INVITED ARTICLE

# UPDATE OF SYSTEMIC ANTIMICROBIALS: EMPHASIS ON ORAL AGENTS

D M Allen, M L Ling

*ABSTRACT*

***There has been a proliferation of antimicrobial agents in the market and we can expect many more new agents to be available for use in the hospital and community later.***

***In the outpatient setting, the number of oral antimicrobial agents are varied, providing greater flexibility in managing community acquired infections. Unfortunately, the extensive use of antimicrobial agents has contributed to the development of resistance of some bacteria to multiple antimicrobials.***

***This paper will review the basis of activity of antimicrobial agents commonly used in the outpatient clinic. The spectrum of antibacterial activity of these agents is discussed in relation to the common organisms encountered in general practice. Guidelines for the control of the development of bacterial antimicrobial resistance are also given.***

***Keywords:*** *antimicrobial, beta-lactam, macrolide, quinolone, aminoglycoside*

**SINGAPORE MED J 1994; Vol 35: 626-630**

## Introduction

A turning point in the history of medicine occurred when antimicrobial therapy was introduced in the 1940's. Almost overnight, illnesses which were uniformly fatal became amenable to curative therapy. Rarely before or since have new modalities of therapy had such an impact. The significance of these drugs in our day-to-day interactions with patients is lost on many of us practising today. We take the availability of broad-spectrum, relatively non-toxic antimicrobial for granted. The result of this nonchalant attitude is now haunting us in the form of multi-resistant bacteria[1,2]. A preliminary step to discussing the problems facing the future of antimicrobial therapy is a review of the drugs in question. As the majority of antimicrobial use occurs in the outpatient setting, this article will focus on currently available oral antibacterial agents. Subsequent articles will address parenteral drugs and means of avoiding antimicrobial obsolescence.

When attempting to understand the many different antimicrobials available, it is essential to group them into categories or families of drugs with a similar mechanism of action. Each drug family may have several subgroups or "generations", each of which shares the family's mechanism of actions but has a distinct spectrum of antibacterial activity when compared to other generations in the same family. With this organisational scheme in mind, most new drugs can be evaluated based on which family (and which generation of that family, where relevant) the drug belongs. Subsequently, every new drug can be compared to other drugs in the family in which it falls by considering antibacterial activity, drug half-life, toxicity and cost. A useful goal for the clinician is to become familiar with the basic characteristics (ie antibacterial spectrum, half-life, toxicity and cost) of one drug representing a family (or generation). This exercise allows the clinician to master the old and new drugs quickly. A list of the antimicrobial families and generations is provided below (Table I).

**Table I – Antimicrobial families and generations**

| Family | Parenteral example | Oral example |
|---|---|---|
| Beta-lactams | | |
| *Penicillins* | | |
| 1st generation | Benzathine penicillin | Penicillin V |
| 2nd generation | Ampicillin | Ampicillin |
| 3rd generation | Ticarcillin | Carbenicillin indanyl sodium |
| 4th generation | Piperacillin | – |
| *Cephalosporins* | | |
| 1st generation | Cefazolin | Cephalexin |
| 2nd generation | Cefoxitin | Cefuroxime axetil |
| 3rd generation | Cefotaxime | Cefixime* |
| *Carbapenems* | Imipenem | – |
| *Monobactam* | Aztreonam | – |
| Macrolides | Erythromycin | Erythromycin |
| Lincosamides | Clindamycin | Lincomycin |
| Sulphonamides | – | Sulphadiazine |
| Quinolones | # | Norfloxacin |
| Aminoglycosides | Gentamicin | Neomycin |
| Glycopeptides | Vancomycin | Vancomycin+ |

* Not available in Singapore
\# Numerous examples – ofloxacin, pefloxacin, ciprofloxacin
\+ Used orally to treat pseudomembranous colitis only

Despite marketing efforts which often suggest dramatic advantages of the drug being promoted, very few of the newly marketed drugs provide significant improvement in antibacterial spectrum over agents currently available. Most of the major

**Department of Infectious Diseases**
**Communicable Disease Centre**
**Moulmein Road**
**Singapore 1130**

D M Allen, MD
Consultant Physician and former Head

**Department of Pathology**
**Singapore General Hospital**
**Outram Road**
**Singapore 0316**

M L Ling, FRCPA
Senior Registrar

**Correspondence to:** Dr M L Ling

advances have come from longer half-lives, which lead to improved compliance. However, the cost of gaining "improved compliance" may be ten times the cost of the still effective prototypic drug. The clinician should be fully knowledgeable of this before prescribing an antimicrobial which has been heavily promoted.

