LEADING ARTICLE

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# Use of Pharmacodynamic Principles to Optimise Dosage Regimens for Antibacterial Agents in the Elderly

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## Abstract

Throughout most of the world we are witnessing an ever increasing number of aged people as a percentage of the general population. In the coming years, the unique spectrum of infections presented by an elderly population, particularly those in long-term care facilities, will challenge our ability to maintain an effective battery of antibacterials. The pharmacokinetic parameters of most antibacterial agents are altered when assessed in the elderly due in part to non-pathological physiological changes. The inability to clear a drug from the body due to declining lung, kidney/bladder, gastrointestinal and circulatory efficiency can cause accumulation in the body of drugs given in standard dosages. While this may have the potential benefit of achieving therapeutic concentrations at a lower dose, there is also a heightened risk of attaining toxic drug concentrations and an increased chance of unfavourable interactions with other medications. Pharmacodynamic issues in the elderly are related to problems that arise from treating elderly patients who may have a history of previous antibacterial treatment and exposure to resistant organisms from multiple hospitalisations. Furthermore, the elderly often acquire infections in tandem with other common disease states such as diabetes mellitus and heart disease. Thus, it is essential that optimised dosage strategies be designed specifically for this population using pharmacodynamic principles that take into account the unique circumstances of the elderly. Rational and effective dosage and administration strategies based on pharmacodynamic breakpoints and detailed understanding of the pharmacokinetics of antibacterials in the elderly increase the chances of achieving complete eradication of an infection in a timely manner. In addition, this strategy helps prevent selection of drug-resistant bacteria and minimises the toxic effects of antibacterial therapy in the elderly patient.

The pharmacokinetic parameters of most antibacterial agents are altered when assessed in the elderly as a result of non-pathological physiological changes. In general, renal function begins to decline in middle age with a profound decrease in creatinine clearance. However, there is significant inter-individual variation.[1] Furthermore, tissue distribution dynamics change dramatically in the elderly because of a higher overall body fat content. This favours movement of lipophilic drugs into the tissues and accumulation of hydrophilic drugs in the plasma.[2] The combination of changes in volume of

distribution, decline in renal function and acquisition of infections in tandem with chronic disease states requiring long-term drug treatments puts the elderly population at significant risk of adverse drug reactions (ADRs) arising from drug-drug interactions and changes in metabolism.

Pharmacodynamic problems arise in the treatment of those elderly patients who may have a history of previous antibacterial treatment. Elderly patients are at increased risk of acquiring drug-resistant strains of *Staphylococcus*, *Streptococcus* and *Enterococcus*, among others, because of longer stays in intensive care units, transitional units and nursing homes. Elderly patients not only have a higher rate of hospitalisations but also longer hospital stays, often followed by entrance or return to a long-term care facility.[3] The elderly population is plagued by multiple chronic diseases combined with significant physical impairments. A German survey found a median of three concomitant diseases among the 125 nursing home patients they studied.[4] Cardiovascular disease and neurological disease/psychiatric disease were most common, occurring in 98% and 86%, respectively, of patients, followed by diabetes mellitus, which occurred in 42% of patients.[4] Such patients generally have a history of infection with drug-resistant bacteria and often act as transmitters, carrying bacterial infections acquired in the hospital setting with them back to the long-term care facility. Thus, outbreaks of infection with multi-drug-resistant strains are common in long-term care facilities. For any particular patient, every day spent in such an environment increases the risk of nosocomial infection and consequent infection-related death.[3-6]

Elderly patients often require long-term use of medical devices such as catheters, which are notorious for colonisation by drug-resistant bacteria such as *Pseudomonas* spp. and multi-drug-resistant forms of *Staphylococcus*.[3-7] Antibacterial agents often fail against biofilms established on indwelling devices by these bacteria, and treatment may require removal of the infected device.[8,9] *S. pneumoniae* is also a significant cause of morbidity and mortality among the elderly. While recent studies have alluded to the benefit of vaccination of young children with the seven-valent pneumococcal conjugate vaccine and the use of the pneumococcal polysaccharide vaccine in adults aged >65 years or within certain populations at high risk for pneumococcal disease, the estimated efficacy for the pneumococcal polysaccharide vaccine is only 44% and total population vaccination rates are suboptimal even in the US. Furthermore, not all strains are covered by the vaccine, which means the risk of infection with drug-resistant *S. pneumoniae* in the elderly is still great.[10-12]

Significant problems arise in the diagnosis of infections in the elderly. The clinical symptoms of infection in the elderly may not include fever and chills, but may instead mimic the normal signs of aging or symptoms of concomitant disease, further complicating the decision to administer antibacterials to the elderly in long-term care facilities. Even community-acquired pneumonia in the otherwise healthy elderly may present first as confusion, without obvious classical signs of respiratory infection. Conversely, patients may have fever without apparent infections.[3,5,13-16]

Selection of treatment for infections in the elderly is often empirical, despite the availability of information for more rational and precise choices. Whenever possible, particularly in the elderly population, the pharmacodynamics of a drug should be assessed against the offending isolate and the information combined with pharmacokinetic information based on the results of individual patient data; most importantly, creatinine clearance and monitoring of free drug concentrations after the initiation of treatment should be considered.[2] This initial assessment and subsequent consistent monitoring are of particular value in the elderly population, in whom variance from the expected result based on general guidelines for treatment may be significant. Rational and effective dosage and administration strategies can be designed for the elderly using a combination of pharmacokinetic and pharmacodynamic parameters that take into account each individual patient's unique circumstances. Because of the wide variability in elderly patients, each patient must be assessed

and treated individually rather than resorting to use of general guidelines based on age alone. Careful assessment also increases the chances of achieving complete eradication of an infection in a timely manner, helps avoid selection of additional populations of drug-resistant bacterial strains and reduces the risk of toxic effects in the patient.

The intent of this article is to merge experimental and clinical pharmacokinetic and pharmacodynamic knowledge regarding antibacterial use in the elderly, thereby creating a constructive guide for optimising antibacterial choice and dosage and administration regimens based on individual patient parameters.

