerative gingivitis, and highlights the efficacy of standard periodontal treatment.

4. Kuriyama T, Williams DW, Yanagisawa M, Iwahara K, Shimizu C, Nakagawa K et al. Antimicrobial susceptibility of 800 anaerobic isolates from patients with dentoalveolar infection to 13 oral antibiotics. *Oral Microbiol Immunol*. 2007 Aug; 22(4):285-288. Available from: www.ncbi.nlm.nih.gov/pubmed/17600542.
    RATIONALE: A clinical prospective study, looking at the antimicrobial susceptibility of 800 anaerobic isolates from dentoalveolar infections. *P. intermedia* (a common pathogen found in acute necrotising ulcerative gingivitis) was found to be 100% susceptible to metronidazole, thus supporting the use of metronidazole in this condition. Fusobacterium species was found to have good susceptibility to amoxicillin/clavulanic acid, a wide range of cephalosporins, clindamycin, and metronidazole.

5. Dahlen G. Microbiology and treatment of dental abscesses and periodontal-endodontic lesions. *Periodontol 2000*. 2002 Jan; 28(1):206-239. Available from: http://onlinelibrary.wiley.com/doi/10.1034/j.1600-0757.2002.280109.x/abstract.

    RATIONALE: A retrospective study suggesting that metronidazole is effective against strict anaerobes (common pathogens seen in acute necrotising ulcerative gingivitis). Four studies demonstrated that Prevotella, Porphyromonas, and Fusobacterium were 100% susceptible to metronidazole. Metronidazole can therefore be used in the face of beta-lactamase-producing anaerobes, and is also suitable for penicillin allergic patients.

6. Scottish Dental Clinical Effectiveness Programme (SDCEP). Management of acute dental problems: guidance for healthcare professionals. 2013 Mar. Available from: www.sdcep. org.uk/wp-content/uploads/2013/03/SDCEP+MADP+Guidance+March+2013.pdf.

    RATIONALE: An SDCEP guideline stating that acute necrotising gingivitis should be treated with a compound sodium chloride mouthwash (300mL diluted with an equal volume of water). Both chlorhexidine 0.2% mouthwash and chlorhexidine oromucosal solution, alcohol-free 0.2% (300mL) are recommended for patients (rinse with 10mL for 1 minute, twice daily). This guideline recommends leaving a 30-minute interval between using chlorhexidine mouthwash and toothpaste, due to staining dilution of chlorhexidine. Mouthwash should be used until lesions resolve, or less pain allows for good oral hygiene.

Pericoronitis:

1. Scottish Dental Clinical Effectiveness Programme (SDCEP). Management of acute dental problems: guidance for healthcare professionals. 2013 Mar. Available from: www.sdcep. org.uk/wp-content/uploads/2013/03/SDCEP+MADP+Guidance+March+2013.pdf.

    RATIONALE: An SDCEP guideline, stating that pericoronitis is the inflammation and infection of perimolar soft tissue, often provoked by emerging molar teeth. This condition should be managed by referral to a dentist for local surgical treatment, primarily with irrigation or incision and debridement of the lesion. If pain or trismus limit good oral hygiene, treatment with analgesia and either 0.2% chlorhexidine mouthwash (rinse with 10mL for 1 minute, twice daily) or hydrogen peroxide 6% mouthwash should be recommended. Mouthwash should be used until lesions resolve, or until less pain allows for good oral hygiene. Antibiotics can be added where there is systemic involvement or ongoing symptoms, including metronidazole 400mg 3 times daily, for 3 days, or amoxicillin 500mg 3 times daily, for 3 days.

2. Ellison SJ. The role of phenoxymethylpenicillin, amoxicillin, metronidazole and clindamycin in the management of acute dentoalveolar abscesses – a review. *Br Dent J*. 2009 Apr; 206(7):357-362. Available from: www.ncbi.nlm.nih.gov/pubmed/19357666.