With the above points in mind, the following text provides a brief overview of currently available oral antibacterial therapy in Singapore. Antifungal, anti-tuberculous and antiviral therapies will not be addressed here. To illustrate antibacterial activity, a list of organisms commonly encountered in general practice is used to compare antimicrobial activity.

**Beta-lactams**

The term "beta-lactam" comes from a chemical structure common to these drugs. Beta-lactams include penicillins and cephalosporins. Related but distinct compounds include monobactams and carbapenems. Beta-lactams comprise the commonly used oral antimicrobials in Singapore. Due to the large number of similar sounding beta-lactams, confusion often prevails. Beta-lactams act by binding to so-called penicillin binding proteins (*aka* PBP's) in bacteria and preventing terminal transpeptidation of the bacteria cell wall. Thus the bacterial cell wall is rendered defective and the organism perishes. Resistance to beta-lactams occurs via inaccessibility to PBP's or by destruction of beta-lactams by enzymes cleverly named "beta-lactamases". Efforts to interfere with degradation by beta-lactamases come from beta-lactamase inhibitors. Two beta-lactamase inhibitors are available in Singapore – clavulanate and sulbactam. Unfortunately, these compounds are only available in fixed combination with amoxycillin and ampicillin respectively, and not available for combination with other beta-lactam agents.

*Penicillins*

Oral first generation penicillins include natural penicillins (eg phenoxymethyl penicillin *aka* penicillin V) and penicillinase-resistant penicillins (eg cloxacillin). Their strength is in coverage of Gram-positive bacteria. Natural penicillins also have activity against oral flora (eg *Fusobacterium, Actinomycetes*), *Leptospira, Neisseria* and *Treponema* among others.

The oral second generation penicillins consist of ampicillin, amoxycillin and bacampicillin. The major differences among these agents are gastrointestinal tract absorption and half-lives. These antimicrobials have less activity against Gram-positive bacteria compared to first generation penicillins, but gain activity against some Gram-negative bacteria (eg *Escherichia coli, Haemophilus* sp etc). Unfortunately, as these drugs are susceptible to commonly found beta-lactamases, they have lost some of their usefulness. The addition of beta-lactamase inhibitors has broadened their spectrum (Table II).

The only oral third generation penicillin is indanyl carbenicillin. It was the first oral beta-lactam with anti-pseudomonal activity. Ticarcillin, which is the other member of this generation, is only available parenterally. Carbenicillin indanyl sodium has become obsolete with the introduction of oral fluoroquinolones.

There are no oral fourth generation penicillins. Piperacillin, azlocillin and mezlocillin are only available parenterally.

*Cephalosporins*

The division of cephalosporins into generations had more to do with the timing of the individual agent's introduction than with spectrum of antibacterial activity. However, a modified generational schema based on antibacterial spectrum can be generated (Tables II and III).

The first generation cephalosporins' spectrum includes most Gram-positive organisms other than *enterococci*. Gram-negative activity is variable with the oral first generation cephalosporins. Cefaclor has a slightly better *Haemophilus* sp. activity compared to the others. In general, these agents are expensive alternatives to first and second generation penicillins or erythromycin.

