CLINICAL GUIDELINE

Guideline for the Management of Upper Respiratory Tract Infections

Working Group of the Infectious Diseases Society of Southern Africa

Introduction. Inappropriate use of antibiotics for upper respiratory tract infections (URTIs), many of which are viral, adds to the burden of antibiotic resistance. Antibiotic resistance is increasing in *Streptococcus pneumoniae*, responsible for most cases of acute otitis media (AOM) and acute bacterial sinusitis (ABS).

Method. The Infectious Diseases Society of Southern Africa held a multidisciplinary meeting to draw up a national guideline for the management of URTIs. Background information reviewed included randomised controlled trials, existing URTI guidelines and local antibiotic susceptibility patterns. The initial document was drafted at the meeting. Subsequent drafts were circulated to members of the working group for modification. The guideline is a consensus document based upon the opinions of the working group.

Output. Penicillin remains the drug of choice for tonsillopharyngitis. Single-dose parenteral administration of benzathine penicillin is effective, but many favour oral administration twice daily for 10 days. Amoxycillin remains the drug of choice for both AOM and ABS. A dose of 90 mg/kg/day is recommended in general, which should be effective for pneumococci with high-level penicillin resistance (this is particularly likely in children ≤ 2 years of age, in day-care attendees, in cases with prior AOM within the past 6 months, and in children who have received antibiotics within the last 3 months).

Alternative antibiotic choices are given in the guideline with recommendations for their specific indications. These antibiotics include amoxycillin-clavulanate, some cephalosporins, the macrolide/azalide and ketolide groups of agents and the respiratory fluoroquinolones.

Conclusion. The guideline should assist rational antibiotic prescribing for URTIs. However, it should be updated when new information becomes available from randomised controlled trials and surveillance studies of local antibiotic susceptibility patterns.

1. Introduction

There is a worldwide increase in antibiotic resistance, largely related to inappropriate use of antibiotics; studies suggest that inappropriate use of antibiotics for upper respiratory tract infections (URTIs) adds to the burden.[1]

Viral infections cause the majority of URTIs. All clinicians should know the natural history of the 'common cold' so that a deviation from normal is managed effectively. Most important is an appreciation that clear nasal secretions frequently become purulent without signifying secondary bacterial disease, and that coughing is a normal accompaniment (Fig. 1).

The organisms responsible for most bacterial URTIs are similar in all age groups. *Streptococcus pneumoniae* is by far the commonest organism causing otitis media and sinusitis. *S. pyogenes* is the only significant bacterial cause of pharyngitis. Systematic reviews suggest that in developed countries the benefit of antibiotics for pharyngitis and otitis media is extremely limited; however, there are few data from poorer countries where rheumatic fever and suppurative complications such as mastoiditis are likely to be more common.[2,3]

South African experience suggests a high prevalence of rheumatic fever, despite poor notification rates. For example, 66

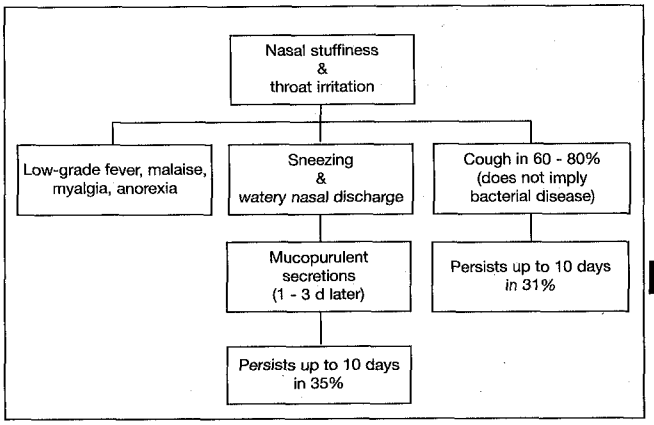

Fig. 1. Natural history of the common cold.

