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tract infections P. Little ESSENTIALS Acute upper respiratory tract infections are one of the commonest reason for patients to seek medical advice in the United Kingdom. Pharyngitis/tonsillitis—this is caused by both bacterial and viral or- ganisms, with sore throat often accompanied by fever, headache, and other symptoms. Investigations are not generally performed or required. Antibiotics have modest benefit, so for patients who are not unwell systemically the physician should either not prescribe, or use a delayed prescribing approach which is likely to have similar bene- fits to an immediate antibiotic prescription, advising the patient to wait for several days before collecting or using their prescription. If an antibiotic is considered, the antibiotic of choice is probably penicillin V, with a short-acting macrolide the second-line agent. The benefits of tonsillectomy in preventing recurrent sore throat are modest. Acute rhinitis—causes nasal congestion and rhinorrhoea, mild malaise, sneezing, sore throat, variable loss of taste and smell, and usually recovers within two weeks. Oral and topical decongestants may help symptoms but have significant side effects, and antibiotics provide limited benefit. Acute sinusitis—usually defined as an infection that lasts for less than three weeks, is an uncommon complication of coryzal illness and pharyngitis. Diagnosis based on a clinical risk score is reasonably sensitive and specific, but the effectiveness of antibiotics or other treatments is questionable. Introduction Acute upper respiratory tract infections (URTIs) include acute pha- ryngitis/tonsillitis and acute rhinitis.

Acute sinusitis, acute otitis media, and influenza also come under the umbrella of infections of the upper respiratory tract. Otitis media and influenza will be dis- cussed elsewhere: this chapter concentrates on acute pharyngitis/ tonsillitis, acute rhinitis, and acute sinusitis. Acute URTIs are one of the commonest reason for patients to seek medical advice in the United Kingdom, and nearly all cases are man- aged in primary care. Respiratory tract infections are also the com- monest reason for antibiotics to be prescribed, leading to serious concern that the inappropriate use of antibiotics for predominantly self-limiting conditions will foster the development of antibiotic resistance, with the danger that serious infections will become un- treatable. Thus it is currently an international priority to discourage the use of antibiotics where there is poor evidence of their efficacy. The evidence for the effectiveness of treatments for URTI in this chapter comes from a search of the Cochrane Library databases of systematic reviews and randomized controlled trials. Pharyngitis/tonsillitis Clinical presentation Pharyngitis is caused by both bacterial and viral organisms, and has been somewhat arbitrarily divided into nasopharyngitis (with 18.4 Respiratory infection

18.4.1 Upper respiratory tract infections 4005 nasal symptoms, i.e. rhinitis), and pharyngitis or tonsillopharyngitis (without nasal symptoms). Causal organisms include: group A β-haemolytic streptococcus; adenoviruses; influenza A and B; parainfluenza 1, 2, 3; Epstein–Barr virus (EBV); enteroviruses; Mycoplasma pneumoniae; and Chlamydia pneumoniae. In addition to a sore throat, pharyngitis is often accompanied by fever, headache, nausea, vomiting, anorexia, and sometimes abdom- inal pain, with or without enlarged and tender cervical lymph nodes, tonsillar erythema, and exudate. Scarlet fever has a characteristic 'scarlatiniform' rash caused by group A β-haemolytic streptococcal exotoxins. Infectious mononucleosis due to EBV may present with or without exudative tonsillitis, cervical or general lymphadenop- athy, palatal petechiae, splenomegaly, rhinitis, and cough. Throat swabs, rapid tests, and clinical algorithms Antibiotics can be targeted to those patients who have positive throat swabs for group A streptococcus; those who have group A, C, or G streptococci; or those who have a positive rapid antigen detec- tion test (RADT designed to detect group A). However, the results of throat swabs take days to return to the clinic, and they signifi- cantly increase the costs of managing what is mostly a self-limiting condition. Alternatively antibiotics can be targeted to individuals with clin- ical characteristics associated with a positive throat swab for patho- genic streptococci. Various systems have been devised to try and do this. The Centor criteria—designed to predict the presence of group A streptococci—awards one point for each of high temperature; pus; nodes; the absence of cough. Patients with scores of 3–4 are typically offered antibiotic treatment. The FeverPAIN score—designed to pre- dict the presence of A, C, or G streptococci—awards one point each for Fever; Pus; rapid Attendance (<=3 days); very Inflamed tonsils; No cough or coryza. The likelihood of streptococcal infection is as follows: score 0–1, 13–18% (no antibiotic strategy recommended); score 2–3, 34–40% (back-up antibiotic prescription strategy recom- mended); score 4 or more, 62–65% (immediate antibiotic strategy recommended if severe). A small Canadian trial compared using the Centor criteria or an RADT and demonstrated reduction in antibiotic use when the RADT was used, but not with the Centor criteria. A larger UK trial of the FeverPAIN score demonstrated both a reduction in antibiotic use and better symptom control when using FeverPAIN, but no add- itional benefit of additionally using an RADT for those with high FeverPAIN scores. Treatment Antibiotics for symptoms The Cochrane review of the efficacy of antibiotics for the treatment of sore throat indicates that antibiotics have modest benefit in redu- cing the symptoms. At day 3, where the maximal benefit was found, 49% of the antibiotic group compared to 66% of the placebo

