Principles of Antimicrobial Therapy

Key Points

- Early and rapid diagnosis of infection and prompt initiation of appropriate antimicrobial therapy**, if warranted**, are fundamental to reducing the mortality and morbidity from serious infections
- Prompt initiation of broader empirical coverage of suspected pathogens followed by the narrowing or discontinuation of antimicrobial coverage based on clinical status and definitive identification of the pathogen
- Use local guidelines that list minimum criteria for initiation of antimicrobial therapy
- Recognition of certain age-related physiologic, pharmacokinetic and pharmacodynamic changes can help optimise antimicrobial dosage regimens and minimise adverse effects
- Prevention of antimicrobial resistance in healthcare settings requires an integrated strategy focusing on the following:
    a. **preventing infection**
    b. **diagnosing and treating infection effectively**
    c. **using antimicrobials wisely, follow local antibiotic stewardship guidelines + risk assessment**
    d. **preventing transmission**

- Many adverse drug events can be prevented by simply adjusting antimicrobial dosages for diminished renal function e.g. in the elderly
- Treat the patient, not the lab report! Consider whether organisms found are truly the cause of a disease requiring treatment, normal flora or contaminants

With fewer and fewer antibiotics being brought to market, it has become increasingly imperative that the judicious use of existing antibiotics be exercised to avoid further erosion of our diminishing effective choices.

The following questions should be considered before prescribing an antimicrobial agent:

- **Is an antibiotic definitely indicated?** Many less serious infections do not require antibiotics and will self resolve without antibiotics
- Have appropriate specimens been obtained, examined, and cultured?
- **What pathogens are most likely?**
- Which antibiotic will provide the best choice **based on pharmacokinetics, toxicology, cost, narrowness of spectrum?**
- Is an antibiotic combination appropriate?
- What is the best **route** of administration?
- What is the appropriate **dose**?
- Will initial therapy require modification after culture data are returned? **Process/timeframe for this?**
- What is the optimal duration of treatment, and is development of resistance during prolonged therapy likely to occur?
- When will the therapy be **reviewed (written instruction)?**
- **Does the catheter have to remain in place or is it just convenient, when will review occur?**

The appropriate selection of an antimicrobial agent is based on a number of criteria that includes the following:

- the proper identification of the pathogen, or reasoned judgement of the most probable pathogen on clinical presentation
- the site of infection
- the unique pharmacokinetic and pharmacodynamic characteristics of the agent
- the potential risk of harm to the patient
- the known antimicrobial resistance patterns – either to this isolate from this patient, or empirical tables for this geographical location and situation **+ known risk assessment factors**

The choice of a specific empirical antimicrobial regimen should be based on the **severity of the patient's illness**, the **site**, the **nature of underlying disease**(s), **prior exposure to antimicrobials** within 6 months, the **history of drug allergies**, **healthcare institution exposure** and **travel history.**
Most infections can be treated with a single antimicrobial agent.

When treating empirically, risk factors for antimicrobial resistance for that individual <u>can vary markedly</u> compared to empirical aggregated local susceptibility tables

<u>Risk factors include</u>:

a. **Residence in a long-term care facility**
b. **Recent hospitalisation, and especially in high antibiotic use areas including intensive care**
c. **Recent past antibiotic administration** (e.g. within last 6 months)
d. **Recent travel to an area or country with high endemic rates of antimicrobial resistance**
e. **Close direct association with someone from the above**

The selection of antimicrobial therapy and the timing of its administration are important determinants of death for critically ill patients with serious infections.

Once an antimicrobial agent, if required, is selected on the basis of known or anticipated activity against the pathogen(s), the goal of therapy is to deliver that drug to the site of infection in concentrations sufficient to inhibit or kill the organism(s). Most serious infections require antibiotic concentrations to exceed the minimum inhibitory concentration (MIC) of the infecting organism at the site of infection.

The combination of two or more antimicrobial agents may be useful in certain clinical situations to broaden the antimicrobial spectrum to cover all probable or known pathogens, to delay or prevent the emergence of resistant microbial strains, to enhance the antimicrobial effect of another drug against a specific organism (e.g. synergism), or to reduce the dose of an agent to avoid toxicity.

Pharmacokinetics ('the body's effect on the drug')

Pharmacokinetics describes the fundamental **mechanics of drug movement through the body over time**, including factors that describe **the absorption, distribution, metabolism, half-life, area under the concentration-time curve and elimination**, or the overall fate of a drug in vivo. Factors which may affect pharmacokinetics include age, body mass, renal, hepatic and gastrointestinal function and (increasingly recognised) genotype.