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new cases of rheumatic heart disease are referred annually to the paediatric cardiology clinic at the Johannesburg General Hospital (personal communication — Dr W Hendson). In the Western Cape, 49 new cases are seen every year at Red Cross War Memorial and Tygerberg Children's hospitals (personal communication — Dr J Lawrenson and Professor P L van der Merwe). At Umtata General Hospital, 125 children with rheumatic fever were admitted between January 1998 and January 2000, comprising 2% of paediatric admissions. The majority (76%) had two or more episodes of rheumatic fever, which was strongly associated with overcrowding (> 6 people per room) (personal communication — Professors A S Savio and A Targonski, University of Transkei).

By establishing simple guidelines recommending antibiotics with a relatively narrow spectrum, patients ought to be well managed and serious complications avoided. The most frequently recommended first-line antibiotics remain penicillin and amoxycillin.

The recommendations for duration of therapy differ; pharyngotonsillitis and acute bacterial sinusitis (ABS) should be treated for 5 - 10 days and acute otitis media (AOM) for 5 - 7 days. In this regard, recent evidence suggests that a shorter duration of antibiotic treatment is associated with less emergence of resistant pathogens.[4]

The recommendations for frequency of administration vary according to the site of infection and the pharmacokinetic/pharmacodynamic (PK/PD) profiles of the drugs used; in AOM a twice-daily dose of amoxycillin has the same clinical efficacy as 3 times a day.

For optimal clinical success, the antibiotic dosage must be tailored to the individual. The most common cause of treatment failure and antibiotic resistance is sub-optimal dosing. For example in AOM, 5 ml is erroneously prescribed as a standard dose for a child weighing 5 - 15 kg instead of individualising doses by body mass. Dosages given in this guideline include both the registered standard doses and higher doses, which are recommended for use in situations where high-level antibiotic resistance has been reported. Except for amoxycillin and amoxycillin-clavulanate, all paediatric doses are given as mg per kg per dose followed by frequency of daily administration.

Recommendations have been made based on national surveillance of appropriate pathogens and relevant publications.[5] For *S. pneumoniae*, the most common pathogen causing otitis media and acute sinusitis, resistance to β-lactam antibiotics can be overcome by increasing dosage. For example, a higher dose of amoxycillin of 90 mg/kg/day is generally recommended for treatment of AOM. Because of concerns about the existence of macrolide resistance among isolates of *S. pneumoniae* in some areas of practice in South Africa, in those circumstances this class should preferably be reserved for patients with β-lactam antibiotic allergy.

The guideline gives indications for recommended first-line agents as well as alternative choices of antibiotics. The first-line antibiotics are the agents of choice and remain penicillin or amoxycillin. The indications for alternative antibiotics may include the following:

- Allergy or intolerance to first-line agents.
- Recent prior use of first-line agents.
- High-risk cases likely or known to be infected with highly resistant organisms. Consideration needs to be given to β-lactam and macrolide resistance.
- Failed initial therapy.

Few guidelines have been subjected to the rigours of prospective evaluation and most are based on best practice, taking into account unique local circumstances. In South Africa, widespread implementation of throat cultures for pharyngitis is unlikely to occur because an extensive infrastructure would need to be established for an easily treated condition.

2. Acute pharyngotonsillitis

Pharyngotonsillitis is an inflammatory condition of the pharyngeal wall, sometimes divided into pharyngitis and tonsillitis. Respiratory viruses are the major cause of pharyngitis and include the Epstein-Barr virus that causes infectious mononucleosis. Bacteria, especially group A β-haemolytic streptococci (GABHS) (*S. pyogenes*), account for between 5% and 30% of cases. In terms of the ability of throat cultures to diagnose streptococcal pharyngotonsillitis, the specificity approaches 80% while the sensitivity is only 30%, when compared with a rise in or a high level of antistreptolysin O titre.[6] Non-infectious causes of pharyngitis include allergy and exposure to irritating substances.