## 1. Pharmacokinetics in the Elderly

The normal physiological changes that occur with aging require attention when determining a course of antibacterial treatment. While there does not appear to be evidence for significant changes in antibacterial absorption via the digestive system in the elderly, there are significant changes in renal clearance and distribution of antibacterials.

Variance in renal clearance among elderly individuals is significant. Although renal function as measured by creatinine clearance does vary with age, age alone is not predictive of impaired renal function, which emphasises the importance of specific consideration of individual patient parameters before beginning treatment.[1] In the patient with decreased renal clearance, renally cleared drugs will be retained in the body if dosage adjustments are not made, and this may result in dangerously high plasma free drug concentrations.[17] Creatinine clearance is thus a crucial parameter on which to base the initial dosage.

The elderly may be particularly sensitive to fat-soluble drugs when drug dosages do not take into account the generally increased fat/muscle ratio found in older people. Elderly patients are therefore at risk not only of accumulation of water-soluble antibacterials in plasma, resulting in increased plasma free drug concentrations, but also of tissue compartment concentrations in excess of recommended levels. While the penetration of a drug to the site of infection is critical to achieving therapeutic concentrations and accumulation may have the potential benefit of achieving therapeutic concentrations at a lower dose, there is also a heightened risk of increased ADRs if the appropriate dosage adjustments are not made.[2,5,13,15,18-21] Conversely, failure of water-soluble drugs to penetrate the site of infection because of decreased total body water and/or muscle mass can lead to treatment failure while plasma drug levels appear to be at steady state. A summary of pharmacokinetic changes relating to use of antibacterials in the elderly is presented in table I.

## 2. Pharmacodynamics

Pharmacodynamic parameters describe the relationship between serum concentration and the extent to which the drug is able to bind or interact with its specific bacterial target and cause cell growth inhibition or death, as measured by minimum inhibitory concentration (MIC).[25,26] MIC measurements provide useful information on the inhibition of a pathogen at a measured endpoint. However, they are static *in vitro* measurements that do not provide data on the time course of antimicrobial action, such as the duration of drug exposure necessary for bacterial eradication, the rate of bactericidal activity or the persistence of effects of antimicrobial agents.[25,27]

Antibacterials display two types of activity: concentration- or time-dependent killing. The time-dependent group of antibacterials includes the β-lactams as well as vancomycin and clindamycin. Bacterial killing assessed for antibacterials in the time-dependent group correlates poorly with peak serum concentration; rather, the best predictor of clinical success for this group is the amount of time during which the plasma antibacterial concentration exceeds the MIC for the organism. Since the primary parameter influencing clinical success is time at or over MIC (T/MIC), use of these agents is optimised by giver smaller, frequent doses or constant infusion.[26,28] The most important parameter for antimicrobial agents that kill bacteria in a concentration-dependent manner is the concentration achieved in the patient's plasma. The rate and extent of bactericidal activity of these drugs increases proportionately as drug concentrations increase, even when the

**Table I.** Pharmacokinetic (PK) changes of antibacterials in the elderly

| PK parameter | Physiologic change | Result | PK effect | References |
|---|---|---|---|---|
| Volume of distribution | Increased proportion of adipose tissue | Increased solubility of lipophilic drugs in tissue compartments | Prolonged drug half-life | 2 |
| | Decrease in total body water and lean mass | Decreased solubility of water-soluble drugs in tissue compartments | Increased plasma concentration | 2 |
| | Oedema | Dilution of standard doses at infection site and in plasma | Standard dose is inadequate | 22 |
| | Increased proteinuria or decreased albumin production because of chronic disease | Decreased plasma albumin | Decrease in protein-bound drug fraction (inactive) and increase in free drug in plasma (active) | 2,21,22 |
| Drug metabolism | Reduced hepatic function as a result of physiological aging or liver disease | Decreased hepatic blood flow or decreased hepatic function | Increased half-life of hepatically cleared drugs | 21 |
| | Polypharmacy (for concomitant disease) | Competition for cytochrome P450 enzyme metabolism | Inhibition of metabolism of competing drug and accumulation of non-metabolised form<br>Enhanced metabolism of competing drug and increased drug activity<br>Competition for albumin binding sites and accumulation of drug not preferentially bound to albumin | 13 |
| Renal drug elimination | Reduced renal function as a result of physiological aging or renal disease | Decreased blood flow and/or decreased glomerular filtration rate | Increased drug half-life, inability to remove drug from the plasma, and accumulation of drug in the plasma | 23 |
| | Renal replacement therapy | Increased drug removal | Dose adjustment for some drugs based on type of therapy | 24 |

levels achieved are substantially above the MIC of the target organism. The aminoglycoside and quinolone drug classes are examples of antibacterials that display concentration-dependent killing.[26,28]

## 3. Pharmacokinetics/ Pharmacodynamics

The rate and extent of bactericidal activity depends initially on the concentration of the drug at the site of action (pharmacokinetic factors) and the MIC of the pathogen (pharmacodynamic factors). This in turn, determines the outcome of therapy.

For example, the pharmacokinetic/pharmacodynamic ratio predicts the therapeutic response of microorganisms to concentration-killing antimicrobials by correlating free drug area under the plasma concentration-time curve over 24 hours of administration ($AUC_{0–24}$) to measures of drug potency (MIC).[26] Thus, the pharmacokinetic/pharmacodynamic parameters of interest in predicting clinical outcomes are the maximum plasma concentration ($C_{max}$)/MIC and the $AUC_{0–24}$/MIC (also sometimes referred to as the area under the inhibitory plasma concentration-time curve) for concentration-dependent killing, and the T/MIC for time-dependent killing antibacterials[26,28] (figure 1).

It is important to mention that a pharmacokinetic/pharmacodynamic prediction of clinical success is specific to the patient, the drug and the infecting organism. As an example, clinical data for the fluoroquinolone levofloxacin predicted a $C_{max}$/MIC ratio of ≥12.2 for eradication of Gram-positive orga-

nisms in respiratory tract infections.[29] A $C_{max}$/MIC ratio of 23.6 for grepafloxacin was required for eradication of *Haemophilus* spp. in patients with chronic bronchitis.[30] In outpatients with community-acquired respiratory infections such as acute exacerbations of chronic bronchitis and community-acquired pneumonia caused by *S. pneumoniae*, animal, *in vitro* and clinical data support an $AUC_{0-24}$/MIC of ≥25 as being predictive of bacterial eradication.[31-34]

Optimising dosage regimens for common infections in the elderly population by focusing on pharmacokinetic/pharmacodynamic principles is addressed in section 5. Important drug class considerations are discussed in section 6.