**Table II – Antibacterial activities of Beta-lactams**

| Drugs | Gram-positive bacteria | | | | | Gram-negative bacteria | | | | Anaerobes | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | MRSA | *Staph aureus* | *Strept* | *Strept pneum* | *Enterococcus* sp. | *Haemo* | *E. coli* | *Kleb* | *Pseudo* | *Clostridia* | *Peptostrept* | *Bacteroides* sp. |
| Penicillin V | 0 | 0 | + | + | + | 0 | 0 | 0 | 0 | + | + | +/– |
| Cloxacillin | 0 | + | + | + | 0 | 0 | 0 | 0 | 0 | + | + | 0 |
| Ampicillin or Amoxycillin | 0 | 0 | + | + | + | + | + | 0 | 0 | + | + | +/– |
| Ampicillin or Amoxycillin with beta-lactam inhibitor | 0 | + | + | + | + | + | + | + | 0 | + | + | + |
| Carbenicillin indanyl sodium | 0 | 0 | +/– | + | 0 | + | + | 0 | + | + | + | 0 |
| Cephalexin | 0 | + | + | + | 0 | +/– | + | + | 0 | +/– | + | 0 |
| Cefuroxime axetil | 0 | + | + | + | 0 | + | + | + | 0 | + | + | 0 |

MRSA = methicillin resistant *Staphylococcus aureus*
*Staph aureus* = *Staphylococcus aureus*
*Strept* = *Streptococcus* sp
*Strept pneum* = *Streptococcus pneumoniae*
*Haemo* = *Haemophilus* sp.
*E. coli* = *Escherichia coli*
*Kleb* = *Klebsiella* sp.
*Pseudo* = *Pseudomonas aeruginosa*
*Peptostrept* = *Peptostreptococcus* sp.

\+ = generally useful; antibacterial activity
+/– = variable antibacterial activity, may not be reliable
0 = poor or no antibacterial activity, unreliable
\# = disagreement in the literature, but generally not useful
NR = not relevant, these drugs are used exclusively to treat UTI's and these organisms are unusual causes of UTI

**Table III – Antibacterial activities of other antimicrobials**

| Drugs | Gram-positive bacteria | | | | | Gram-negative bacteria | | | | Anacrobes | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | MRSA | *Staph aureus* | *Strept* | *Strept pneum* | *Enterococcus* sp. | *Haemo* | *E. coli* | *Kleb* | *Pseudo* | *Clostridia* | *Peptostrept* | *Bacteroides* sp. |
| Erythromycin | 0 | + | + | + | 0 | +/– | 0 | 0 | 0 | + | + | +/– |
| Azithromycin or clarithromycin | 0 | + | + | + | 0 | + | 0 | 0 | 0 | + | + | +/– |
| Clindamycin | +/– | + | + | + | 0 | 0 | 0 | 0 | 0 | + | + | + |
| Sulphamethoxazole /trimethoprim | +/– | + | + | + | # | +/– | + | + | 0 | 0 | + | 0 |
| Nalidixic acid | NR | NR | NR | NR | 0 | NR | + | + | 0 | NR | NR | NR |
| Ciprofloxacin Pefloxacin Ofloxacin | +/– | +/– | +/– | +/– | +/– | + | + | + | + | 0 | 0 | 0 |
| Vancomycin | + | + | + | + | + | 0 | 0 | 0 | 0 | + | + | 0 |
| Chloramphenicol | +/– | +/– | + | + | 0 | + | +/– | +/– | 0 | + | + | + |
| Fusidic acid | + | + | +/– | +/– | 0 | 0 | 0 | 0 | 0 | + | + | 0 |
| Metronidazole | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | 0 | + |
| Nitrofurantoin | NR | NR | NR | NR | +/– | NR | + | +/– | +/– | NR | NR | NR |

MRSA = methicillin resistant *Staphylococcus aureus*
*Staph aureus* = *Staphylococcus aureus*
*Strept* = *Streptococcus* sp
*Strept pneum* = *Streptococcus pneumoniae*
*Haemo* = *Haemophilus* sp.
*E. coli* = *Escherichia coli*
*Kleb* = *Klebsiella* sp.
*Pseudo* = *Pseudomonas aeruginosa*
*Peptostrept* = *Peptostreptococcus* sp.

