Oral antibiotics

optimal prescribing in the community

Recently, there have been several additions to the oral antimicrobial options for common infections, and it is often difficult to know when to use the newer antibiotics. This article discusses the optimal use of both the newer and the more classical oral antibiotics.

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It is hard for most doctors to imagine trying to practise medicine without antibiotics. Even in ancient Babylon in 2000 BC, doctors treated infected eyes with a salve made of frog's bile and sour milk (used in conjunction with a swig of beer and a sliced onion taken orally).[1] However, it was not until earlier this century that the current antibiotic era began – with the use of salvarsan (an arsenical) for the treatment of syphilis. Between the 1930s and 1960s, a flurry of other antibiotic compounds (including sulfur drugs) were developed. Death rates from a number of infectious diseases plummeted. Unfortunately, microorganisms rapidly learned to adapt and new infectious agents also emerged, so the need for ongoing research and development of new antibiotics has not diminished.

Over the last few years, several new antibiotics have either been given PBS listing in Australia or been strongly marketed, particularly for respiratory tract infections, and their use has greatly increased. The patterns and level of antibiotic prescribing in the community, particularly by GPs, have changed a great deal over this period. New antibiotics are often easier to use than their predecessors because of easier dosage schedules or fewer side effects, and they have a wide spectrum of efficacy (at least, moderate efficacy). However, these benefits can lead to antibiotic overuse in the community, which has grave implications in terms of the development of microbiological resistance.

The advance of highly resistant organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococcus (VRE), and the emergence of multiresistant *Streptococccus pneumoniae* in the community,

IN SUMMARY

- **Most community acquired upper respiratory infections are viral and will not respond to antibiotics.**
- **Bacterial infections may complicate primary viral infections (especially in the upper respiratory tract) but do so in a minority of cases.**
- **Patient education is very important in avoiding the overuse of antibiotics.**
- **Be familiar with local bacterial resistance patterns.**
- **When empirically treating an infection, start with as specific an antibiotic as is reasonable. Reassess and change if there is no clinical response by about 48 hours.**
- **If there are factors that make the consequences of ineffective treatment catastrophic (e.g. immunocompromise, CNS involvement, newborn), it may be wise to seek specialist advice initially.**
- **The newer oral antibiotics increase the repertoire from which we can choose; they don't necessarily have huge advantages over the more classical oral antibiotics.**

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Table 1. Causes of acute bacterial upper respiratory infections

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Staphylococcus aureus*
- *Mycoplasma pneumoniae*
- *Chlamydia pneumoniae*
- *Chlamydia trachomatis*

highlight the continuing need for GPs to use all antimicrobial agents prudently and appropriately.

The main aim of this article is to review some general approaches to antibiotic prescribing in the community and try to suggest where some of the newer oral antibiotics fit into this approach. Respiratory tract infections are the most common reason for antibiotic prescriptions in the community and will be used here to illustrate many of the points, but the general approach is applicable to antibiotic prescribing for most infections.

Prescribing in the community

When discussing antibiotic prescribing in the community, a number of basic questions need to be addressed:

- when should antibiotics be used?
- should GPs initially prescribe antibiotics that provide a very broad antimicrobial cover?
- what factors should influence the initial choice of antibiotic?
- when should a clinician change an antibiotic?

When should antibiotics be used?

This first question is perhaps the hardest to answer, and the hardest for GPs to deal with in their everyday decision making. The difficulty of deciding when to use antibiotics is well illustrated by the dilemma posed by acute upper respiratory tract infections (such as sinusitis and otitis media). These infections are still the most common cause of morbidity and mortality of infants and children,[2] and they account for about two-thirds of antibiotic prescribing.[3]

Around the world, the epidemiology of acute upper respiratory infections in children is remarkably similar. Viruses cause about 80 to 90% of these infections, and then about six species are responsible for 90% of the 10% that are bacterial respiratory infections (Table 1).[2] Mixed viral and bacterial infections occur in about 30% of cases. This means that although antibiotics are usually not indicated initially, the need for them may emerge as the illness evolves, and a viral 'cold' may develop secondary bacterial complications. In an adult, a sore throat has only a 10% chance of being bacterial in aetiology.[4]

It is important for doctors to remember (and explain to patients) that in most patients antibiotics will have absolutely no impact on the course of the upper respiratory infections (and are not without side effects). Thus, the key elements for managing acute upper respiratory infections involve supportive measures and education of patients and parents of patients about the likely cause of the