Although in most instances GABHS tonsillitis is usually self-limited, antibiotics are recommended to prevent the suppurative and non-suppurative (acute rheumatic fever, glomerulonephritis) post-streptococcal sequelae. The only known risk factor for rheumatic fever is pharyngitis caused by rheumatogenic strains of GABHS, common in both poor rural and urban environments in South Africa. The recommendations of the guideline should therefore be easy to apply and should be such that they would be associated with prevention of rheumatic fever.

2.1 Treatment of streptococcal pharyngotonsillitis

The treatment of choice is penicillin.

2.1.1 Penicillin

There is evidence that intramuscular penicillin prevents rheumatic fever.[7] Although intramuscular injections are not popular, attempts should be made to administer penicillin parenterally if compliance and follow-up are unlikely. The mixture of benzathine penicillin and procaine penicillin results in a less painful injection.[8] Penicillin can be given twice or 3 times daily by mouth instead of 4 times a day, as previously

recommended. Penicillin should be given 30 minutes before a meal as food may reduce its absorption. A 10-day course is still recommended. An important point for continued use of penicillin is the lack of resistance by GABHS, as opposed to erythromycin and other macrolides, where resistance is associated with excessive use.[9,10] Furthermore, a particular advantage of penicillin is its narrow spectrum of activity.

Children

- Penicillin VK
  250 mg twice daily for 10 days (≤ 27 kg)
  500 mg twice daily for 10 days (> 27 kg)
  (given 30 minutes before food).
- Benzathine penicillin (intramuscular injection)*
  3 - 5 yrs: 600 000 U
  > 5 yrs: 1.2 MU.

Adults and adolescents

- Penicillin VK, 500 mg twice daily for 10 days (given 30 minutes before food)
- Benzathine penicillin (intramuscular injection), 1.2 MU as single dose.*

2.1.2 Amoxycillin

Amoxycillin is an alternative to penicillin VK and has the advantage of no food restrictions. However, a rash can occur where pharyngotonsillitis is due to Epstein-Barr virus infection. This can lead to an erroneous diagnosis of penicillin allergy or, rarely, a severe skin reaction. Therefore amoxycillin should preferably only be used when GABHS has been identified by culture.

Children

- Amoxycillin, 25 mg/kg twice daily for 10 days.

Adults

- Amoxycillin, 500 mg twice daily for 10 days.

2.1.3 Short-course therapy (3 - 5 days)

Short-course therapy is a recent development.[12-17] Adam and colleagues[12] showed equivalence between penicillin given 3 times daily for 10 days and a number of regimens (including use of new macrolides or second-generation cephalosporins) given for 5 days.[12]

The list of agents that have been used for short-course therapy is given below.

Children

- Amoxycillin-clavulanate, 40 mg/kg/day in 3 divided doses
- Azithromycin, 10 - 20 mg/kg once daily for 3 days
- Clarithromycin, 7.5 mg/kg twice daily
- Cefpodoxime, 4 mg/kg twice daily
- Cefprozil, 7.5 mg/kg twice daily
- Cefuroxime, 10 mg/kg twice daily.

Adults

- Amoxycillin-clavulanate, 375 mg 3 times daily
- Azithromycin, 500 mg once daily for 3 days
- Clarithromycin (modified release), 500 mg once daily
- Cefpodoxime, 100 mg twice daily
- Cefprozil, 500 mg twice daily
- Cefuroxime, 250 mg twice daily
- Telithromycin, 800 mg once daily.

*Note: To minimise the discomfort of parenteral administration, the medication should be given at room temperature. For patients receiving 1.2 million U, 300 000 U can be given as procaine penicillin.[11]

3. Acute otitis media

AOM is one of the most common childhood illnesses — an estimated 75% of children have had more than 1 episode by 3 years of age. The prevalence is increasing in children less than 2 years of age, and in those attending day-care facilities or exposed to passive smoking.[18]

The main bacterial causes of AOM are *S. pneumoniae*, non-typable *Haemophilus influenzae* and *Moraxella catarrhalis*. While there is a high rate (~60 - 70%) of spontaneous resolution of AOM caused by *H. influenzae* and *M. catarrhalis*, *S. pneumoniae* infection is the least likely to resolve spontaneously and therefore the most important target for antibiotic therapy. Antibiotic resistance in *S. pneumoniae* is often clinically relevant because of the relatively poor permeability of antibiotics into the middle ear fluid (MEF).