    RATIONALE: A literature search of over 5,000 references worldwide, recommending the use of metronidazole 200mg 3 times daily, for 3 days, as first line treatment in pericoronitis. The author concludes that, given the current climate of evidence-based research, the need to keep antibiotic prescribing to an acceptable minimum, increasing levels of resistance of microorganisms, and widespread hospital infections with 'superbugs', there is a distinct need for appropriate antibiotic prescribing guidelines.

3. Sixou JL, Magaud C, Jolivet-Gougeon A, Cormier M, Bonnaure-Mallet M. Evaluation of the mandibular third molar pericoronitis flora and its susceptibility to different antibiotics prescribed in France. *J Clin Microbiol.* 2003 Dec; 41(12):5794-5797. Available from: www.ncbi.nlm.nih.gov/pmc/articles/PMC308963/pdf/0390.pdf.

   RATIONALE: A French prospective study, looking at the microbial flora isolated from samples taken from 35 patients with pericoronitis, and evaluating their susceptibility to amoxicillin, pristinamycin (a macrolide), and metronidazole (alone, or in combination with spiramycin). Obligate anaerobes were isolated in 91% of cases, and resistance to metronidazole was not evident in any species. Amoxicillin was highly active against 91.5% of aerobes and anaerobes isolated, and therefore, in severe infections, amoxicillin can be added to treatment with metronidazole.

Dental abscess:

1. Matthews DC, Sutherland S, Basrani B. Emergency management of acute apical abscesses in the permanent dentition: a systematic review of the literature. *J Can Dent Assoc.* 2003 Nov; 69(10):660. Available from: www.ncbi.nlm.nih.gov/pubmed/14611715.

   RATIONALE: A systematic review of the literature, suggesting that in the management of localised acute apical abscess in the permanent dentition, regular analgesia should be used before the abscess can be drained through a pulpectomy, or incision and drainage. Pus should be sent for investigation, where possible. This review indicated that antibiotics are of no additional benefit in the treatment of dental abscess. In the event of systemic complications (for example fever, lymphadenopathy, or cellulitis), or for an immunocompromised patient, antibiotics may be prescribed in addition to drainage of the tooth.

2. Dahlen G. Microbiology and treatment of dental abscesses and periodontal-endodontic lesions. *Periodontol 2000.* 2002 Jan; 28(1):206-239. Available from: http://onlinelibrary.wiley.com/doi/10.1034/j.1600-0757.2002.280109.x/abstract.

   RATIONALE: A retrospective study, recommending that definitive surgical treatment to drain the abscess (through incision, extraction, or removal of necrotic pulp) by a dentist is the primary management of a dentoalveolar abscess. The use of antibiotic treatment is required only in cases where there is evidence of systemic illness, or in the severely immunocompromised. Antibiotic treatment is only used when it is aimed at limiting spread of infection, and in preventing serious complications.

3. Robertson D, Smith AJ. The microbiology of the acute dental abscess. *J Med Microbiol.* 2009 Feb; 58(2):155-162. Available from: www.ncbi.nlm.nih.gov/pubmed/19141730.

   RATIONALE: A review article stating that, despite few well controlled trials, the literature available supports the use of urgent surgical management of the dental abscess, by incision, tooth extraction, or via root canal, in combination with antimicrobial agents, where there is evidence of cellulitis or sepsis.

4. Ellison SJ. The role of phenoxymethylpenicillin, amoxicillin, metronidazole and clindamycin in the management of acute dentoalveolar abscesses – a review. *Br Dent J.* 2009 Apr; 206(7):357-362. Available from: www.ncbi.nlm.nih.gov/pubmed/19357666.

   RATIONALE: A literature search of over 5,000 references worldwide, concluding that

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there is little evidence-based antibiotic prescribing in the case of dental infections, and to help control the increase of antimicrobial resistance, it is important to only prescribe antimicrobials if indicated. Antimicrobials should be prescribed if there are systemic signs of acute dental abscess, including: pyrexia; trismus; lymphadenopathy; gross facial or ocular oedema; dysphagia; tachycardia; malaise; rigors.