Table 2. Antibiotic activity against S. pneumoniae strains*

Agent	Susceptible (%)	Intermediate (%)	Resistant (%)	Total resistant† (%)
Penicillin	74.6	16.8	8.6	25.4
Amoxycillin	99.7	0.2	0.1	0.3
Amoxycillin–clavulanate	99.7‡	0.2‡	0.1‡	0.3‡
Cefaclor	78.6‡	4.0‡	17.4‡	21.4‡
Erythromycin	83.7	0.7	15.6	16.3
Tetracycline	84.1	0.2	15.7	15.9
Trimethoprim–sulfamethoxazole	54.2	12.4	33.4	45.8

* Results for 1020 strains isolated in Australia in 1997. Table adapted from reference 6 (Turnidge JD et al). † Total resistant = intermediate + resistant.
‡ Figures adjusted to reflect breakpoints in National Committee for Clinical Laboratory Standards (NCCLS) MIC testing (supplemental testing tables/ M100-S0 [M7], Jan 2000, table 2G: 34-35).

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infection. Medical review may also be necessary so that antibiotic therapy can be instituted if and when appropriate.

The clinician should remember that if throat swabs or sputum cultures are performed, any microbiological results have to be put into the clinical context to be useful. Even if potentially pathogenic bacteria are isolated from sputum cultures, they are not necessarily the cause of the illness. Similarly, in other clinical circumstances, the microbiology results are only useful in conjunction with the clinical assessment. For instance, if wound swabs from an ulcer or wound grow a bacterium, this organism does not necessarily need to be treated with antibiotics, unless there is a clinical suspicion of actual infection (as opposed to colonisation) by this organism. Microbiology results can be even more difficult to interpret if the swab or sample is taken while the patient is on antibiotics. Sometimes specialist advice is very useful.

In general, antibiotics should be instigated if there are any symptoms or signs to suggest secondary bacterial infection, such as increased fever, pain or any other deterioration in clinical state. The other reason for early use of antibiotics is if the patient has any underlying medical problems or immunocompromise that puts him or her at risk.

Should GPs initially prescribe a very broad spectrum antibiotic?

The next question is whether one should use broad rather than narrow antibiotic cover when empirical antibiotic therapy is being used. Obviously, very important to answering this question is knowledge of usual organisms and local resistance patterns. If resistance levels are still low, first-line agents do not need to be effective against beta-lactamase-producing bacteria and a narrow spectrum agent is preferred.

It is important to remember that the emergence of resistant bacteria is closely linked to antibiotic consumption in the community,[5] and the rate of antimicrobial resistant strains of *S. pneumoniae* is rapidly rising in Australia.[6] In 1997, the level of penicillin-resistant *S. pneumoniae* was about 25% (Table 2),[6] and in general the level of ampicillin-resistant *Haemophilus influenzae* is about 30%. Most of the *S. pneumoniae* resistance to penicillin is of intermediate level, so for noninvasive infections (not meningitis), amoxycillin can still be used. (Levels of resistance are explained in the box on page 56.)

Luckily in Australia, resistance rates for *S. pneumoniae* have been found to be lower in isolates causing invasive infections (such as meningitis), as opposed to noninvasive ones. In invasive infection, even intermediate level resistance would preclude the use of an antibiotic. In noninvasive infections, intermediate

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Resistance reporting

An organism's antimicrobial resistance may sometimes be broken down into intermediate and high level resistance. In practical terms, microbiological resistance reporting can generally be interpreted in the following way.

Sensitive

The organism is sensitive to usual blood concentrations of the antibiotic.

Intermediate resistance

The organism shows intermediate resistance but will often still be susceptible to an increased dose of the antibiotic.

(Note: an antibiotic would not be used, even in increased concentration, for an organism with intermediate resistance if the infection were invasive or in a serious site, such as meningitis.)

High level resistance

The organism is resistant even to high concentrations of the antibiotic.

resistance may not be a problem clinically (or may be overcome by increasing drug dosage).

In most upper respiratory tract infections, amoxycillin is still adequate and appropriate first-line antimicrobial therapy. It continues to be a good choice because it is generally well tolerated, effective and inexpensive.

It is important to note that about 16% of pneumococci are resistant to macrolides and tetracyclines, and close to 50% are resistant to trimethoprim–sulfamethoxazole.[6] Virtually all of this is 'high level' resistance (see Table 2), which means that these antibiotics would be ineffective. Remember that the minimal inhibitory concentrations (MICs) for cephalosporin antibiotics are increased in penicillin-resistant *S. pneumoniae* strains. This is an issue in the treatment of middle ear infections in which the concentration of cephalosporin will be inadequate to treat these resistant organisms. This highlights a treatment paradox that, as pneumococcal resistance increases, the new agents are becoming less effective and the treatment of choice may still be an older, narrower spectrum antibiotic such as amoxycillin (albeit in a higher dose). Some clinicians recommend either changing to or just adding amoxycillin–clavulanate (Augmentin Duo, Ausclav, Clamoxyl) if there is no clinical response by 48 hours because this antibiotic will provide additional cover against organisms such as *H. influenzae* and *Moraxella catarrhalis*. However, the cost–benefit of this stepwise approach has recently been brought into question.[7]