While most of the drugs approved for AOM have good *in vitro* activity against the common AOM pathogens, there are many differences in their *in vivo* activity and penetration into the MEF. Studies in which efficacy of antibiotics used for AOM is measured by symptomatic relief fail to discern major differences between drugs because of the so-called 'Pollyanna phenomenon': drugs with poor *in vivo* activity appear to be effective because of the high rate (67%) of spontaneous recovery of the infection.[19]

Given the high rate of spontaneous resolution of AOM, and the probable viral aetiology, particularly in older infants, some authorities argue that antibiotics should be deferred for at least 48 hours during which the patient is given analgesics and decongestants.[20] A useful approach may be to dispense the antibiotic or provide a prescription, with the instruction that it is to be given (or the prescription filled) if there has not been resolution by 48 hours. This approach is reasonable where good follow-up is possible in children ≥ 2 years of age.

However, because of the risks of a serious infection with *S. pneumoniae* and possible limited access of some patients to health care in South Africa, we recommend that all cases be

treated from the first visit provided that the AOM is correctly diagnosed and distinguished from otitis media with effusion (glue ear); for this reason the eardrum must be visualised during examination. Because pneumatoscopy is seldom used in South Africa and crying can cause a red tympanum, AOM is probably seldom correctly diagnosed. In a recent survey of paediatricians attending a training session on otitis media management from four countries including South Africa, only half were able to make an accurate otoscopic diagnosis after training.[21] For otitis media associated with a bulging tympanum and a temperature > 38°C, immediate treatment should be considered. Another reason for immediate antibiotic use is inability to predict whether the patient will have spontaneous resolution.

Antibiotics are essential if AOM is diagnosed in the following patients:

- Recurrent AOM
- Immunocompromised patients
- Neonates
- Structural ENT or immunological abnormalities
- Fever (temperature > 38°C) or pain > 48 hours
- Day-care attendees or siblings of children attending day-care centres.

Risk factors for resistant *S. pneumoniae* infections include age (≤ 2 years), attendance at day-care centres or siblings of children attending day-care centres, prior AOM within the past 6 months, and receipt of antibiotics within the last 3 months. These influence the choice and dosage of antibiotics.

Paracetamol (10 - 15 mg/kg 4 - 6-hourly) or ibuprofen (10 mg/kg 8-hourly) should be given for analgesia (under- and overdosing are common). Although decongestants are widely prescribed for rhinitis, their use in AOM is controversial. If used, topical application for a maximum of 3 days is preferable to oral administration.

Otitis media may be part of neonatal sepsis and any neonate with fever should be evaluated for sepsis. Investigations should include a blood culture, urine microscopy, culture and sensitivity testing and lumbar puncture in cases where hypothermia (temperature < 35°C) or pyrexia (temperature > 38°C) have been noted. Possible causative organisms in AOM include coliforms, group B streptococci and *Staphylococcus aureus*. Where neonatal sepsis has been excluded and oral therapy is indicated for treatment of AOM, amoxycillin-clavulanate should be given.[22] In a recent Israeli study of infants under 2 months of age in whom tympanocentesis had been done, the spectrum of pathogens cultured was similar to that in older children. *S. pneumoniae* was the most common isolate (46%), of which 20% were not susceptible to penicillin. For this reason, the use of a higher dose of amoxycillin (90 mg/kg/day) or amoxycillin-clavulanate, plus additional amoxycillin (to a total dose of amoxycillin of 90 mg/kg/day), would be appropriate.[23]

3.1 Treatment of AOM

The treatment of choice, except in neonates, is amoxycillin.

3.1.1 Amoxycillin

The dosage recommended is 90 mg/kg/day. This higher dosage is generally recommended since it should provide adequate cover for pneumococcal isolates with high-level penicillin resistance, particularly prevalent in the following circumstances:

- Age ≤ 2 years
- Day-care attendees or siblings of children attending day-care centres
- AOM in previous 6 months
- Receipt of antibiotics during the 3 months preceding the AOM episode.