## 4. Adverse Drug Reactions in the Elderly

Antibacterials are a significant cause of ADRs in the elderly with up to 20% of re-admissions to hospitals occurring as a result of ADRs.[21] The two reactions of greatest concern are gastrointestinal and CNS effects. CNS-related reactions are particularly troublesome because they are often indistinguishable from normal age-related decline such as confusion and muscle weakness.[2,5,13,18] In elderly patients with cardiovascular disease, chronic obstructive pulmonary disease, diabetes, cancer, orthopaedic injury, autoimmune disease or other chronic diseases common in the elderly population, designing a successful antibacterial treatment regimen is more complicated because of the likelihood

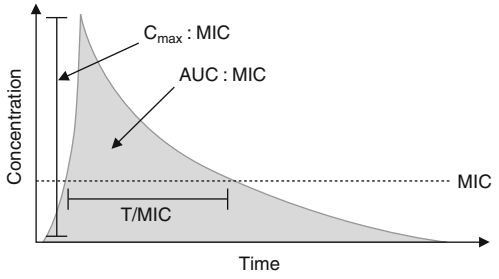


**Fig. 1.** Antimicrobial pharmacodynamic parameters predictive of bacterial eradication leading to favourable clinical outcome. **AUC** = area under the plasma concentration-time curve; **$C_{max}$** = maximum plasma concentration; **MIC** = minimum inhibitory concentration; **T/MIC** = time that the plasma antibacterial concentration exceeds the MIC for the organism.

of polypharmacy.[3,13,18,23] Of particular note is the fact that a large proportion of drugs are metabolised via the cytochrome P450 (CYP) enzyme pathway. There is limited capacity to metabolise multiple drugs by this pathway and many common antibacterials such as erythromycin act as inhibitors of CYP enzymes, thereby contributing to potentially toxic combinations.[18,21]

An example of an antibacterial ADR with dire consequences is dysglycaemia caused by gatifloxacin. Park-Wylie et al.[35,36] have studied the medical records of 1.4 million elderly Canadian patients, of whom >3000 were treated as outpatients with antibacterials and subsequently hospitalised for dysglycaemia. In this study, gatifloxacin was compared with moxifloxacin, levofloxacin and ciprofloxacin as well as with macrolides and second-generation cephalosporins as a cause of hospitalisation for dysglycaemia in elderly patients who were receiving antibacterials. Gatifloxacin is somewhat unique in causing opposing effects of both hypoglycaemia and hyperglycaemia. The study showed that elderly patients treated with gatifloxacin were four times more likely than control patients to be hospitalised with hypoglycaemia. Furthermore, patients hospitalised for hyperglycaemia were 17 times more likely to have been treated with gatifloxacin than with macrolides, and there was no evidence of hyperglycaemia in any patient treated with the other respiratory fluoroquinolones or cephalosporins. The investigators recommended use of alternate, safer antibacterial choices in the elderly population.

However, an earlier study by Ambrose et al.[37] of hyperglycaemia induced by gatifloxacin suggested a reduction in the dosage based on age and/or renal function, particularly in elderly patients prone to disturbances in serum glucose levels. These investigators[37] and Noreddin et al.[20] used clinical data and *in vitro* methods to predict the ability to attain bacterial killing with a reduced dosage of gatifloxacin in the elderly. However, reduced antibacterial dosages may lead to selection of resistant strains, and it was unclear from these studies whether the reduced dose of gatifloxacin would encourage pro-

duction of bacterial resistance. Furthermore, dysglycaemia was not confirmed as being dose related.[38] Gatifloxacin was recently removed from most markets because of idiosyncratic dysglycaemia.

## 5. Common Infections in the Elderly

The elderly population in general has its own specific mix of infective organisms that is unique in terms of the severity and prevalence of particular types of infections, and in the fact that it varies from the assortment of infections acquired in younger populations.[5,13] We now focus on antibacterials preferred for the treatment of the three most common forms of infection experienced by the elderly population: respiratory tract infections, soft tissue infections and urinary tract infections (UTIs).

### 5.1 Respiratory Tract Infections

Pneumonia is associated with high morbidity and mortality in the elderly population compared with younger age groups. In general, pneumonia acquired in a community setting is likely to be *S. pneumoniae*, *Haemophilus influenzae* or *Moraxella catarrhalis*. Other Gram- negative bacteria and atypicals such as *Chlamydia pneumoniae* are less common but should be considered when choosing empirical therapy. The new respiratory fluoroquinolones and macrolides as well as the ketolide telithromycin provide adequate coverage against these common respiratory pathogens. However, attention must be paid to the pharmacokinetics of the chosen drug in an elderly patient to ensure maximum bacterial eradication and prevent development of resistant bacterial strains.

Examination of nosocomial infections from either a hospital setting or a long-term care facility reveals that the most likely culprits are *P. aeruginosa* and other multi-drug-resistant Gram-negative bacteria, meticillin (methicillin)-resistant *S. aureus*, anaerobes from oral microflora, and drug-resistant *S. pneumoniae*.[3,5,6,13,15] A combination therapy option might be considered to eradicate such hard-to-treat infections. Using a concentration-dependent antibacterial as an example, the $AUC_{0–24}$/MICs in a patient population treated with ciprofloxacin for nosocomial lower respiratory tract infections were found to be ≥125 for efficacy and >250 for optimal effect, significantly higher than the accepted 25–40 values for typical Gram-positive infections.[39]