The dilemma of how to avoid aggravating the problem of emerging resistance is very relevant to the treatment of upper respiratory tract infections such as otitis media. Although there is still debate about whether antibiotics are indicated at all, a recent meta-analysis has shown that antibiotics do reduce the period of illness and increase the rate of complete resolution.[4] In otitis media, the three most common bacterial pathogens are *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*.[3] Amoxycillin is still highly successful in the treatment of otitis media, sinusitis, bronchitis and community acquired pneumonia.[6,8]

There are a number of reasons why empirical therapy should be as specific and as simple as possible, relating both to the patient being treated and the community in general. These are listed in the box at left.

Use of specific empirical antibiotic therapy

Advantages

- Narrow spectrum agents are less likely to cause common side effects (such as oral and genital candidiasis and gastrointestinal upset) than broad spectrum antibiotics.
- If specific therapy is ineffective, there are many broader spectrum options from which to choose.
- When used widely or inappropriately within a community, any antibiotic promotes the development of resistant organisms. If resistance develops to lower level antibiotics, we still have alternatives further up the antibiotic hierarchy. When resistance to the higher level or broader spectrum antibiotics develops, we may run out of therapeutic options and the implications for the community can be devastating.
- The narrow spectrum agents are usually cheaper.

Disadvantages

- In some cases, the pathogen will be either an organism for which the antibiotic is inappropriate or a strain in which resistance to the antibiotic has developed.
- The potential consequence of a delay in effective treatment will always need to be weighed against the benefits of specific therapy.

What factors should influence the initial choice of antibiotic?

Factors influencing the initial choice of antibiotic are listed in Table 3. As stated before, knowledge of local patterns of antimicrobial resistance is important.

Upper respiratory tract infections

Risk factors that increase the likelihood of resistant organisms being a cause of upper respiratory tract infections include:[9]

- multiple previous courses of antibiotics
- prophylactic use of antibiotics
- previous hospitalisation

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Table 3. Factors affecting the initial choice of antibiotic

- Patient's past history of respiratory tract infection and treatment
- Patient's age (< 2 years or elderly)
- Patient's history of allergies and tolerance of antibiotic
- Dosing regimen and palatability (often particularly important in children)
- Other compliance issues
- Pre-existing medical conditions
- Cost of the drug to the patient

- age less than 2 years
- children in childcare.

Unfortunately local data are not available for levels of resistance in these subgroups.

In these patients, it would be reasonable to select an antibiotic such as cefaclor (Ceclor, Keflor, Vercef) or amoxycillin–clavulanate for initial therapy of an upper respiratory tract infection, although the problems associated with using such alternatives in the face of increasing bacterial resistance have been discussed in the previous section. Alternatively, one could have a very low threshold for change to a second-line agent if there was no clinical response to therapy within 48 hours.

It should be noted that the efficacy of cefaclor for *S. pneumoniae* is not as good as that of the penicillin agents. A recently licensed (in Australia) second generation cephalosporin, cefuroxime axetil (Zinnat), probably provides better anti-streptococcal cover than cefaclor does and is therefore quite a useful agent in this situation. Unfortunately, the paed - iatric formulation of cefuroxime axetil is not likely to be available in Australia for at least another year.

Also affecting the initial choice of antibiotic are factors that increase the risk to the patient of an infection and the potential catastrophe of therapy not being immediately effective. This includes pre-existing conditions such as immunocompromise, malignancy, diabetes or pulmonary disease.

If beta lactam allergy exists, initial therapy for acute upper respiratory infections needs to be modified and depends on the type of allergy reported. If the initial allergy was a rash related to penicillin or its derivatives, then cephalosporins may still be used – although there is about a 7 to 8% risk of a crossreaction (and this should be explained to patients). If the reaction was immediate or anaphylactoid, or the nature of the reported reaction is unclear, then all beta lactam agents should be avoided (even though the risk of cross-reaction is probably about 1%). It is in this situation that second-line agents for upper respiratory infections, such as a macrolide, trimethoprim–sulfamethoxazole (Bactrim, Cosig Forte, Resprim, Septrin) or a tetracycline, are usually recommended. However, it is very important to establish a true history of antibiotic-related allergy and not just a vague history of rash, which may even be virus related.