At the standard dosage of 40 - 50 mg/kg/day, amoxycillin is likely to be reasonably effective for an initial episode of AOM in cases infected with non-β-lactamase-producing *H. influenzae* and penicillin-susceptible and possibly intermediate-resistant *S. pneumoniae*. This dosage may not be high enough to eradicate highly penicillin-resistant strains with minimum inhibitory concentrations (MICs) ≥ 2 μg/ml.

3.1.2 Amoxycillin-clavulanate

The addition of a β-lactamase inhibitor extends the spectrum of amoxycillin against β-lactamase-producing *H. influenzae* and *M. catarrhalis*. A higher dosage of amoxycillin-clavulanate (90 mg/kg/day of amoxycillin and a constant amount of clavulanate 6.4 mg/kg/day) was recently evaluated in a double-tap study (tympanocentesis at the beginning and end of treatment course). All penicillin-susceptible and intermediate-resistant and 91% of high-level penicillin-resistant pneumococci were eradicated. In addition, 95% of *H. influenzae* and all *M. catarrhalis* were eradicated.[24] Until this formulation is registered in South Africa, amoxycillin should be added to amoxycillin-clavulanate to give 90 mg/kg/day of amoxycillin.

3.1.3 Oral cephalosporins

Cefuroxime axetil, cefprozil and cefpodoxime are the only oral cephalosporins that may reach MEF levels sufficiently above the MIC for both penicillin-sensitive and some intermediate-resistant *S. pneumoniae* and for *H. influenzae*.[25] Considering the high prevalence of β-lactam resistance in many areas of South Africa, it is recommended that if these cephalosporins are used for treatment of AOM, they should be prescribed at the higher dosages detailed below. The bacterial efficacy of cefpodoxime has not been evaluated in prospective, comparative, double-tap studies. Cefaclor, cefixime and loracarbef are less active *in vitro* against *S. pneumoniae* and are not recommended.

3.1.4 Parenteral cephalosporins

The MEF concentration of ceftriaxone exceeds the MICs for AOM pathogens for > 50 hours after a single 50 mg/kg intramuscular injection. However, a 3-day regimen is clinically superior, particularly in non-responsive AOM caused by penicillin-resistant *S. pneumoniae*.[26] Ceftriaxone use should be restricted to cases with failure of high-dose amoxycillin-clavulanate or for severe presentations.

3.1.5 Macrolides/azalide/clindamycin

Erythromycin should not be used for the empiric treatment of AOM owing to substantial resistance of *S. pneumoniae* and *H. influenzae* and sub-optimal PK/PD parameters. Azithromycin and clarithromycin have good *in vitro* activity against macrolide-susceptible pneumococci and *M. catarrhalis* and acceptable activity against *H. influenzae*. However, double-tap studies have recently demonstrated that azithromycin at standard doses failed to eradicate macrolide-resistant pneumococci and *H. influenzae*.[27] In areas with a high prevalence of macrolide resistance macrolides should therefore preferably be restricted to cases with β-lactam allergy, or used for suspected or proven infections with 'atypical' pathogens.

Clindamycin retains activity against most penicillin-resistant *S. pneumoniae* but has no activity against *H. influenzae* or *M. catarrhalis*. It can be used in confirmed, clindamycin-susceptible, pneumococcal AOM, unresponsive to β-lactam antibiotics.

3.1.6 Trimethoprim-sulfamethoxazole (TMP-SMX)

The high rate of resistance of *S. pneumoniae* in South Africa precludes the use of TMP-SMX. High bacteriological failure rates have been noted to occur in double-tap studies.[28]

3.2 Duration of therapy for AOM

Most antibiotics are clinically effective for uncomplicated AOM when used in regimens of 5 - 7 days, since eradication of organisms takes place within 72 hours.[29] However, therapy beyond 72 hours is required for adequate eradication of potentially pathogenic bacteria colonising the nasopharynx, because if these are not successfully eradicated they may predispose to relapses of AOM.