### 5.2 Soft Tissue Infections

Elderly patients, particularly long-term care facility patients, are prone to outbreaks of soft tissue infections. Pressure ulcers, cellulitis, diabetic foot infections and infected wounds are common because of a lack of mobility, thin skin, malnutrition and decreased blood flow. Soft tissue infections are often polymicrobial. Common organisms include *S. pyogenes*, *Staphylococcus* spp., meticillin-resistant *S. aureus* (MRSA), *Proteus mirabilis*, *Escherichia coli* and other Gram-negative bacteria.[3,13] As with other infections in the elderly, antibacterial resistance is a major concern. Long-term care facilities often harbour endogenous multi-drug-resistant *P. aeruginosa* and MRSA, which can spread rapidly from patient to patient within such a facility.[6,14,40] Additionally, a high proportion of patients arriving at these facilities are already colonised by MRSA and have a very high risk of developing an infection involving these organisms.[3,14,40] A worldwide increase in the number of reported community-acquired MRSA infections led to recognition of vancomycin as the new first line of defence. However, vancomycin-resistant isolates have been reported in the US since 2002 together with intermediately susceptible isolates in both Japan and France.[40] Bacterial resistance to β-lactams, fluoroquinolones, vancomycin and other broad-spectrum treatments for soft tissue infections is also increasing, thereby limiting treatment options for complicated skin infections. Furthermore, the new antibacterial linezolid for MRSA must be used carefully as resistant strains are already appearing and there are few other drugs from which to choose.[40,41] Thus, empirical treatment for soft tissue infections may no longer be appropriate. Instead, obtaining specific drug susceptibility profiles for isolates and considering patients' creatinine clearance and history of prior antibacterial treatment are imperative elements in the rational design of a specific treatment for an

infection, with combination therapy becoming the norm.[42]

### 5.3 Urinary Tract Infections

UTI is probably the most common infection of the three discussed in this article. It is often present as asymptomatic bacteriuria in the elderly population because of decreased hormone levels, prostate dysfunction and poor bladder function. Indwelling catheters and immobility heighten the potential for infection.[5,13,14] Asymptomatic bacteriuria is treated only in specific circumstances such as the lead up to surgery.[42] In community acquired UTI, *E. coli* is the most commonly isolated bacterium in women while *P. mirabilis* is more commonly isolated from men.[13,14] Pharmacokinetic/pharmacodynamic ratios predictive of treatment success against Gram-negative bacteria are generally higher than those for Gram-positive organisms as might be expected given the known difficulty of treating Gram-negative infections. Failure of antibacterial therapy with standard treatment protocols may occur as a result of inability to achieve adequate drug concentrations at the site of infection and/or because of a patient history that includes previous suboptimal treatment with antibacterials.[25]

Achieving adequate drug penetration to the infection site is critical for the treatment of any infection as initial suboptimal treatment may lead to first-step resistance of microbes that upon sensitivity testing may appear to still be within the susceptibility range, although with a slightly higher MIC. However, with additional suboptimal treatments, an upward drift of MIC can be observed as additional resistance gene-expressing mutants are selected and eventually fully resistant isolates may be recovered.[16,22,25,42,43] Due consideration to a drug's ability to penetrate to the site of the specific infection should always be given when choosing a drug.

## 6. Drug Class Considerations

### 6.1 Aminoglycosides

Aminoglycosides are concentration-dependent drugs and as such their $C_{max}$/MIC and $AUC_{0–24}$/MIC ratios are the critical parameters.[15] However, the prolonged post-antibiotic effect (PAE) of aminoglycosides means once-daily dosing may be appropriate. Interestingly, aminoglycosides appear to work best using the concept of 'dose-dependent killing', such that concentrations significantly above MIC are preferred, followed by a low trough to allow for reversal of adaptive resistance and relief of drug accumulation in the kidney.[44-46] Aminoglycosides are generally not optimal for the treatment of respiratory infections in the elderly. This is because of the combination of relatively poor penetration into the lung tissue, high potential for nephrotoxicity and ototoxicity, narrow treatment window and a lack of evidence for benefit in elderly patients with respiratory infections, particularly in those with concomitant disease, compared with relatively safer and more effective drugs, such as the fluoroquinolones or macrolides, which also have a prolonged PAE but fewer ADRs and good penetration into the lung.[13,15,19,47-50]

When aminoglycosides are chosen, dosages should be reduced in patients with reduced creatinine clearance.[49] However, in patients with oedema, the loading dose may need to be increased.[22] Once-daily administration with the dosage interval adjusted based on creatinine clearance, determined both before and during aminoglycoside administration, is necessary to monitor for possible kidney damage in elderly patients.[51] Duration of treatment (preferably ≤7 days) is also a critical parameter regarding development of nephrotoxicity and ototoxicity.[51] Because there is a finite amount of drug that can be retained in the kidney, administration of large loading doses early in the treatment course can provide the highest dose possible to infected sites with a lessened effect on the kidney.[52] This can achieve faster resolution of the infection and less exposure of the kidney over time to the drug, the goal being to eradicate the infection and conclude antibacterial treatment as soon as possible. However, patients already exhibiting electrolyte imbalances or signs of kidney dysfunction prior to initiation of treatment are, in general, poor candidates for aminoglycoside use.[49-51]

Aminoglycosides may play a role in the treatment of *P. aeruginosa* and other infections caused by Gram-negative organisms or multiple organisms when used in conjunction with β-lactams. However, this is dependent on the site of infection and local resistance profiles. A large survey conducted at the All India Institute of Medical Sciences in 2004 found that among hospitalised patients, aminoglycosides (even when combined with β-lactams) would most likely not be adequate treatment for soft tissue infections caused by the most common trio of bacteria: MRSA, *E. coli* and *Pseudomonas* spp.[53]

### 6.2 β-Lactams

β-Lactams (penicillins, cephalosporins and carbapenems) are strictly time-dependent drugs, and increasing the dose more than 5-fold of MIC does not increase their effectiveness. The critical parameter for β-lactams is T/MIC,[15,26] such that trough levels must remain above MIC to prevent bacterial recovery and regrowth and the emergence of resistant strains.[22] Thus, the dosage and administration strategy for this class of drug requires the administration of many (up to six) smaller doses per day. However, elderly patients treated with β-lactams may be better served by continuous infusion so that compliance is assured and the likelihood of dropping below MIC values is low. Preference for continuous infusion of β-lactams is supported by the results of some clinical studies[54,55] that appear to predict a need to increase the pharmacodynamic target for β-lactams compared with previous predictions obtained from *in vitro* studies. In fact, the T/MIC must be 100% for the dosing interval in some cases to achieve successful eradication of infection, particularly against Gram-negative bacteria.[43]