5. Kuriyama T, Absi EG, Williams DW, Lewis MA. An outcome audit of the treatment of acute dentoalveolar infection: impact of penicillin resistance. *Br Dent J.* 2005 Jun; 198(12):759-763. Available from: www.ncbi.nlm.nih.gov/pubmed/15980845.

   RATIONALE: An audit of 112 patients with dentoalveolar infection who underwent incisional or dental pulp chamber drainage, and were then assigned to 1 of 6 different antibiotic regimes. No significant differences in outcome were found with any regime, and the presence of penicillin-resistant strains did not influence the outcome where surgical management was already established, questioning the indication for antibiotics at all. This study did not look at cases where antibiotics were not prescribed when adequate drainage had not been achieved, and reinforced that it would be unethical to undertake such a study where systemic signs of infection were evident.

6. Scottish Dental Clinical Effectiveness Programme (SDCEP). Management of acute dental problems: guidance for healthcare professionals. 2013 Mar. Available from: www.sdcep. org.uk/wp-content/uploads/2013/03/SDCEP+MADP+Guidance+March+2013.pdf.

   RATIONALE: An SDCEP guideline, stating that, in dental abscess, if the airway is compromised or the patient is having trouble swallowing their own saliva, or are unable to push their tongue forward out of their mouth, the patient should be admitted urgently to emergency care. This guideline recommends that 400mg metronidazole, 3 times daily, or 500mg amoxicillin, 3 times daily, can be prescribed for the treatment of severe dental abscess. Concentrations can be increased at the site of infection above the minimum inhibitory concentration needed to eradicate the infecting bacteria, especially for more resistant bacteroides species. In the case of severe infection, the dose of amoxicillin can be doubled (from 500mg to 1g 3 times daily), as can the dose of phenoxymethylpenicillin (from 500mg to 1g 4 times daily). Clindamycin, clarithromycin, cephalosporins, and amoxicillin/clavulanate should be avoided as first line agents, as there is no advantage over amoxicillin, phenoxymethylpenicillin, metronidazole, or erythromycin. Clindamycin and amoxicillin/clavulanate can be used as second line agents where infection has not resolved; however, there is an increased risk of *Clostridium difficile*. An alternative diagnosis should be sought if the abscess is not resolving with local measures, in combination with first line antimicrobials. Clarithromycin can be used in true penicillin allergy, at a dose of 500mg, twice daily, for up to 5 days.

7. Eick S, Pfister W, Straube E. Antimicrobial susceptibility of anaerobic and capnophilic bacteria isolated from odontogenic abscesses and rapidly progressive periodontitis. *Int J Antimicrob Agents.* 1999 Jun; 12(1):41-46. Available from: www.ncbi.nlm.nih.gov/pubmed/10389646.

   RATIONALE: A German prospective study, looking at the susceptibility of microbiological samples taken from 140 patients with dentoalveolar disease (periodontitis or odontogenic abscess). Findings indicated that the isolates consisted mainly of Gram-negative anaerobes, which were highly susceptible to metronidazole and clindamycin. 6% of the periodontal isolates (plaque), and 22% of the abscess isolates (pus) were resistant to

penicillin, but were highly susceptible to clindamycin and metronidazole. The authors conclude that both clindamycin and metronidazole could be useful antibiotics and could be recommended for empirical antimicrobial treatment.

8. Kuriyama T, Absi EG, Williams DW, Lewis MA. An outcome audit of the treatment of acute dentoalveolar infection: impact of penicillin resistance. *Br Dent J.* 2005 Jun; 198(12):759-763. Available from: www.ncbi.nlm.nih.gov/pubmed/15980845.

    RATIONALE: A prospective study looking at the antimicrobial susceptibility of 800 anaerobic isolates from dentoalveolar infection in Japan. The authors conclude that amoxicillin is still advocated as a first line agent, as it exhibits a high level of activity against the majority of organisms responsible for dentoalveolar infections. Resistance was, however, seen in beta-lactamase-producing Prevotella species, and therefore, in more severe infections, these organisms need to be covered. Amoxicillin/clavulanate, clindamycin, and metronidazole have excellent activity against Prevotella species and other anaerobes found in dentoalveolar infections. Susceptibility and resistance profiles of cephalosporins were found to be similar to amoxicillin, and therefore, have no advantage over amoxicillin, and are associated with greater side-effects and resistance.