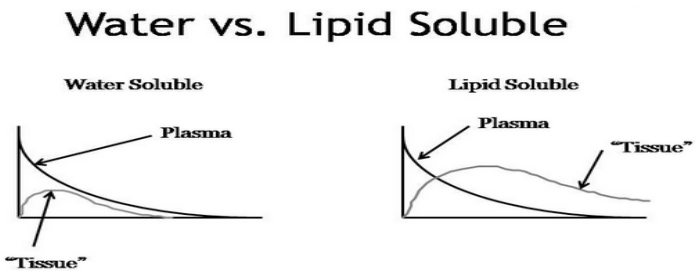
A summary of age-related physiological changes is shown in the table below/over.

Absorption

Age, drug or other related changes in the gastrointestinal tract may influence drug/antibiotic absorption.
A decrease in gastric acid secretion and an increase in gastric pH are associated with the aging process.
The absorption of antimicrobials that are dependent on increased acidity (e.g. sulfonamides, ketoconazole) may be decreased, whereas drugs that are degraded in an acidic environment will have altered bioavailability. The significance of these changes is generally minimal and uncommonly affects dosing requirements.

Distribution

Age-related changes that can affect the distribution of drugs include changes in body composition and cardiac output. In the elderly, the ratio of body fat to total body water is usually increased compared with younger individuals.
A decrease in lean body mass, coupled with a decrease in total body water, is associated with a decreased volume of distribution for water-soluble drugs.
Thus, with older adults, antimicrobials that are distributed primarily in body water or lean mass may have higher blood concentrations than in younger adults, which can lead to potential toxicity (e.g. aminoglycosides).
Conversely, in the elderly, lipid-soluble drugs have a greater body fat distribution, which may reduce blood concentrations and lead to potential sub therapeutic blood concentrations.



Metabolism
Age appears to have no significant effect on the functional activity of various cytochrome P450 isoenzymes for older patients as compared with younger patients.

Physiological Changes Associated with Aging

Pharmacokinetic parameter	Physiological change with aging
Absorption	↑ Gastric emptying
	↓ Gastric acidity
	↓ Gastrointestinal motility
	↓ Absorptive surface
Distribution	↓ Lean body mass
	↑ Body fat
	↓ Serum albumin
	↑ α1-acid glycoprotein
Elimination	↑↓ Enzyme activity
	↓ Hepatic (liver) blood flow
	↓ Renal (kidney) blood flow
	↓ Glomerular filtration rate
	↓ Tubular secretion

Key: ↓, decrease activity or function; ↑, increase activity or function; ↑↓, may increase or decrease activity or function.

Tissue Penetration
Some drugs e.g. aminoglycosides, macrolides, and fluoroquinolones bind extensively to certain tissue components. Intracellular accumulation of aminoglycoside is slow however because of its poor membrane permeability.
Intracellular aminoglycoside concentrations tend to be low after initial drug exposure but are high after more sustained exposure and multiple dosing. However the drug is microbiologically inactive in an acidic environment. The high intracellular aminoglycoside concentrations achieved in the renal cortex after multiple doses may be the cause of their nephrotoxicity.

Clearance
Age-related changes in **renal function** are probably the most significant contributors to alteration in drug clearance. Reduction in kidney mass, renal blood flow, and the subsequent number of functioning nephrons, glomerular filtration rate, and the rate of tubular secretion accounts for the decreased renal excretory capacity observed with aging.
Diminishing renal function and lack of compensatory increases in non renal clearance in elderly patients have been associated with prolongation of the serum half-lives of the beta-lactams, aminoglycosides, glycopeptides, sulfonamides and fluoroquinolones.

The primary route of clearance for selected antimicrobial agents is listed below/over:

Routes of Antimicrobial Clearance

Drug	Primary route of clearance
Penicillins	
Ampicillin	Tubular secretion
Ampicillin/sulbactam	Tubular secretion
Methicillin	Tubular secretion
Nafcillin	Hepatic/biliary excretion/renal
Oxacillin	Hepatic/biliary excretion/renal
Penicillin G	Tubular secretion
Piperacillin	Tubular secretion/hepatic
Ticarcillin	Tubular secretion
Cephalosporins	
Cefazolin	Tubular secretion
Cephapirin	Tubular secretion
Cefotetan	Tubular secretion
Cefoxitin	Tubular secretion
Cefuroxime	Tubular secretion
Cefoperazone	Biliary excretion
Cefotaxime	Hepatic/tubular secretion
Ceftazidime	Tubular secretion
Ceftizoxime	Tubular secretion
Ceftriaxone	Renal/hepatic
Carbapenems	
Ertapenem	Tubular excretion
Imipenem/cilastatin	Tubular excretion
Meropenem	Tubular excretion
Monobactams	
Aztreonam	Glomerular filtration and tubular secretion
Quinolones	
Ciprofloxacin	Hepatic/tubular secretion
Ofloxacin	Tubular secretion
Lomefloxacin	Tubular secretion
Levofloxacin	Hepatic/tubular secretion
Moxifloxacin	Hepatic
Gatifloxacin	Hepatic/tubular secretion
Tetracyclines	
Doxycycline	Hepatic
Minocycline	Hepatic
Tetracycline	Glomerular filtration
Macrolides	
Azithromycin	Hepatic
Clarithromycin	Hepatic/renal
Erythromycin	Hepatic
Vancomycin	Glomerular filtration
Aminoglycosides	Glomerular filtration