Further studies are needed to determine optimal duration of therapy in children younger than 2 years of age and in patients with non-responsive AOM.[25,30] Until then, therapy for 7 - 10 days is recommended for AOM in the following groups:

- Age ≤ 2 years
- Recurrent or chronic AOM
- Complicated AOM.

3.3 Failure to respond to antibiotics

In cases of clinical failure (e.g. persistent fever) after 72 hours of appropriate, compliant initial antibiotic therapy, consider referral to an otorhinolaryngologist for tympanocentesis and MEF culture. This is of relevance in areas with a high prevalence of antibiotic-resistant *S. pneumoniae*, as is the case for the majority of major urban centres in South Africa, particularly in the private sector.

3.4 Antibiotic recommendations for AOM

3.4.1 Children

First-line recommended therapy:

- Amoxycillin, 90 mg/kg/day into 2 or 3 divided doses for 5 - 7 days.

Alternative antibiotic choices:

(a) Beta-lactamase-stable antibiotics:

- Amoxycillin-clavulanate, plus additional amoxycillin (to a total dose of amoxycillin of 90 mg/kg/day) divided into 2 or 3 doses for 5 - 7 days
- Cefpodoxime proxetil, 8 - 16 mg/kg twice daily for 5 - 7 days
- Cefprozil, 15 - 30 mg/kg twice daily for 5 - 7 days
- Cefuroxime axetil, 15 - 30 mg/kg twice daily for 5 - 7 days.

The higher dosages of cephalosporins recommended would cover for most pneumococcal isolates of intermediate resistance to penicillin, but not necessarily for pneumococcal isolates with high-level resistance. The particular choice of cephalosporins would depend on physician or patient preference, availability and cost. Risk factors for AOM caused by β-lactamase-producing pathogens may include immunocompromised patients and/or neonates.

(b) Antibiotics for β-lactam allergy:

- Azithromycin, 10 mg/kg once daily for 3 days*
- Clarithromycin, 7.5 - 15 mg/kg twice daily for 5-7 days*
- Erythromycin estolate, 40 mg/kg twice daily for 5 - 7 days*
- Cefpodoxime proxetil, 8 - 16 mg/kg twice daily for 5 - 7 days†
- Cefprozil, 15 - 30 mg/kg twice daily for 5 - 7 days†
- Cefuroxime axetil, 15 - 30 mg/kg twice daily for 5-7 days†.

(c) Failed initial therapy:

- Amoxycillin-clavulanate, plus additional amoxycillin (to a total dose of amoxycillin of 90 mg/kg/day) divided into 2 or 3 doses for 5 - 7 days for failed initial therapy with amoxycillin alone
- Ceftriaxone, intravenous (IV) or intramuscular (IM), 50 - 75 mg/kg once daily for 3 days. This is also recommended in the case of isolates of known high-level antibiotic resistance and in severe presentations, e.g. threatened mastoiditis,

*Macrolides/azalide are recommended for patients who have severe β-lactam allergy.
†Cephalosporins may be considered initially for patients with penicillin intolerance/non-type 1-hypersensitivity reactions (e.g. rash).

preferably in consultation with an otorhinolaryngologist.

3.4.2 Adults

The treatment options for AOM in adults are the same as for acute bacterial sinusitis.

4. Acute bacterial sinusitis

ABS is most often preceded by a viral URTI. Allergy, trauma, dental infection, or other factors that lead to inflammation of the nose and paranasal sinuses may also predispose individuals to ABS.

The most common bacterial isolates from the maxillary sinuses of patients with ABS are similar to those isolated in AOM, namely *S. pneumoniae, H. influenzae* and *M. catarrhalis*. As with AOM, *S. pneumoniae* causes most of the serious sequelae and antibiotic therapy must be capable of eradicating it. Other streptococcal species, anaerobic bacteria and *S. aureus* occur in a small percentage of cases. *Chlamydia pneumoniae* and other 'atypical' pathogens should be considered in patients with chronic sinusitis.[31] Fungi have been associated with sinusitis and may be seen in allergic sinusitis and immunocompromised hosts. However, their clinical significance in immunocompetent patients is unclear.