### 6.3 Macrolides and Ketolides

The macrolides have traditionally been considered concentration-independent agents; however, recent data suggest that azithromycin may be concentration-dependent. The critical parameters for macrolides are T/MIC and $AUC_{0–24}$/MIC.[43,56] However, treatment success with azithromycin occurs despite serum concentrations that do not achieve levels above the recommended MIC with standard dosage and administration strategies. This is attributed to the pharmacokinetic property of azithromycin of accumulating in phagocytic cells that move into the interstitial spaces of the tissue where the infection is present, such that the concentration of the drug in other tissues and body fluids (e.g. the epithelial lining fluid) exceeds the plasma concentration.[57] Thus, for azithromycin, the concentration of drug in the epithelial lining fluid of patients with lung disease may be a better predictor of clinical outcome than serum concentrations.[15,57] Azithromycin has the potential advantage that a single dose provides 5 days of antibacterial therapy directly at the infection site in association with only the typical ADRs experienced with antibacterials and no requirement for dose adjustment in patients with renal impairment, because the drug is eliminated primarily via the faeces.[22] Indeed for many antibacterials, the trend is moving toward studies involving increased dosages of the antibacterial over shorter time periods, which is designed to achieve maximal antibacterial effect and minimal exposure of the bacterial population to the drug, decreasing the chance for relapse as a result of appearance of endogenous-resistant clones.[58-60]

Telithromycin is a ketolide that is also used to treat respiratory tract infections. Like azithromycin and other members of the macrolide class, it has very high penetration into epithelial lining fluid and alveolar macrophages.[61] Telithromycin levels can be maintained well above the MIC of infecting organisms within the epithelial lining fluid and alveolar macrophages, and at levels always in excess of those measured in plasma. Overall, this ketolide appears to be well tolerated by elderly patients; however, there have been very rare instances of telithromycin hepatotoxicity.[61,62]

### 6.4 Glycopeptides and Glycylcyclines

Glycopeptides such as vancomycin are time-dependent antibacterials. Thus, as for β-lactams, ideal treatment means continuous infusion to maintain T/MIC at optimal levels. However, glycopeptides are nephrotoxic when infused and have poor penetration

into the lung.[41] Although vancomycin is the standard choice for treatment of MRSA, which can cause both lung and soft tissue infections in the elderly, a high mortality rate in patients with ventilator-associated pneumonias makes this class overall a poor choice for treatment of respiratory infections in the elderly.[15] As intermediate- and fully resistant MRSA emerge worldwide, newer broad-spectrum antibacterials such as the glycylcycline tigecycline have recently been approved as alternative treatments. While tigecycline has the disadvantage of requiring intravenous infusion every 12 hours, it has superior tissue penetration with high levels achievable in polymorphonuclear leukocytes, a significantly longer half-life and no requirement for dosage adjustment based on age or renal function.[40,63]

### 6.5 Fluoroquinolones

The fluoroquinolones levofloxacin, ciprofloxacin, gatifloxacin, moxifloxacin and gemifloxacin are among the first-line therapies for UTIs and respiratory infections in the elderly, regardless of aetiology.[14,25,64] Some clinical studies indicate that these drugs are tolerated by the elderly population at least as well as non-fluoroquinolone therapies, and with excellent therapeutic results compared with other drug regimens.[64]

Overall, fluoroquinolones are considered to be a concentration-dependent drug class and their $AUC_{0–24}$/MIC and $C_{max}$/MIC ratios are considered to be the major parameters predictive of bacteriological eradication and clinical efficacy. However, clinical trials appear to indicate that a high fluoroquinolone $C_{max}$/MIC helps prevent selection of resistant bacterial strains, and this may therefore be the more important parameter if there is a significant risk of emergence of resistant subpopulations.[15,65-67]

Evaluation of the optimal $AUC_{0–24}$/MIC for fluoroquinolones in a patient population with nosocomial lower respiratory tract infections demonstrated a breakpoint for bacterial killing of approximately 100, which was significantly higher than the breakpoint of 25–40 for typical Gram-positive infections suggested in *in vitro* studies.[39,65] While $AUC_{0–24}$/MIC ratios >175 are associated with more rapid bacterial killing, recent *in vitro* studies and a study conducted in the mouse thigh model showed that for Gram-negative bacteria, suppression of resistance and treatment success require drug $AUC_{0–24}$/MIC ratios of 157 and 190, respectively.[28,43,68-70]

These findings parallel the results of *in vitro* analyses indicating that $AUC_{0–24}$/MIC ratios for fluoroquinolones can be significantly lower for Gram-positive pathogens.[65] However, while previous breakpoints of 30–40 for fluoroquinolones versus *S. pneumoniae* were considered adequate, new evidence indicates that this may not be the case. An investigation into the activity of moxifloxacin against *S. aureus* and β-haemolytic streptococci reported optimal antibacterial effects with $AUC_{0–24}$/MIC ratios of 150–200.[28] With rising *S. pneumoniae* MIC values worldwide, several groups have concluded that $AUC_{0–24}$/MIC ratios for fluoroquinolones in the range of 100–400 maximise bacterial eradication. More importantly, the new targets may prevent second-step resistance development in populations already containing the *par*C first-step mutation.[28,43,47]

The clinician has two issues complicating the choice of optimal target $AUC_{0–24}$/MIC ratios for fluoroquinolones: (i) the longer-acting fluoroquinolones display comparable antimicrobial effects at much lower ratios because of their longer half-lives; and (ii) agents in this class exhibit variability in terms of penetrating tissues at the site of infection. The target ratio should thus be chosen based on MICs determined for several specific fluoroquinolones against the offending isolate(s) and consideration should be given to the potential for tissue penetration of that fluoroquinolone to the site of infection, as well as to the probability of achieving that target in an elderly patient without reaching toxic concentrations.[19,48,71,72]