Pharmacodynamics (' the drug's effect on the body')

Pharmacodynamics refers to **the action of drugs** or the biological effects resulting from the interaction of a drug and its receptor site e.g. microorganism death. Pharmacodynamics describes **the antimicrobial effect at the site of infection as well as toxic effects in relation to the concentrations of the antimicrobial drug during the course of drug therapy**.

The three main pharmacodynamic parameters that are used are the

1. peak to minimal inhibitory concentration (MIC) ratio (peak/MIC)
2. area under the curve (AUC) to MIC ratio (AUC/MIC)
3. time the drug concentration remains above the MIC (T>MIC).

For antibiotics with particular concentration-dependent bacterial activity, such as aminoglycosides and fluoroquinolones, the rate and extent of bactericidal action increases with increasing antibiotic concentrations above the minimum bactericidal concentration (MBC) up to a point of maximum effect, **usually 5 to 10 times the MBC**. In addition, the duration of the post antibiotic effect (PAE) is concentration dependent with these drugs, and thus longer PAE's are induced by higher antibiotic concentrations.

In contrast, the bactericidal activity of most beta-lactam antibiotics against gram-negative bacilli is relatively slow and continues as long as the concentrations are in excess of the MBC. It does not increase as the antibiotic concentration is increased, that is the bactericidal action of beta-lactams is time-dependent and not concentration-dependent. For time-dependent agents that exhibit little to no post antibiotic intervals — such as extended-spectrum beta-lactams effective against most gram-negative bacilli — multiple, small, frequent doses or continuous intravenous infusion produces similar or superior bactericidal effects compared with infrequently administered larger doses.

Antibiotic/drug Interactions

Drug interactions constitute an often predictable and avoidable cause of adverse drug events. It has been well documented that the potential for drug–drug interactions increases with both age and with the number of medications prescribed. One publication suggests that the potential for an interaction reaches 100% once the number of drugs used reaches eight. The mechanisms of adverse drug interactions are varied, but the inhibition or induction of drug metabolism is considered of highest importance.

Oxidative metabolism by cytochrome p450 enzymes is a primary method of drug metabolism. The purpose of drug metabolism is to make drugs more water-soluble so that they can be more easily excreted from the body. Drug interactions involving the cytochrome p450 system are common and generally result from either enzyme inhibition or induction. Enzyme inhibition generally involves competition with another drug for enzyme binding sites and usually begins with the first dose of the inhibitor. Duration of inhibition corresponds to the half-lives of the respective drugs. Inhibitors and inducers of the hepatic monoxygenase system include the following antimicrobial agents: fluconazole, miconazole, ketoconazole, erythromycin, clarithromycin, sulphonamides and fluoroquinolones.

Aminoglycosides

Aminoglycosides must be prescribed with caution because of the well-documented risks of enhanced ototoxicity and nephrotoxicity associatedwith these agents and the availability of safer and less toxic drugs with comparable spectra (i.e.cephalosporins, monobactams, carbapenems, betalactam/beta-lactamase inhibitor combination antibiotics, and quinolones).

However, these agents are rapidly bactericidal against staphylococci and gram-negative aerobic bacteria, including often Pseudomonas sp., and they can provide synergy with other agents (e.g. beta-lactams) for treatment of serious or life-threatening infections, such as enterococcal endocarditis. **Renal impairment (generally reversible) and ototoxicity (generally irreversible) are the two most common and important potential adverse effects of these antibiotics**. Because plasma half-life is increased in patients with decreased renal function (most common in elderly persons), the dose should be reduced on the basis of the creatinine clearance. Nephrotoxicity may lead to high serum levels of aminoglycosides, which in turn can cause irreversible ototoxicity. Risk of ototoxicity increases with age and is highest in patients with pre-existing hearing deficiencies. Thus, aminoglycoside use in older LTCF residents should be reserved for those with serious or life-threatening infections that require hospitalisation and are caused by pathogens susceptible to aminoglycosides.

Monitor aminoglycoside blood levels during treatment to reduce toxicity risks.