\+ = generally useful; antibacterial activity
+/– = variable antibacterial activity, may not be reliable
0 = poor or no antibacterial activity, unreliable
\# = disagreement in the literature, but generally not useful
NR = not relevant, these drugs are used exclusively to treat UTI's and these organisms are unusual causes of UTI

The only second generation oral cephalosporin is cefuroxime axetil. It has better activity against *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella* sp. compared to first generation cephalosporins. Like all available oral or parenteral cephalosporins, it does not have meaningful activity against *Enterococcus* sp. As with first generation oral cephalosporins, amoxycillin, erythromycin, cloxacillin or co-trimoxazole are less expensive first-line therapies for most conditions where cefuroxime axetil might be considered.

There are no oral third generation cephalosporins (ie cephalosporins with reliable *Escherichia coli, Klebsiella*, etc activity) in Singapore as yet. Cefixime is available in Europe and the United States. In the light of other oral agents with a similar spectrum, it is not clear what role this drug would have in a clinician's antimicrobial armamentarium. Common oral cephalosporins available in Singapore are listed in Table IV.

**Table IV – Common oral cephalosporins available in Singapore**

| Generic | Trade names in Singapore |
|---|---|
| Cephalexin | Cefalin, Cefaxin, Ceporex, Ceporin, Erocetin, Felexin, Ibilex, Kefexin, Keflex, Ospexin, Pralexin, Servispor |
| Cephradine | Cefamid, Velosef |
| Cefaclor | Distaclor |
| Cefradoxil | Duricef, Evacef, Ibidroxyl |

**Macrolides**

This is the erythromycin family. These drugs work by interfering with the 50s ribosome, thus disrupting bacterial protein synthesis. In addition to the numerous salts, esters and enteric coated formulations of erythromycin itself, there are several new macrolides available: roxithromycin, azithromycin and clarithromycin. Erythromycin's activity is primarily against *Streptococcus pyogenes, Streptococcus pneumoniae, Legionella* sp., *Mycoplasma pneumoniae, Corynebacterium diptheriae* and *Campylobacter jejuni*. Minor *Staphylococcus aureus* infections can be treated as well. Activity against *Haemophilus influenzae* is variable.

Spiramycin's antibacterial spectrum is similar to erythromycin's, but it is 8-16 times less active than erythromycin against most of the relevant organisms[3]. Its role in treating human toxoplasmosis or cryptosporidiosis is not established.

The newer macrolides have several features which make them attractive: long half-lives, less gastrointestinal intolerance, intracellular accumulation and excellent *in vitro* activity. However, when treating the common infections where they should excel (ie bronchitis, sinusitis, otitis, pneumonia, etc) they have not proved superior to standard (ie cheaper) therapy. This point is not raised when the new macrolides are promoted. While their lack of improved efficacy in managing common infections has been disappointing, the new macrolides may have an advantage in treating other infections such as atypical mycobacteria and chlamydial urethritis.

A quote from *The Medical Letter* may help put these drugs into perspective, "... clarithromycin and azithromycin are well-tolerated expensive alternatives to erythromycin for treatment

of... pharyngitis, community-acquired respiratory infections, skin and soft tissue infections, and acute sinusitis".[4]

**Lincosamides**

Clindamycin and lincomycin also act on the 50s bacterial ribosome to interrupt protein synthesis. These agents have good coverage of *Staphylococcus aureus, Streptococcus* sp. and anaerobic bacteria. They are alternatives to cloxacillin in the penicillin-hypersensitive individual. The association of clindamycin use with pseudomembranous colitis may be related to epidemiologic factors[5].

**Sulphonamides and other folate antagonists**

Sulphonamides work by interfering with folic acid metabolism which is essential for nucleotide synthesis. There are only a few sulphonamides remaining in Singapore as monotherapeutic agents. They are primarily used to treat urinary tract infections. When combined with other folate antagonists (eg trimethoprim or pyrimethamine), sulphonamides are useful in managing a broad spectrum of Gram-positive and Gram-negative bacterial infections, but have no activity against anaerobic bacteria. Additionally, specific combinations may be used to treat toxoplasmosis, listeriosis, melioidosis, pneumocystis and selected cases of *Plasmodium falciparum* malaria.