9. Ellison SJ. An outcome audit of 3 day antimicrobial prescribing for the acute dentoalveolar abscess. *Br Dent J.* 2011 Dec; 211(12):591-594. Available from: www.ncbi.nlm.nih.gov/pubmed/22193484.

    RATIONALE: An audit of 6,586 patients in pain attending the Primary Care Department at Bristol Dental Hospital, between 2005 and 2007. Following drainage and removal of the cause of infection, only the 2.9% (n=188) with systemic involvement were given 3 days amoxicillin 250mg, 3 times daily (first line), or 3 days metronidazole 200mg, 3 times daily (second line). The combination of drainage and a 3 day antibiotic regimen in these patients was effective in 100% of cases, where review was obtained.

10. Martin MV, Longman LP, Hill JB, Hardy P. Acute dentoalveolar infections: an investigation of the duration of antibiotic therapy. *Br Dent J.* 1997 Aug; 183(4):135-137. Available from: www.ncbi.nlm.nih.gov/pubmed/9293130.

    RATIONALE: A prospective study, looking at 759 patients with acute dental abscess (and associated systemic features), managed with either abscess drainage or tooth extraction, in combination with amoxicillin, clindamycin, or erythromycin. The outcome measured was the resolution of systemic symptoms (swelling and temperature) after 2 to 3 days, and then again at 10 days. Findings indicated that 98.6% of cases had resolution of symptoms at the first review when antibiotics were discontinued, and these patients did not need an additional course of antibiotics at a later stage. The authors conclude that, if drainage has been established, antibiotics may not be needed beyond 2 to 3 days. Clinical review should be conducted at 3 days, where possible. Antibiotics may be stopped if symptoms have resolved, or can be continued to 5 days duration.

11. Kulik EM, Lenkeit K, Chenaux S, Meyer J. Antimicrobial susceptibility of periodontopathogenic bacteria. *J Antimicrob Chemother.* 2008 May; 61(5):1087-1091. Available from: www.ncbi.nlm.nih.gov/pubmed/18326855.

    RATIONALE: A retrospective, laboratory-based microbiological study based in

Switzerland, looking at the resistance profiles of 3 predominant periodontopathogenic bacteria isolated from dental abscesses over a 14-year period. Findings showed there was limited antibiotic resistance to phenoxymethylpenicillin, amoxicillin/clavulanic acid, clindamycin, tetracycline, and metronidazole and reiterated the polymicrobial nature of periodontal infections. While resistance may well be present amongst commensal flora, resistance to individual species implicated in dental abscesses is not currently an issue.

General comments on selected antibiotics and doses recommended

1. Anderson JT, Peterson M, Jimenez-Solem E, Broedbaek K, Anderson NL, Torp-Pederson C et al. Clarithromycin in early pregnancy and the risk of miscarriage and malformation: a register based nationwide cohort study. *PLoS One*. 2013 Jan; 8(1):1-6. Available from: www.ncbi.nlm.nih.gov/pmc/articles/PMC3534696/.

    RATIONALE: A nationwide cohort study of all women in Denmark with a known conception between 1997 and 2007. 931,504 pregnancies were identified. Of the 401 women who redeemed a prescription of clarithromycin in the first trimester, 40 (10%) experienced a miscarriage, and among the live born, 9 (3.6%) had offspring with malformations. The hazard ratio of having a miscarriage after exposure to clarithromycin was 1.56 (95% CI 1.14 to 2.13). There was no increased hazard of having a miscarriage when being exposed to penicillin or erythromycin, and there was no increased prevalence (OR 1.03; 95% CI 0.52 to 2) of having offspring with malformations after exposure to clarithromycin. The authors conclude that there is an increased hazard of miscarriage, but no increased prevalence of having offspring with malformations among women redeeming a prescription of clarithromycin in early pregnancy. However, further research is required to explore the possible effect of treatment indication on the associations found.