The fluoroquinolone class provides a good example of the PAE, which is defined as the continued suppression of an organism's growth persisting after antimicrobial exposure. Most relevant to the elderly in long-term care situations is that fluoroquinolones

**Table II.** Antibacterial time- or concentration-dependence and adjustments for renal or hepatic clearance

| Drug class/drug | Dose | Time dependence | Concentration dependence | Adjust for severe liver dysfunction | Adjust for renal dysfunction | Notes |
|---|---|---|---|---|---|---|
| **Aminoglycosides** | | | | No[22] | Yes[22] | Nephro- and ototoxicity related to duration of treatment<br>Possible exacerbation by concomitant use of NSAIDs, allopurinol or vancomycin[51,52]<br>Slow tissue penetration: used commonly in combination with other antibacterials[76] |
| Gentamycin | 7 mg/kg,[64] 240mg IV od | | Yes | | | |
| Tobramycin | Adjusted per patient: peak 8 μg/mL; trough 2 μg/mL[76] | | Yes | | | |
| **Fluoroquinolones** | | | | | | Possible increased risk of tendinopathy with renal failure and corticosteroid use[77,78]<br>Minimally prolonged corrected QT interval in patients with predisposing factors[73,78]<br>High risk of selection for fluoroquinolone-resistant *Escherichia coli* (urinary tract infection) in long-term care facilities[79] |
| Moxifloxacin | 400mg od | | Yes | No[25] | No[25] | Does not appear to interact significantly with CYP system; reduced absorption if taken with antacids or iron[78,80] |
| Levofloxacin | 75mg od<br>500mg od | | Yes | | Yes[25] | |
| Gatifloxacin | 400mg od | | Yes | No[25] | Yes[25] | May cause hypo/hyperglycaemia in predisposed patients[2,5,35,36] |
| Ciprofloxacin | 1000mg XR od | | Yes | No[25] | Yes[25] | Inhibits CYP1A2 metabolism of theophylline, warfarin and digoxin[78,81] |
| **Macrolides** | | | | | | Inhibit CYP metabolism: erythromycin use leads to toxicity when combined with warfarin, calcium channel antagonists[22,81,82]<br>Dose adjustments based on renal clearance not age[83] |
| Azithromycin | 500mg × 1,<br>250mg × 4 | Yes | Yes | Yes[22] | Yes[22] | |
| Clarithromycin | 500mg od | Yes | | No[84] | Yes[83] | Use in elderly patients treated with colchicine can be fatal[85] |
| **Ketolides** | | | | | | |
| Telithromycin | 800mg od | | Yes | No[62] | No,[62] except if creatinine clearance <30 mL/min | Rare incidence of hepatotoxicity[86]<br>Interferes with CYP metabolism similar to macrolides<br>Adjustment for renal impairment only if creatinine clearance <30 mL/min[62,81] |

*Continued next page*

**Table II.** Contd

| Drug class/drug | Dose | Time dependence | Concentration dependence | Adjust for severe liver dysfunction | Adjust for renal dysfunction | Notes |
|---|---|---|---|---|---|---|
| **Glycylcyclines** | | | | | | |
| Tigecycline | 100mg IV, 50mg × 6 every 12h | | Yes | Yes[63] | No[63,87] | No adjustment required based on age or sex, no apparent interference with digoxin[87] |
| **β-Lactams** | | | | | | |
| Penicillin | 3MU load, continuous infusion 10–12MU every 12h | Yes | | | Yes[88] | Neurotoxic in patients with renal failure on standard or high dose. Dose adjustment in elderly based on renal clearance[88] |
| Piperacillin/ tazobactam | 4g/0.5g IV three to four times daily[89] | Yes | | | | |
| **Carbapenems** | | | | | Yes[24] | |
| Ertapenem | 1g IV for 7d[90] | Yes | | | | Elderly tend to have higher unbound fraction than younger patients. Dose adjustment based on individual renal function not age[89,90] |
| Meropenem | 0.5–1g IV three to four times daily[89] | Yes | | | | Does not appear to induce seizures as frequently as imipenem[91] |
| Imipenem | 0.5–1g IV three to four times daily[89] | Yes | | | | Risk of adverse effects in elderly related to estimation of renal function<br>Rare risk of seizures in predisposed patients[91] |
| **Glycopeptides** | | | | | | |
| Vancomycin | 80–120 mg/h IV | Yes | | | Yes[24] | Narrow dosing range: serum levels >40 mg/L are toxic; optimum 20–25 mg/L<br>Poor soft tissue penetration in diabetic patients[92] |
| **Oxazolidinones** | | | | | | |
| Linezolid | 600mg bid | Yes | | No[93] | No[94] | One report of neuropathy with long-term treatment >1mo[95]<br>Possible MAO inhibitor, caution for serotonin syndrome in some patients[96]<br>Dose- and time-dependent inhibition of mitochondrial protein synthesis, lactic acidosis, bone marrow suppression with long-term use[97,98] |

**bid** = twice daily; **CYP** = cytochrome P450 enzyme; **IV** = intravenous; **MAO** = monoamine oxidase inhibitor; **MU** = million units; **od** = once daily; **XR** = extended-release formulation.

display prolonged PAEs for Gram-negative bacilli. The PAEs for fluoroquinolones for both Gram-positive and -negative isolates are generally in the range of 1.5–2.5 hours.[28] Prolonged PAEs protect against bacterial regrowth during troughs when serum levels fall below the MIC value. Post-antibacterial leukocyte enhancement is also an important factor in the persistence of antimicrobial action and refers to the observed characteristic increase in the susceptibility of bacteria to leukocyte phagocytosis that occurs in the post-antibacterial phase. This added bacterial susceptibility to intracellular killing doubles the duration of the PAE of fluoroquinolones for Gram-negative bacilli. These prolonged effects allow administration of large, infrequent doses of fluoroquinolones. Thus, one high daily dose confers a rapid, high-level attack on the bacterial population. The resultant high AUC and $C_{max}$ levels provide optimal eradication times and, more importantly, decreased selection of resistant bacteria.[28]

In clinical practice for elderly patients, optimisation by achieving high concentrations of fluoroquinolones at the target site must be balanced against the risk of toxicity and potentially serious ADRs. ADRs of particular concern for this class of agents when used in the elderly include CNS effects, cardiotoxicity and tendon ruptures.