**Quinolones**

Quinolones constitute a unique family of drugs whose antibacterial action is directed toward bacterial DNA gyrase. DNA gyrase is an enzyme which allows tightly wound bacterial DNA to be "read", an essential step in bacterial metabolism and reproduction. Nalidixic acid was the first quinolone with clinical value. It is active against common Gram-negative bacteria. Poor absorption, low tissue levels, narrow antimicrobial spectrum and side effects have limited nalidixic acid to the treatment of urinary tract infections.

Norfloxacin, pefloxacin, ciprofloxacin and ofloxacin are newer quinolones which differ from nalidixic acid by being fluorinated. Fluorination broadens the antimicrobial spectrum, enhances gastrointestinal absorption and diminishes side effects. Some or all of these drugs are active against a broad range of Gram-negative bacteria (including *Pseudomonas aeruginosa*), *Chlamydia* sp. and some *Mycobacteria* sp. Like anything too good to be true, quinolones are double-edged swords. On the one hand, their excellent oral absorption allows earlier hospital discharge of patients who previously would have remained in hospital for parenteral therapy of Gram-negative infections. On the other hand, misinterpretation of the indications for fluoroquinolones use can lead to tragedy[6]. Recommending quinolones for outpatient pneumoniae would be an example. Despite moderate *in vitro* activity against *Streptococcus pneumoniae*, bacteriological and clinical failures are not rare[7]. Most relevant to the clinic-based physician is the limited *Streptococcus pneumoniae* coverage and the rapid development of quinolone resistance among *Staphylococcus* species. As such, the current group of quinolones should be used to treat infections where Gram-negative bacilli are felt to be the cause of infection. Newer fluoroquinolones with better Gram-positive activity may be available in Singapore soon.

**Aminoglycosides**

Aminoglycosides interfere with bacterial protein synthesis by binding to the 30s ribosome. They are poorly absorbed from the gastrointestinal tract and are generally only used orally in pre-operative bowel preparation.

**Vancomycin**

Vancomycin is a member of the glycopeptide family of drugs. Its main use parenterally is to treat methicillin (and thus, cloxacillin)-resistant *Staphylococcus aureus* (MRSA) infections. Oral vancomycin is poorly absorbed by the gastrointestinal tract. As such, it is only used orally to treat pseudomembranous colitis caused by *Clostridium difficile*.

**Chloramphenicol**

Chloramphenicol remains an effective drug, albeit with a limited role due to its potential for toxicity and the availability of more active agents against many organisms for which it is useful. While no longer considered first-line therapy for any infection, current practice would find it a useful option in the management of brain abscesses, enteric fever, melioidosis, rickettsia-related disease and common bacterial meningitis.

**Tetracyclines**

Tetracyclines disrupt bacterial protein synthesis by binding to the 30s ribosome. Bacteria develop resistance to tetracyclines primarily by actively pumping the drug out of the cell before it has a chance to bind to the 30s ribosome. Tetracyclines have activity against a broad range of Gram-positive and Gram-negative bacteria. Additionally, many anaerobes are inhibited by tetracyclines. However, for most of the common organisms causing serious infections, better drugs exist. Tetracyclines still have a significant role to play in the treatment of brucellosis, *Vibrio* sp. infections (including cholera), Lyme disease, leptospirosis, melioidosis, mycoplasma infections, rickettsial diseases and many non-gonococcal sexually transmitted diseases. The longer acting tetracyclines – doxycycline and minocycline – have an identical spectrum to tetracyclines HCl. They require less frequent dosing and doxycycline can be used in renal insufficiency, but their much higher cost does not justify their routine use over tetracyclines HCl.

**Fusidic acid**

Fusidic acid works by interfering with bacterial protein synthesis. Its spectrum of activity includes many Gram-positive bacteria; however, it is a poor *Enterococcus* sp. agent and *Streptococcus* sp. activity is variable. In general, it should be reserved for staphylococcal infections.