group still had sore throat (i.e. the number needed to treat for benefit (NNTB) was 6, and the estimated NNTB at one week was 21). This marginal benefit of antibiotics in resolving symptoms suggests that, for patients who are not unwell systemically, the physician should either not prescribe, or use a delayed prescribing approach, ad- vising the patient to wait for several days before collecting or using their prescription. Both these approaches have been shown in a large randomized controlled trial to be acceptable, to change atti- tudes and behaviour, and not to delay symptom resolution appre- ciably (Fig. 18.4.1.1). Antibiotics to prevent complications The Cochrane review of antibiotics for treating a sore throat sup- ports the use of antibiotics to prevent complications, but the evi- dence is limited by both clinical importance and generalizability. For the commoner complications (e.g. otitis media), more than 50 people would have to be treated to prevent one case of a self-limiting illness, and from more recent trials nearer 200 people would need to be treated: in other words, it is not important clinically. For the rarer complications—rheumatic fever and glomerulonephritis—the evidence is not generalizable; for instance, evidence of efficacy in rheumatic fever is based largely on trials where intramuscular peni- cillin was used in barracked military personnel after the Second World War. This evidence cannot be sensibly applied to modern set- tings where the attack rate is much lower and oral antibiotics are used. However, the benefits of antibiotics are likely to be greater in settings where complications are much more common. The commonest complication of practical importance to health services is quinsy (peritonsillar abscess), but this is still relatively uncommon—about 1 in 200 to 1 in 400 following presentation in primary care with sore throat. The Cochrane systematic review, which demonstrates that antibiotics prevent quinsy, relies on data from patients with tonsillitis who were systemically unwell enough to be admitted to hospital shortly after the Second World War, when the prevalence of quinsy in untreated patients was very high (1 in 18). Clearly, this data cannot be extrapolated to patients pre- senting from modern populations who are not systemically unwell, 100 80 60 40 20 0 Days with sore throat Cumulative percentage 0 1 2 3 4 5 6 7 8 9 ≥10 Group 1 Immediate antibiotics Group 2 No antibiotics Group 3 Offer of delayed antibiotics Fig. 18.4.1.1 A trial of three pragmatic antibiotic prescribing strategies: the graphs show the percentage of patients cured in the days following seeing the doctor. Reproduced from BMJ, Little et al., 314, 722–7, copyright 1997 with permission from BMJ Publishing Group Ltd.

 treated with oral antibiotics, and where the prevalence of quinsy is much lower. Quinsy following sore throat is possibly slightly more common (1 in 60) in those who are unwell, with three out of four Centor criteria, most of whom have fever. Rigorously con- ducted placebo-controlled trials in patients with these criteria suggest quinsy may be prevented by oral penicillin, but in routine clinical practice, where compliance is not assessed, the preventive benefit of penicillin is not likely to correspond to trials where com- pliance is more tightly controlled. The lesser effect of antibiotic in preventing complications in routine practice compared with trial data has been confirmed in the recent large DESCARTE pro- spective observational study. There has been no increase in admissions with quinsy since the uptake of the delayed prescribing strategy in the United Kingdom. In the DESCARTE cohort study it was not possible to predict accurately which individuals developed complications, and al- though immediate antibiotic or delayed antibiotics both reduced complications effectively, complications of acute sore throat were uncommon (1%) and mostly not serious (otitis media or sinus- itis). Delayed antibiotics and immediate antibiotics both reduced reconsultations, but delayed antibiotic prescription was associated with a larger reduction in reconsultations than immediate anti- biotics. This suggests that most people do not need any antibiotic for acute sore throat, but that if a clinician is