Lower respiratory tract infections

The antibiotic dilemmas are a little different when one is empirically treating a lower respiratory tract infection. Although viral pneumonia does occur, it is less likely than bacterial pneumonia, especially in adults. In treating pneumonia, the management question is usually whether the patient is likely to have a typical or an atypical pneumonia. There is no one antibiotic agent that covers all organisms well. The most common agents of a typical bacterial pneumonia are *S. pneumoniae* and *H. influenzae*; indeed *S. pneumoniae* still accounts for up to 75% of all community acquired pneumonia.[9,10]

The oral antibiotic approach to classical pneumonia (in the outpatient setting) is much the same as for upper respiratory tract infection. In Australia, amoxycillin is still recommended as initial therapy.[6,9]

Atypical pneumonia (caused most commonly by *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*) is becoming increasingly recognised throughout the community. The most appropriate first-line therapy for it is currently a macrolide or a tetracycline.

A therapeutic dilemma occurs when it is not obvious to the clinician whether a classical or an 'atypical' pathogen is most likely to be the cause. For this reason, the treatment of community acquired pneumonia is problematic. Many authoritative bodies, particularly in the USA, advise that empirical therapy for community acquired pneumonia should cover both types of pathogens, and recommend ofloxacin (a fluoroquinolone not licensed in Australia), doxycycline and azithromycin (Zithromax).[11,12] Australian experts do not necessarily agree with this approach – the emergence of resistance being the major problem.[6] Current Australian recommendations for the empirical therapy of community acquired pneumonia are very general. They suggest that either amoxycillin, roxithromycin (Biaxsig, Rulide) or doxycycline be used initially.[10]

It is important to note that the available fluoroquinolones in Australia, such as ciprofloxacin, have fairly poor activity against *S. pneumoniae* and so are not recommended for pneumonia. Most infectious disease physicians feel it prudent for the clinician to try to decide whether the pneumonia is typical or atypical and treat accordingly. Then, if the response is poor, add in an antibiotic of the other class (for example, use amoxycillin then a macro - lide, or vice versa). The other approach is to give two antibiotics initially, but this would lead to gross overprescribing.

When should a clinician change antibiotic?

Once again, the answer to this question depends on the clinical situation. Generally, we expect to see a clinical response within 48 hours of therapy with an appropriate antibiotic. When treating respiratory tract infections, if there is no clinical response over this period, it may indicate

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antimicrobial resistance to the antibiotic in question, such as that seen with beta-lactamase-producing organisms, or a more unusual microbial pathogen for which the antibiotic is not appropriate. It may, however, also suggest other problems or factors in management that need attention, such as physical measures (relief of obstruction or drainage of secretions), or it may indicate that there is no bacterial pathogen involved. Clinical reassessment is the key to appropriate management when there is no response, and specialist advice may be appropriate.

The role of the newer antibiotics

Having considered the previous questions, we can now discuss the place of the newer oral antibiotics. Essentially, they increase the range of antibiotic options; none, so far, take the place of the more traditional antibiotics, at least not in the setting of respiratory tract infections (which is their most common use).

As mentioned before, cefuroxime axetil is a newer second generation cephalosporin. It has the advantage over other cephalosporins of slightly better antistreptococcal activity.

There have been a number of additions (or extensions to marketing) in the macrolide group, which in Australia now includes erythromycin, roxithroxmycin, clarithromycin and azithromycin. These agents are all broad spectrum, but are not quite as effective as the beta lactams against the classical respiratory pathogens – and resistance develops quite rapidly.[6] In this group, there has recently been a huge change in prescribing practices: roxithromycin has largely replaced erythromycin in many circumstances because of its similar spectrum but lesser incidence of side effects and twice daily dosing. Clarithromycin (Klacid) shows similar efficacy for both upper and lower respiratory tract infections,[13] and is now licensed for treating these infections. Azithromycin also has a similar spectrum and efficacy and is widely used in the USA, but is not on the PBS for use in respiratory tract infections in Australia.

Another broad spectrum oral antibiotic, ciprofloxacin (Ciproxin), is a member of the fluoroquinolone group. It is very effective for complicated respiratory infections, but to preserve its efficacy it is available on the PBS only for therapy of these infections in immunocompromised patients and authority is still required.

Conclusion

Antibiotics have brought enormous benefits in our ability to treat common infections. We are now at a different point in our battle against the pathogens that cause so much global morbidity and mortality, but we still face therapeutic dilemmas when attempting to use anti - biotics, especially newer ones, appropriately – the most ominous of these being the emergence of antibiotic resistance in the community. Treating infectious diseases such respiratory tract infections is perhaps just as complicated and difficult today as it was 40 years ago, despite the antibiotics available to us. The words of Frank Meleney, a professor of surgery at Columbia University, are just as relevant today as in 1947 when he wrote about antibiotics that, 'there is a temptation to use them promiscuously, and yet certainly if we are to improve our results we must use them with discrimination'.[1] MT

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