CNS ADRs in elderly patients taking fluoroquinolones may be as mild as confusion and may be incorrectly assumed to be due to age rather than to the effects of the drug. However, effects as severe as seizures and psychosis may also be seen.[72]

The fluoroquinolones sparfloxacin and grepafloxacin are associated with prolongation of the corrected QT (QTc) interval, which may lead to torsades de pointes.[73] While these two drugs are not in use, fluoroquinolones as a class nevertheless continue to be associated with prolongation of the QTc interval. However, two recent studies focusing on moxifloxacin have indicated that the minimal change in the QTc interval produced by moxifloxacin may not be significant. In one of these studies, Morganroth et al.[73] evaluated 400 elderly patients (mean age 77.8 years) in 47 US hospitals in a prospective, randomised, double-blind comparison of levofloxacin and moxifloxacin for community-acquired pneumonia. All patients were considered high-risk patients; more than 70% had a known history of cardiac disorders and 30% were diabetic. The study confirmed a previously reported 6ms prolongation of the QTc interval with moxifloxacin and no prolongation of the QTc interval with levofloxacin. There was no significant difference between groups in terms of cardiac events and no clear relationship between prolongation of the QTc interval and cardiac events.

Additionally, a small study by Tsikouris et al.[74] found no difference in QTc interval or QT dispersion when healthy subjects were treated with successive rounds of ciprofloxacin, levofloxacin or moxifloxacin, assigned in random order. The QTc interval in subjects receiving moxifloxacin was prolonged by 6–16ms but there was no prolongation of the QTc interval with levofloxacin or ciprofloxacin, and no cardiac events were reported in any subject. As such, the role of fluoroquinolones as a cause of torsades de pointes because of minimally prolonged QTc interval remains under investigation.

Tendon ruptures, particularly involving the Achilles tendon, in patients taking fluoroquinolones may have some relation to age, renal status and dosage.[64] However, exceptions occur and there are reports of ruptures occurring several months after drug withdrawal.[64]

The most commonly used fluoroquinolones (ciprofloxacin and levofloxacin) undergo renal clearance and, as such, the already long half-life of fluoroquinolones is considerably extended in elderly patients, who may have decreased renal function (particularly if aged >80 years) and decreased muscle mass. Although dosages can be adjusted downward for the elderly, creatinine clearance should be determined if possible so that dosages can be optimised based on patient creatinine clearance, rather than purely on age.[64]

## 7. Conclusion

The pharmacokinetic parameters of most antibacterial agents are altered when measured in the elderly. Consequently, treatment outcomes in elder-

**Table III.** Tissue penetration for selected antibacterial drugs into infected soft tissue, pneumonic lung tissue or epithelial lining fluid (ELF), alveolar macrophages (AM) and urine

| Drug class/drug | Dose | Compartment[a] |
|---|---|---|
| **Aminoglycosides** | | |
| Gentamicin | 7 mg/kg,[49] 240mg IV od[99] | ALF $C_{max}$/serum $C_{max}$ 0.32 (4.27 mg/L), which is sufficient for some organisms in VAP/ICU patients (MIC ≤4 mg/L)[99] |
| Tobramycin | Adjusted per patient: peak 8 μg/mL; trough 2 μg/mL[76] | ELF 1.53 (at peak 8h); ELF levels not always above MIC for organism. Slow tissue penetration; high serum peak required to achieve effective concentration in tissue[76] |
| **Fluoroquinolones** | | Associated with high risk for selection of fluoroquinolone-resistant *Escherichia coli* in urinary tract infections in long-term care facilities[79] |
| Moxifloxacin | 400mg od | ELF 5 (*Streptococcus pneumoniae*)/AM 32: adequate for intracellular organisms[48]<br>Soft tissue (inflamed) 0.5 in diabetic patients/1.2 in non-diabetic patients; sufficient for *Streptococcus* spp. and MRSA[100] |
| Levofloxacin | 750mg od | ELF 98.6%[19] |
| | 500mg od | ELF 2.1 (*S. pneumoniae*)/AM 5.8: adequate for intracellular pathogens[48] |
| | 500mg od | Soft tissue 1.2: generally sufficient; high individual variation[101] |
| | 500mg od | UE 80.4%[102] |
| Gatifloxacin | 200mg od | ELF 91.4%[20] |
| | 400mg od | ELF 97.9%[20] |
| Ciprofloxacin | 1000mg XR od | UE (XR) 40.5%[102] |
| **Macrolides** | | |
| Azithromycin | 500mg × 1, 250mg × 4 | ELF inadequate for *S. pneumoniae*/AM 2483:[48] both levels adequate for intracellular organisms[48,103] |
| Clarithromycin | 500mg bid | ELF 11–31/AM 543–1265 over 24h (healthy adults)[103] |
| **Ketolides** | | |
| Telithromycin | 800mg od | ELF AUC/plasma AUC 40/15; ELF AUC/$MIC_{90}$ intracellular pathogens >1000, extracellular pathogens 10–320; AM AUC/plasma AUC 1000/15[61]<br>Nasal mucosa 5.9; bone 1.6[104]<br>ELF T/MIC 100%, $C_{max}$/MIC and $AUC_{24h}$/MIC seven or more times that of serum for a panel of macrolide-resistant *S. pneumoniae* isolates: all isolates eradicated[105] |
| **Glycylcyclines** | | |
| Tigecycline | 100mg IV, 50mg every 12h × 6 | ELF AUC/$MIC_{90}$ exceeded $MIC_{90}$ for 100% of dosing interval for *S. pneumoniae* and 25% of dosing interval for *Chlamydia pneumoniae*, but did not exceed the $MIC_{90}$ at any time during the dosing interval for *Mycoplasma pneumoniae*, *Moraxella catarrhalis* and *Haemophilus influenzae*[106]<br>AC AUC/$MIC_{90}$ exceeded $MIC_{90}$ for all above organisms for 100% of dosing interval[106]<br>UE 32%[87] |
| **β-Lactams** | | |
| Penicillin | 3MU load, continuous infusion 10–12MU every 12h | ELF – poor penetration: 20–50% of serum levels<br>AM – generally poor accumulation[107] |