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

    RATIONALE: There are few published data on the use of clarithromycin in human pregnancy, but 1 study has reported an increased risk of spontaneous abortion after in utero exposure. To date, exposure to clarithromycin during pregnancy has not been associated with teratogenic effects. Associations with an increased incidence of cardiovascular defects and pyloric stenosis have been made with macrolides as a class, though causality has not been conclusively established. If treatment is required, penicillins along with cephalosporins may be used if clinically appropriate. If a macrolide antibiotic is required in pregnancy, erythromycin would be considered the preferred agent as there is more data on its use. Use of the newer macrolides, such as clarithromycin, should be reserved for compelling indications.

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

    RATIONALE: A nested case-control study within the Quebec Pregnancy Cohort between 1998 and 2009, aiming to quantify the association between antibiotic exposure during pregnancy and risk of spontaneous abortion. Spontaneous abortion was defined as having

a diagnosis or procedure related to spontaneous abortion before the twentieth week of pregnancy. Use of antibiotics was defined by filled prescriptions between the first day of gestation and the index date. Results indicated that azithromycin (OR 1.65; 95% CI 1.34 to 2.02), clarithromycin (OR 2.35; 95% CI 1.90 to 2.91), metronidazole (OR 1.70; 95% CI 1.27 to 2.26), sulphonamides (OR 2.01; 95% CI 1.36 to 2.97), and tetracyclines (OR 2.59; 95% CI 1.97 to 3.41) were associated with an increased risk of spontaneous abortion. The authors conclude that the use of macrolides (excluding erythromycin), quinolones, tetracyclines, sulphonamides, and metronidazole should be avoided during early pregnancy due to the increased risk of spontaneous abortion. Erythromycin may be used as an alternative treatment for pregnant women.

4. Lewis RE, Klepser ME, Ernst EJ, Snabes MA, Jones RN. Comparison of oral immediate-release (IR) and extended-release (ER) metronidazole bactericidal activity against Bacteroides spp. using an in vitro model of infection. *Diagn Microbiol Infect Dis.* 2000 May; 37(1):51-55. Available from: www.ncbi.nlm.nih.gov/pubmed/10794941.

   RATIONALE: A prospective study using an in vitro infection model inside of an anaerobic chamber, simulating the human serum pharmacokinetic profile of oral metronidazole regimens. Findings indicated that the rapid bactericidal activity in vitro of metronidazole administered as a simulated extended-release formulation at 750-1,500mg/day to be equivalent to metronidazole 500mg 3 times daily. This confirms that metronidazole exhibits rapid, concentration-dependent bactericidal activity over a broad range of clinically achieved concentrations against Bacteroides species, and demonstrates a prolonged post-antibiotic effect (>3 hours). This supports the 400mg 3 times daily dosing regimen over 200mg, as 400mg will attain about twice the tissue concentrations, and as killing rate is concentration-dependent, this will be improved.

5. Cudmore SL, Delgaty KL, Hayward-McClelland SF, Petrin DP, Garber GE. Treatment of infections caused by metronidazole-resistant *Trichomonas vaginalis. Clin Microbiol Rev.* 2004 Oct; 17(4):783-793. Available from: www.ncbi.nlm.nih.gov/pmc/articles/PMC523556/.
   RATIONALE: A review article discussing different dosing regimens (250mg 3 times daily; 500mg twice daily; 2g single dose) of oral metronidazole. This article states that the concentration of metronidazole in serum, specifically peak concentration in plasma and minimum lethal concentration, are dependent on dosage. All 3 of the oral dose regimens achieve peak concentrations in plasma in 1 to 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 minimum lethal concentration, before slow, steady elimination.