Beta-Lactams

Beta-lactam antibiotics (penicillins, cephalosporins, carbapenems, monobactams, and beta-lactamase inhibitors) are widely used and useful in the management of many infections because of their broad spectrum, favourable pharmacokinetics, and favourable safety profiles.

However the broader spectrum ones especially risk driving up antimicrobial resistance and *C. difficile* rates.

Macrolides

e.g. Erythromycin, clarithromycin, roxithromycin and azithromycin.

These antibiotics are moderately active against many strains of streptococci, methicillin-sensitive *Staphylococcus aureus*, anaerobes, *Moraxella catarrhalis, Haemophilus influenzae, Legionella, Mycoplasma pneumoniae,* and *Chlamydia pneumoniae*. Macrolides often have a role in treating atypical pneumonia (e.g. *Legionella, Mycoplasma*).

Clindamycin

This antibiotic is commonly used for anaerobic infections and staphylococcal infections and for life-threatening group A beta-haemolytic streptococcal infections including streptococcal toxic shock syndrome and necrotising fasciitis, the latter especially requiring acute facility care. The elderly and residents of LTCFs are particularly susceptible to antibiotic-associated colitis caused by *C. difficile* - clindamycin use is also a relatively common association (along with other broad spectrum antibiotics).

Fluoroquinolones

The fluoroquinolones are a group of synthetic antibiotics that have a broad spectrum of antimicrobial activity, good absorption from the gastrointestinal tract, a unique mechanism of action (inhibition of bacterial topoisomerases), favourable pharmacokinetic properties, and a good safety profile.

As a group, the fluoroquinolones have excellent activity against a wide range of gram-positive bacteria and many gram-negative bacteria such as Enterobacteriaceae, *Aeromonas, Campylobacter, Haemophilus, Legionella, Moraxella, Neisseria,* and *Vibrio.* These agents are often active against *P. aeruginosa* but are significantly less active against other pseudomonal species including *P. cepacia* and *P. fluorescens*. The newer generation fluoroquinolones have activity against gram-positive bacteria, including *S. pneumoniae* and staphylococcal species, i.e. methicillin-sensitive *S. aureus* and coagulase-negative species.

The fluoroquinolones have less activity against streptococcal species and enterococci.

These agents in general have very poor activity against anaerobes.

These antibiotics are used because they allow the convenience of oral therapy with an agent with good bioavailability, are easily administered by one or twice-daily dosing, are perceived to be safe, and have wide spectrum of activity.

In the elderly, quinolones are useful in the treatment of complicated urinary tract infections, bacterial prostatitis, skin and soft-tissue infections, pneumonia and bacterial diarrhoea caused by susceptible pathogens. The newer generation fluoroquinolones (e.g. levofloxacin, gatifloxacin, moxifloxacin) have improved gram-positive (including *S. pneumoniae*) activity over that of the older agents in this class.

Adverse effects of quinolones in the elderly occur in 5% to 15% of cases, including gastrointestinal (nausea, vomiting, diarrhoea) and central nervous system (dizziness, headache, insomnia) effects.

Associated drug interactions with other medications include decreased theophylline clearance associated with increased serum levels of ciprofloxacin, but not norfloxacin or levofloxacin, and multivalent ions (e.g. calcium, iron, aluminium) contained in foods or drugs that significantly reduce absorption of quinolones from the upper gastrointestinal tract.

With increased quinolone use, quinolone resistance of many organisms has increased. Norfloxacin selects for resistance significantly more than ciprofloxacin. In turn there is a strong association between quinolone use and increasing *C. difficile* rates (spores not affected or inhibited by antibiotics at all).

Resistance via gene mutations along with increased antibiotic efflux from the bacteria is common in clinical isolates.

What is effective for the individual patient's infection now has wider implications for others both now and in future.

Co-Trimoxazole (Trimethoprim–Sulfamethoxazole)

This antibiotic is commonly prescribed for urinary tract infections, chronic bacterial prostatitis and lower respiratory tract infections. Oral drug absorption does not appear to be affected by age. Renal clearance of trimethoprim is decreased in older persons. This antibiotic should be avoided if the creatinine clearance is less than 15 mL/min.

Vancomycin

Is a glycopeptide antibiotic used primarily for gram-positive bacterial infections. It is highly active against staphylococci (including most MRSA) and streptococci (including vancomycin sensitive enterococci). Lower parenteral doses are recommended for the frail elderly, and the dose should be adjusted according to the serum peak and trough levels as well as the creatinine clearance.

Linezolid

An oxazolidinone, is active against infections caused by susceptible gram-positive bacteria, as well as MRSA and vancomycin resistant enterococci (VRE). This antibiotic's availability, both in parenteral and oral formulations, as well as its relatively safe profile, is particularly advantageous in management of infections caused by such gram-positive-resistant organisms.

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