Multiple factors play a role in the antibiotic selection for ABS. *S. pneumoniae* may be associated with serious intracranial and extrasinus complications, so it should be adequately covered in initial therapy. Gram-negative cover for *H. influenzae* (and *M. catarrhalis* in children) cannot be ignored.

Prior antibiotic use is a major risk factor for infection with antibiotic-resistant strains. Because recent antibiotic exposure increases the risk of carriage and infection with resistant organisms, the choice and dosage of antimicrobial therapy should take into account a history of recent antibiotic use. Other factors to consider are the severity of disease, its rate of progression and varying rates of resistance within South Africa.

4.1 Duration of antibiotic treatment for ABS

The duration of antibiotic treatment for ABS is 10 days. This is based on published studies of clinical trials in which pre-treatment and post-treatment sinus aspirates were performed.[32] However, recent evidence for gatifloxacin, moxifloxacin and telithromycin suggests that a shorter course of 5 - 7 days is clinically and/or bacteriologically equivalent to a 10-day course.[33-35]

4.2 Failure to respond to antibiotics

In cases of clinical failure (e.g. persistent fever) after 72 hours of appropriate, compliant antibiotic therapy, consider referral to an otorhinolaryngologist for further evaluation. A computed tomography (CT) scan, fibre-optic endoscopy, or sinus aspiration and culture may be necessary. This is of relevance in areas with a high prevalence of antibiotic-resistant *S. pneumoniae*, as is the case for the majority of major urban centers in South Africa, particularly in the private sector.

4.3 Beta-lactam allergy

Clinicians should differentiate an immediate type-1 hypersensitivity reaction from other less dangerous side- effects. Urticaria, angio-oedema and bronchospasm are especially dangerous signs and should contraindicate use of antibiotics that have caused these reactions in a patient in the past. Patients with other types of reactions and side-effects may tolerate one specific β-lactam but not another. The cross-reactivity for penicillin and first-generation cephalosporins is higher than for second- or third-generation cephalosporins. Consensus opinion suggests that if the previous reaction to penicillin was an itchy maculopapular rash, it would be relatively safe to use cephalosporins.[36] This approach may be followed if the allergy to penicillin was mild, the indication for cephalosporins is well motivated and skin testing for penicillin is impractical.

4.4 Antibiotic recommendations for ABS

4.4.1 Children

First-line recommended therapy:

- Amoxycillin, 90 mg/kg/day into 3 divided doses for 10 days.

Alternative antibiotic choices:

(a) Beta-lactamase-stable antibiotics:

- Amoxycillin-clavulanate, plus additional amoxycillin (to a total dose of amoxycillin of 90 mg/kg/day) divided into 3 doses for 10 days
- Cefpodoxime proxetil, 8 - 16 mg/kg twice daily for 10 days
- Cefprozil, 15 - 30 mg/kg twice daily for 10 days
- Cefuroxime axetil, 15 - 30 mg/kg twice daily for 10 days.

The higher dosages of cephalosporins recommended would cover for most pneumococcal isolates of intermediate resistance to penicillin but not necessarily for pneumococcal isolates with high-level resistance. The particular choice of cephalosporins would depend on physician or patient preference, availability and cost. Risk factors for ABS caused by β-lactamase-producing pathogens may include immunocompromised patients and/or neonates.

(b) Antibiotics for β-lactam allergy:

- Azithromycin, 10 mg/kg once daily for 3 days*
- Clarithromycin, 7.5 - 15 mg/kg twice daily for 10 days*
- Erythromycin estolate, 40 mg/kg twice daily for 10 days*

*Macrolides/azalide are recommended for severe β-lactam allergy in children.

- Cefpodoxime proxetil, 8 - 16 mg/kg twice daily for 10 days*
- Cefprozil, 15 - 30 mg/kg twice daily for 10 days*
- Cefuroxime axetil, 15 - 30 mg/kg twice daily for 10 days*.