6. Medicines.org. *Flagyl 400mg Tablets.* Available from:
   www.medicines.org.uk/emc/medicine/21216 [Accessed: 23 September, 2016].
   RATIONALE: An EMC webpage outlining the therapeutic indications and side-effects of 400mg metronidazole tablets. This webpage states that the frequency of adverse events are either rare, very rare, or not known. Serious adverse reactions occur rarely with standard recommended regimens.

7. Pahkla ER, Koppel T, Saag M, Pahkla R. Metronidazole concentrations in plasma, saliva and periodontal pockets in patients with periodontitis. *J Clin Periodontol.* 2005 Feb; 32(2):163-

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166. Available from: www.ncbi.nlm.nih.gov/pubmed/15691346.

    RATIONALE: A prospective study aiming to compare the concentrations of metronidazole in plasma, saliva, and gingival crevice fluid in patients with periodontitis, after multiple administration. 11 patients with severe generalised adult periodontitis participated in the study, and metronidazole concentrations in all fluids were measured 2 hours after the last dose. The authors conclude that metronidazole penetrates well into gingival crevice fluid and saliva. General pharmacokinetic data of metronidazole can be applied in the treatment of periodontal disease, and in the design of respective treatment regimens.

8. Lamp KC, Freeman CD, Klutman NE, Lacy MK. Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials. *Clin Pharmacokinet.* 1999 May; 36(5):353-373. Available from: www.ncbi.nlm.nih.gov/pubmed/10384859.

    RATIONALE: A review article covering the pharmacokinetics of metronidazole, and highlighting that the volume of distribution at steady state in adults is 0.51 to 1.1L/kg. This means that, as body mass increases, the tissue concentrations decrease. Metronidazole reaches 60-100% of plasma concentrations in most tissues studied. As the BMI of the general population is increasing, it is likely that higher doses of metronidazole will be needed to attain similar concentrations attained in patients in trials undertaken more than 10 years ago.

9. Wexler H. Metronidazole resistance in *Bacteroides fragilis*: an integrated approach. National Institutes of Health. 2015 Nov. Available from: http://grantome.com/grant/NIH/R21-AI109545-02.

    RATIONALE: A large prospective laboratory study seeking to identify mechanisms that confer metronidazole resistance in *Bacteroides fragilis*, using an integrated approach combining classical genetics, Next Generation Sequencing technology, and molecular manipulation to relate function to specific genes. This study determined susceptibility of 579 different anaerobes, and found that the minimum inhibitory concentration levels were similar in oral bacteria to other anaerobes. The authors conclude that the same antibiotics used for *Bacteroides fragilis* throughout the body can also be used for dental infections.

10. Poulet PP, Duffaut D, Barthet P, Brumpt I. Concentrations and in vivo antibacterial activity of spiramycin and metronidazole in patients with periodontitis treated with high-dose metronidazole and the spiramycin/metronidazole combination. *J Antimicrob Chemother.* 2005 Mar; 55(3):347-351. Available from: www.ncbi.nlm.nih.gov/pubmed/15695539.

    RATIONALE: A prospective randomised controlled trial, demonstrating that metronidazole 500mg TDS alone, or in combination with spiramycin (1,500,000 units, plus 250mg metronidazole) is an effective treatments for active periodontitis. The metronidazole at 250mg and 500mg TDS consistently exceeds the MICs for the pathogens isolated in the corresponding sites (most of the bacterial species were eradicated during treatment and at follow-up). The authors conclude that the currently used metronidazole dose of 250mg 3 times daily could be sufficient for the treatment of active periodontitis. As killing by metronidazole is time dependent, it is better to attain crevice fluid concentrations several times that of the measured MICs, 400mg 3 times daily can be recommended.