**Metronidazole**

Indications for metronidazole include many anaerobic infections, trichomoniasis, amoebiasis, giardiasis and in mild-to-moderately severe *Clostridium difficile*-induced pseudomembranous colitis. Activity against Gram-positive oral anaerobes such as *Peptostreptococcus* sp. is poor. Therefore, if used to treat an oral anaerobic infection, it should be used in combination with another drug active against these organisms (eg penicillin, clindamycin or erythromycin).

**Nitrofurantoin**

Nitrofurantoin is useful against a wide spectrum of pathogens causing urinary tract infections. Side effects may be limiting for some patients. Use for longer than six months can be associated with pulmonary fibrosis.

**Conclusion**

The large number of oral antimicrobial agents currently available provides greater flexibility in managing outpatient infections. There is a drug to meet just about every individual's needs. However, the authority to prescribe such drugs comes with

responsibility to use them correctly. Inappropriate antimicrobial use may lead to toxicity from drug interactions, bacterial and/or fungal superinfections, acceleration of the evolution of antimicrobial resistant organism and diagnostic confusion (eg are the current symptoms due to the underlying illness or the antimicrobial?). While prescribing antimicrobials for a patient with a viral syndrome may satisfy the patient's desire for "strong" therapy, it is performing a disservice to the community. The antimicrobial resistant bacteria they shed will enter the community bacterial pool, raising the level of resistance in the community[8,9]. This is demonstrated locally by the high level of community *Escherichia coli* resistant to ampicillin/amoxycillin in Singapore.

The clinician can avoid antimicrobial-related problems by keeping in mind the following guidelines:

1. Appreciate that fever is not always caused by bacterial infection; drugs, collagen vascular disease, thyrotoxicosis, malignancy and viral infections among others can all cause fever.
2. Know the spectrum of antibacterial activity of the antimicrobials you commonly use.
3. Consider the most likely organism to cause the infection you plan to treat (eg *Streptococcus pyogenes* causing cellulitis, *Escherichia coli* causing urinary tract infection).
4. Select an antimicrobial which covers the most likely organisms, but not any broader than necessary.
5. Avoid using antimicrobials in viral syndromes as diagnostic tools or to pacify demanding patients.
6. Appreciate that your prescribing habits have an impact on the communal bacterial antimicrobial resistance pattern.
7. Educate your patients as to the detrimental aspects of antimicrobial misuse.
8. Obtain objective information about new antimicrobials from sources which do not have a financial interest in their use. There are numerous microbiologists, infectious disease physicians, pharmacologists and drug information services in tertiary care hospitals which can meet your informational needs.

## References


1. Kunin CM. Resistance to antimicrobial drugs – a worldwide calamity. Ann Intern Med 1993; 118: 557-61.
2. Meyer KS, Urban C, Eagan JA, Berger BJ, Rahal JJ. Nosocomial outbreak of *Klebsiella* infection resistant to late-generation cephalosporins. Ann Intern Med 1993; 119: 353-8.
3. Fernandes PB. The macrolide revival: Thirty-five years after erythromycin. The Antimicrobic Newsletter 1987; 4: 25-36.
4. Anonymous. The new macrolides. The Medical Letter 1992; 34: 45-7.
5. Tedesco FJ. Clindamycin and colitis: a review. J Infect Dis 1977; 135:S95-8.
6. Friedan TR, Mangi RJ. Inappropriate use of oral ciprofloxacin. JAMA 1990; 264: 1438-40.
7. Thys JP, Jacobs F, Motte S. Quinolones in the treatment of lower respiratory tract infections. Rev Infect Dis 1989; 11 (Suppl 5): S1212-1219.
8. Lester SC, del Pilar Pla M, Wang F, Schael IP, Jiang H, O'Brien TF. The carriage of *Escherichia coli* resistant to antimicrobial agents by healthy children in Boston, in Caracas, and in Qin Pu, China. N Engl J Med 1990; 323:285-9.
9. Neu HC. The crisis in antibiotic resistance. Science 1992; 257: 1064-73.