concerned and an antibiotic is being considered, a delayed antibiotic prescription is preferable.
Lemierre syndrome—a rare complication This syndrome, caused by fusobacterium—an anaerobe that is part of normal throat flora—has been highlighted recently following a rise in reports between 1990 and 2000 to about 20 per year in the United Kingdom. A patient with pharyngitis does not improve, remains pyrexial, and develops pharyngeal swelling due to a local abscess. Internal jugular thrombosis or embolism to the lungs com- monly occurs or is suspected, and in such cases prompt referral to hospital is needed. The condition responds to metronidazole, but—since the differential diagnosis is incipient quinsy—high-dose peni- cillin should also probably be given. Isolates in case series have been sensitive to metronidazole, with a small minority resistant to peni- cillin or erythromycin. However, to encourage increased prescribing of antibiotics on the basis of an increase in Lemierre's syndrome is unwarranted: it would increase the dangers of both resistance and anaphylaxis—and anaphylaxis, although rare, is still commoner than Lemierre's syndrome. Which antibiotic and for how long? A Cochrane systematic review has concluded that cephalosporins may provide minimal additional benefit to penicillin in acute sore throats. There was no significant difference in symptom resolution between cephalosporins and penicillin (odds ratio for absence of resolution of symptoms (OR) 0.79), but clinical relapse was lower with cephalosporins (OR 0.55), although the absolute effect was very small (overall NNTB 50, and found only in adults, OR 0.42, NNTB 33). Hence, if an oral antibiotic is to be prescribed, then it is probably preferable to give a narrow-spectrum antibiotic (penicillin V) to minimize side effects and the risk of resistance developing. If penicillin V is used, there are arguments for using a large dose given the variable absorption (e.g. 2 g/day adults and 1 g/day children). A 10-day course will better eradicate streptococcus, but the clinical significance of this is unclear. Longer courses have the disadvantage of poorer compliance, and greater likelihood of antibiotic resistance developing in the long term. Twice-daily dosing of penicillin V com- pared with the same total dose of more than four doses per day may result in better compliance and better clinical/microbiological out- comes. Intramuscular injection of penicillin can be used, although in practice is rarely employed in the United Kingdom. Ampicillin will cause a rash in patients with infectious mononucleosis, so erythromycin is a suitable second-line agent among patients with penicillin allergy. Treatment of patients with rheumatic fever Patients who have had one attack of rheumatic fever are at a higher risk from new infections since they are likely to develop recurrent attacks of rheumatic fever and complications. Although most of the evidence for the prevention of rheumatic fever comes from old trials in unusual settings, it seems reasonable to treat patients with a past history who are at a high risk of recurrence and secondary com- plications, since what evidence there is suggests penicillin prevents rheumatic fever. (See Chapter 16.9.1 for further discussion of the issues involved.) Other medical treatments Treatment with aspirin in children is contraindicated because of the small but avoidable risk of Reye's syndrome. There are sev- eral trials of the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in providing effective relief of pain and fever in tonsil- litis and pharyngitis, but a Cochrane review suggests very limited benefit among participants with the common cold. Furthermore, the limited trial evidence comparing them with standard treat- ment (paracetamol) does not clearly demonstrate their superiority. A recent pragmatic trial documented some harm in advising the regular use of ibuprofen compared with the use of paracetamol, resulting in more reconsultations with a nonresolution of illness and also increased complications, presumably due to suppressing the inflammatory component of the immune response. Limited trial data suggest that other useful analgesic adjuncts may in- clude caffeine, and benzydamine hydrochloride gargle. There is also evidence from a systematic review that patients with more severe presentations who are receiving antibiotics may benefit from steroids, but there is no

evidence as yet from a more typ- ical primary care sample, nor among those where no antibiotic are prescribed. Recurrent attacks Surgery A Cochrane review of nine trials assessed the role of surgery for chronic/recurrent sore throat. For episodes of moderate/severe sore throat, children had on average 1.1 episodes of sore throat in the first postoperative year, compared with 1.2 episodes in the control group of less severely affected children had more episodes of moderate/severe sore throat after surgery (1.2 episodes) than in the control group (0.4 episodes), and as with the more severe episodes, one episode was the predictable postoperative episode. When discussing options with parents, the modest benefits of surgery must be weighed against its disadvantages: tonsillectomy