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Abbreviations

°C = Degrees centigrade

ABRS = Acute bacterial sinusitis

AIDS = Acquired immune deficiency syndrome

AKI = Acute kidney infection

AmB = Amphotericin B deoxycholate

AMT = Abbreviated mental test

AOM = Acute otitis media

AOM-SOS = Acute Otitis Media Severity of Symptoms Scale

AOR = Adjusted odds ratio

ARD = Adjusted risk difference

ARR = Adjusted risk ratio

ASB = Asymptomatic bacteriuria

ASD = Autism spectrum disorder

AUC = Area under the curve

BD = Twice daily

B-haemolytic = Beta-haemolytic

BMI = Body mass index

BP = Blood pressure

CAP = Community-acquired pneumonia

C. difficile = *Clostridium difficile*

CDAD = *Clostridium difficile*-associated disease

CFU = Colony-forming unit

CI = Confidence interval

COPD = Chronic obstructive pulmonary disease

COX2 = Cyclooxygenase-2

CPD = Continued professional development

CRB65 = Confusion; Respiratory rate; BP systolic; Age >65

CrCl = Creatinine clearance

CRP = C-reactive protein

d = Day

DU = Duodenal ulcer

E. coli = *Escherichia coli*

104

eGFR = Estimated glomerular filtration rate

ESBL(s) = Extended-spectrum beta-lactamase(s)

FEV1 = FEV1/FVC ratio

FeverPAIN = Fever; Purulence; Attend rapidly; Inflamed tonsils; No cough or coryza

g = Gram(s)

GABHS = Group A Beta-haemolytic Streptococci

GAS = Group A Streptococci

GC = Gonorrhoea

GFR = Glomerular filtration rate

GORD = Gastro-oesophageal reflux disease

GP(s) = General practitioner(s)

GU = Gastric ulcer

GUM = Genitourinary medicine

H. influenzae = *Haemophilus influenzae*

HIV = Human immunodeficiency virus

H. pylori = *Helicobacter pylori*

HR = Hazard ratio

i/r = Immediate release

iGAS = Invasive Group A Streptococci

IM = Intramuscular

IV = Intravenous

kg = Kilogram(s)

K. pneumoniae = *Klebsiella pneumoniae*

l = Litre(s)

m/r = Modified release

MALToma = Mucosa-associated lymphoid tissue lymphoma

mcg = Microgram(s)

MD = Mean difference

MDRD = Modification of Diet in Renal Disease

MDREB = Multi-drug resistant Enterobacteriaceae

mg = Milligram(s)

MIC(s) = Minimum inhibitory concentration(s)

ml = Millilitre(s)

M. pneumoniae = *Mycoplasma pneumoniae*

105

MRC = Medical Research Council dyspnoea (breathlessness) scale

MRSA = Methicillin-resistant *Staphylococcus aureus*

MSM = Men who have sex with men

MSU = Midstream urine

n = Number

NI(s) = Neuraminidase inhibitor(s)

NNT = Number needed to treat

NNTB = Number needed to benefit

NNTH = Number needed to harm

NPV = Negative predictive value

NSAID(s) = Non-steroidal anti-inflammatory drug(s)

OD = Once daily

OPAT = Outpatient parenteral antibiotic therapy

OR(s) = Odds ratio(s)

PHN = Post-herpetic neuralgia

PID = Pelvic inflammatory disease

P. intermedia = *Prevotella intermedia*

PNS *S. pneumoniae* = Penicillin-nonsusceptible *Streptococcus pneumoniae*

PP = Per-protocol

PPI = Proton pump inhibitor

PPV = Positive predictive value

PVL = Panton-Valentine Leukocidin

QDS = Four times daily

RCT(s) = Randomised controlled trial(s)

RD = Risk difference

RR = Relative risk

RTI(s) = Respiratory tract infection(s)

SAT = Stool antigen test

S. aureus = *Staphylococcus aureus*

S. pneumoniae = *Streptococcus pneumoniae*

SLCI = Symptomatic laboratory-confirmed influenza

STI(s) = Sexually transmitted infection(s)

T = Temperature

TARGET = Treat Antibiotics Responsibly: Guidance, Education, Tools

106

TDS = Three times daily

TMP-SMX = Trimethoprim sulfamethoxazole

TSS = Toxic shock syndrome

U = Units

UBT = Urea breath test

UHD(s) = Ulcer healing drug(s)

UK = United Kingdom

USA = United States of America

UTI(s) = Urinary tract infection(s)

WCC = White cell count