*Continued next page*

**Table III.** Contd

| Drug class/drug | Dose | Compartment[a] |
|---|---|---|
| Piperacillin/tazobactam | 4g/0.5g IV three to four times daily[89] | Pneumonic lung interstitium 0.63/1.93; muscle 0.4/0.7: useful for extracellular bacteria but not for *Pseudomonas* spp.[108]<br>Inflamed tissue (diabetic soft tissue infection) 0.45/1.36: T/MIC acceptable for organisms with MIC <16 mg/L but not appropriate for *Pseudomonas* spp.[109]<br>ELF 0.56/0.91 (nosocomial pneumonia): these values were insufficient based on the MICs of causative organisms[110]<br>UE 70%[89] |
| **Carbapenems** | | |
| Ertapenem | 1g IV od for 3 days[111] | Blister fluid 0.61, blister fluid MIC >4 mg/L, T/MIC 100%: sufficient for *Staphylococcus* spp., *Streptococcus* spp. and *Enterobacteriaceae* (healthy adults)[111] |
| | 1g IV od for 7 days[89] | Lung tissue 23.6, ELF 9.4: lung concentration >$MIC_{90}$ for most CAP organisms including penicillin-resistant *S. pneumoniae*[112]<br>UE 44%[89] |
| Meropenem | 0.5–1g IV three to four times daily[89] | Pneumonic lung tissue concentration >$MIC_{90}$ for most clinically relevant pathogens[113]<br>UE 70%[89] |
| Imipenem | 0.5g IV three to four times daily[114] | Healthy (plasma AUC/tissue AUC)/critical elderly (plasma AUC/tissue AUC): muscle 2/9, subcutaneous tissue 2.3/7.1[114]<br>Critically ill elderly had significantly lower and slower tissue penetration, concentrations were not sufficient using maximum dose for this population[114] |
| | 0.5–1g IV three to four times daily[89] | UE 60–70% with cilastatin[89] |
| **Glycopeptides** | | |
| Vancomycin | 80–120 mg/h IV[92] | Soft tissue infection: diabetic patients 0.1; non-inflamed tissue 0.3. Plasma levels were kept high at 36.5 mg/L but tissue levels were still insufficient compared with MIC. Serum concentration >40 mg/L is toxic; serum concentration <10 mg/L is ineffective[92] |
| **Oxazolidinones** | | |
| Linezolid | 600mg orally every 12h for 48h + 1h before surgery[115] | Synovial fluid 0.92, synovium 0.82, muscle 0.84, bone 0.4 (healthy elderly): all levels were >$MIC_{90}$ for susceptible Gram-positive organisms[115] |
| | 600mg bid for six doses[116] | ELF 8.35, AM 0.71, mucosal biopsy 0.79: all tissue concentrations exceeded $MIC_{90}$ for MRSA and *S. pneumoniae* (41- to 75-year-old ex-smokers, some with COPD, but without infection)[116]<br>UE 30%[93] |

a Reported numbers are the predicted percentage of elderly patients in whom target can be achieved (ELF%) or reported compartment/plasma concentration ratio or percentage UE (UE%).

**AC** = alveolar cells; **ALF** = alveolar lining fluid; **AUC** = area under the plasma concentration-time curve; **bid** = twice daily; **CAP** = community-acquired pneumonia; $\mathbf{C}_{max}$ = maximum plasma concentration; **COPD** = chronic obstructive pulmonary disease; **ICU** = intensive care unit; **IV** = intravenous; **MIC** = minimum inhibitory concentration; **MRSA** = meticillin-resistant *Staphylococcus aureus*; **MU** = million units; **od** = once daily; **T/MIC** = time at or over MIC; **UE** = urinary excretion of unchanged drug; **VAP** = ventilator-assisted pneumonia; **XR** = extended-release formulation.

ly patients can be influenced by decreased renal function and alteration in the volume of distribution, leading to treatment failure and/or increased risk of ADRs. Additional problems arise in the treatment of elderly patients who may have a history of previous antibacterial use. These patients may already harbour resistant bacterial strains selected by previous inadequate treatments, and long-term care facilities often harbour endogenous multi-drug-resistant bacteria that can spread rapidly from patient to patient. Furthermore, these patients often acquire infections in tandem with other common disease states such as heart disease and diabetes so that interference with multiple other treatments can cause changes in the

availability of active antibacterials. Another potential problem in elderly patients is that atypical presentations of infection, for example, pneumonia, are common in this patient group. Even individuals with community-acquired pneumonia can present with atypical symptoms that may lead to a delay in antibacterial treatment. Waterer et al.,[75] for example, recently reported that a delay of >4 hours in time to first antibacterial dose because of atypical presentation in the elderly significantly increased adverse outcomes. While the association between infection in the elderly and mortality most likely has more to do with co-morbidity than a 4-hour delay in treatment, this finding nevertheless emphasises the confounding situations that can arise in the elderly and the vigilance required when diagnosing infections and choosing antibacterials for patients in this group. For elderly patients, antibacterial agents with high tissue penetration, low potential for interaction with many drugs commonly prescribed to the elderly and a clearance not affected by a decline in kidney function may be a preferred choice (tables II and III).

Because of the fragility of elderly patients, the first drug prescribed must be effective for the best chance at an optimal outcome. Therefore, attention must be paid to the pharmacokinetics of the chosen drug in order to ensure the correct drug is prescribed in the first instance for maximum bacterial eradication and to prevent selection of resistant bacterial strains. Obtaining drug susceptibility profiles and taking into account the patient's pharmacokinetic information and any history of prior antibacterial treatment are imperative considerations in the rational design of individual, specific and effective treatments of infections in the elderly patient. Overall, more studies focusing exclusively on antibacterial dosage and the timing of administration of antibacterials in elderly patients are clearly needed to improve our ability to maintain and support these members of the population.

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