(c) Failed initial therapy:

- Amoxycillin-clavulanate, plus additional amoxycillin (to a total dose of amoxycillin of 90 mg/kg/day) divided into 3 doses for 10 days for failed initial therapy with amoxycillin alone
- Ceftriaxone, IV or IM, 50 - 75 mg/kg once daily for 3 - 5 days. This is also recommended in the case of isolates of known high-level antibiotic resistance and in severe presentations, e.g. peri-orbital inflammation, preferably in consultation with an otorhinolaryngologist.

4.4.2 Adults

First-line recommended therapy:

- Amoxycillin, 1 g 3 times daily for 10 days.

Alternative antibiotic choices:

(a) Beta-lactamase-stable antibiotics:

- Amoxycillin-clavulanate, 1 g twice daily plus amoxycillin 500 mg twice daily for 10 days
- Cefpodoxime proxetil, 200 - 400 mg twice daily for 10 days
- Cefprozil, 500 mg - 1 g twice daily for 10 days
- Cefuroxime axetil, 500 mg - 1 g twice daily for 10 days.

The higher dosages of cephalosporins recommended would cover for most pneumococcal isolates of intermediate resistance to penicillin but not necessarily for pneumococcal isolates with high-level resistance. The particular choice of cephalosporins would depend on physician or patient preference, availability and cost. Risk factors for ABS caused by β-lactamase-producing pathogens may include immunocompromised patients, including pregnant patients and diabetics.

(b) Antibiotics for β-lactam allergy:

- Azithromycin, 500 mg once daily for 3 days†
- Clarithromycin (modified release), 1 000 mg once daily for 10 days†
- Erythromycin, 500 mg 4 times daily for 10 days†
- Telithromycin, 800 mg once daily for 5 - 10 days†
- Cefpodoxime proxetil, 200 - 400 mg twice daily for 10 days*
- Cefprozil, 500 mg - 1 g twice daily for 10 days*
- Cefuroxime axetil, 500 mg - 1 g twice daily for 10 days*
- Gatifloxacin, 400 mg once daily for 5 - 10 days‡
- Levofloxacin, 500 mg once or twice daily for 10 days‡
- Moxifloxacin, 400 mg once daily for 7 - 10 days‡
- Clindamycin, 450 mg three times daily for 10 days.§

(c) Failed initial therapy:

- Amoxycillin-clavulanate, 1 g twice daily plus amoxycillin 500 mg twice daily for 10 days for failed initial therapy with amoxycillin alone
- Respiratory fluoroquinolones:
  - Gatifloxacin, 400 mg once daily for 5 - 10 days
  - Levofloxacin, 500 mg once or twice daily for 10 days
  - Moxifloxacin, 400 mg once daily for 7 - 10 days
- Telithromycin, 800 mg once daily for 5 - 10 days
- Ceftriaxone, IV or IM, 1 - 2 g once daily for 3 - 5 days.

Ceftriaxone or the respiratory fluoroquinolones may also be used as first-line therapy in severe initial presentations, e.g. peri-orbital oedema, preferably in consultation with an otorhinolaryngologist.

*Cephalosporins may be considered initially for patients with penicillin intolerance/non-type-1 hypersensitivity reactions (e.g. rash).
†Macrolides/azalide, fluoroquinolones and ketolides are alternative recommendations for severe β-lactam allergy in adults.
‡Respiratory fluoroquinolones are recommended for patients who have recently not responded to other therapy or are intolerant of β-lactams. Ciprofloxacin provides inadequate cover for *S. pneumoniae* and is not recommended.
§Clindamycin use is restricted to confirmed pneumococcal ABS unresponsive to β-lactam antibiotics or as additional therapy to provide for anaerobic and *S. aureus* cover, despite the lack of clinical evidence at this time of the safety or efficacy of combination therapy for ABS.

5. References

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7. Working Group of the Infectious Diseases Society of Southern Africa

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8. Disclosure statement

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