18.4.1 Upper respiratory tract infections 4007 has complications (4–7% requiring operative surgery for haemor- rhage, or other significant symptoms such as severe nausea and dehydration). Other treatments There is preliminary trial evidence for the use of α-streptococci spray, immune stimulants, and pneumococcal vaccination, but fur- ther confirmation is required. Nasal congestion and rhinorrhoea Nasal symptoms are a common reason for attending the doctor. They may be due to a variety of causes—commonly acute viral in- fection (common cold), allergic rhinitis and sinusitis, vasomotor rhinitis and rhinitis medicamentosa, and less commonly atrophic rhinitis, hormonal rhinitis, and mechanical/obstructive rhinitis. Colds are responsible for significant morbidity: on average there are 0.4 episodes and 1.2 days of restricted activity per person per year for the common cold. Acute rhinitis Symptoms are acute nasal congestion and rhinorrhoea, mild mal- aise, sneezing, sore throat, variable loss of taste and smell, and usu- ally last from 1 to 2 weeks unless sinusitis is present. Examination reveals a hyperaemic and oedematous mucosa, with or without purulent secretions. Treatment Symptomatic Trial evidence supports the use of both oral and topical decongestants for the symptoms of rhinitis. Intranasal ipratropium bromide is also effective symptomatic treatment, but only available (in the United Kingdom) on prescription. However, topical decongestants should probably not be used for more than a maximum of 7 days: rhinitis medicamentosa starts to develop at 10 days. A Cochrane review of oral antihistamines, with or without decongestants and analgesics, suggests they do help, but side effects such as drowsiness, dry mouth, insomnia, and dizziness are common. Because of their moderate systemic effects, care should be taken with oral decongestants in pa- tients with heart disease and hypertension. Saline drops are com- monly advocated, but saline or medicated nose drops have been shown to be ineffective in trials in both children and adults. A recent trial of steam inhalation for respiratory infections demonstrated no benefit and some harm (mild thermal injury). Antibiotics The use of antibiotics for the common cold has been assessed in a Cochrane systematic review and shown to provide modest benefit. Other Reviews of trials indicate little benefit from antihistamines or zinc lozenges. A Cochrane review of the herb echinacea demonstrated very modest results in most studies, and there was not enough evi- dence to recommend the use of a specific product. Acute sinusitis Diagnosis Acute sinusitis, usually defined as an infection that lasts for less than 3 weeks, is an uncommon complication of coryzal illness and pha- ryngitis. There is no absolute standard against which symptoms and signs can be compared for accuracy of diagnosis: aspiration by sinus puncture is probably the definitive investigation, since it indicates the presence of infecting organisms, but for obvious reasons this is rarely performed, and contamination by commensal organisms can occur. A four-item clinical risk score developed to predict bacterial infections—of purulent rhinorrhoea with unilateral predomin- ance, local pain with unilateral predominance, bilateral purulent rhinorrhoea, and presence of pus in the nasal cavity—is as sensitive and specific as any other method in predicting the results of antral sinus puncture. Thus, for acute sinusitis, diagnostic tests are not cur- rently indicated, and until valid near-patient

tests are available, clin- ical targeting probably performs as well as any other method. Treatment Antibiotics A Cochrane review of all controlled trials in a primary care setting, where the vast majority of sinusitis is managed, suggests that the absolute benefit for symptom resolution is moderate and must be balanced against the disadvantages of prescribing antibiotics. An in- dividual patient data meta-analysis of trials using a clinical diagnosis documented a number needed to treat of 15 for all patients and 8 for those with purulence, and no greater benefit for those with symp- toms for longer than a week. Thus both the effectiveness and cost- effectiveness of antibiotic treatment of acute sinusitis in primary care is questionable for most patients. Other There is limited evidence that antihistamines may be helpful for pa- tients with a history of allergic rhinitis who develop sinusitis, and very limited evidence that some proteolytics (e.g. bromelain) and mucolytics may help. There is mixed trial evidence for the benefit of topical steroids. Although trials of NSAIDs suggest they are helpful, they may not be significantly more effective than paracetamol. FURTHER READING Little PS, et al. (1997). An open randomised trial of prescribing strat- egies for sore throat. BMJ, 314, 722–7. Little PS, et al. (1997). Reattendance and complications in a random- ised trial of prescribing strategies for sore throat: the medicalising effect of prescribing antibiotics. BMJ, 315, 350–2. Little P, et al. (2013). Ibuprofen, paracetamol, and steam for patients with respiratory tract infections in primary care: pragmatic ran- domised factorial trial. BMJ, 347, f6041. Little P, et al. (2014). Antibiotic prescription strategies for acute sore throat:a prospective observational cohort study. Lancet Infect Dis, 14, 213–9. Little P, et al. (2014). PRImary care Streptococcal Management (PRISM) study: in vitro study, diagnostic cohorts and a pragmatic adaptive

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