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Selecting Antibacterials for Outpatient Parenteral Antimicrobial Therapy

Pharmacokinetic-Pharmacodynamic Considerations

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Abstract

Some infectious diseases require management with parenteral therapy, although the patient may not need hospitalisation. Consequently, the administration of intravenous antimicrobials in a home or infusion clinic setting has now become commonplace. Outpatient parenteral antimicrobial therapy (OPAT) is

considered safe, therapeutically effective and economical. A broad range of infections can be successfully managed with OPAT, although this form of treatment is unnecessary when oral therapy can be used. Many antimicrobials can be employed for OPAT and the choice of agent(s) and regimen should be based upon sound clinical and microbiological evidence. Assessments of cost and convenience should be made subsequent to these primary treatment outcome determinants. When designing an OPAT treatment regimen, the pharmacokinetic and pharmacodynamic characteristics of the individual agents should also be considered.

Pharmacokinetics (PK) is the study of the time course of absorption, distribution, metabolism and elimination of drugs (what the body does to the drug). Clinical pharmacokinetic monitoring has been used to overcome the pharmacokinetic variability of antimicrobials and enable individualised dosing regimens that attain desirable antimicrobial serum concentrations. Pharmacodynamics (PD) is the study of the relationship between the serum concentration of a drug and the clinical response observed in a patient (what the drug does to the body). By combining pharmacokinetic properties (peak [C_{max}] or trough [C_{min}] serum concentrations, half-life, area under the curve) and pharmacodynamic properties (susceptibility results, minimum inhibitory concentrations [MIC] or minimum bactericidal concentrations [MBC], bactericidal or bacteriostatic killing, post-antibiotic effects), unique PK/PD parameters or indices ($t > MIC$, C_{max}/MIC, AUC_{24}/MIC) can be defined.

Depending on the killing characteristics of a given class of antimicrobials (concentration-dependent or time-dependent), specific PK/PD parameters may predict *in vitro* bacterial eradication rates and correlate with *in vivo* microbiologic and clinical cures. An understanding of these principles will enable the clinician to vary dosing schemes and design individualised dosing regimens to achieve optimal PK/PD parameters and potentially improve patient outcomes. This paper will review basic principles of useful PK/PD parameters for various classes of antimicrobials as they may relate to OPAT.

In summary, OPAT has become an important treatment option for the management of infectious diseases in the community setting. To optimise treatment course outcomes, pharmacokinetic and pharmacodynamic properties of the individual agents should be carefully considered when designing OPAT treatment regimens.

1. Definition and Current Role of Outpatient Parenteral Antimicrobial Therapy (OPAT)

The administration of intravenous antimicrobials in a home or infusion clinic setting has been popular since the mid-1970s.[1,2] Outpatient parenteral antimicrobial therapy (OPAT) arose from the recognition that some infectious diseases will require management with parenteral therapy, although the patient may not require hospitalisation. Twenty-five years of experience has demonstrated that this treatment modality can be undertaken in a safe and effective manner.[3-8] It is estimated that more than 250 000 patients in the US alone are treated with OPAT each year, and that this practice is growing at a rate of about 10% per annum.[9]

1.1 Benefits of OPAT

The benefits of OPAT are numerous. Most importantly, however, is the fact that treatment of patients in a home or clinic setting reduces or eliminates the need for a hospital bed and permits the patient to remain in their natural setting during therapy. This in turn translates into both economic and quality of life benefits.

We recently assessed the economic impact of our OPAT programme. Over a 3-year assessment period in a two-site hospital, we successfully completed 140 treatment courses and realised an overall cost avoidance of Canadian dollars ($Can) 1 730 520 (hospital perspective) and $Can 1 009 450 (Ministry of Health perspective).[10] Similar achievements have been described by others.[11-14] When extrapolated to all centres and programmes providing OPAT, the cost avoidance associated with this form of therapy is significant.

The benefits of OPAT should be measured not only in terms of clinical outcomes and costs, but also in terms of patient preferences and health-related quality of life (HRQOL). We recently conducted two multidisciplinary, single-centre, prospective investigations at a 1000-bed Canadian adult tertiary care teaching hospital to address these issues.[15] In a 9-month study designed to elicit treatment location preferences and willingness-to-pay (WTP) from patients referred to our OPAT programme, we determined that 89% of the patients preferred treatment at home, whereas the remaining 11% of patients preferred treatment in the hospital setting. In a parallel 15-month investigation of HRQOL for 134 patients who were actually enrolled in our OPAT programme, we were also able to demonstrate that patients experienced a significant improvement in three SF-36 domains (physical functioning, bodily pain and role emotional) and the mental component summary scale scores when they were transferred from the hospital to home setting. To our knowledge these are the first published preliminary reports of this type that involve an assessment of adult OPAT programme patients.

1.2 Infections Typically Managed with OPAT

A broad range of infections can be successfully managed with OPAT and these have been well described by Williams et al.[9] (table I) Although the quality of evidence to support the use of OPAT as an alternative to the traditional management of some infections in a hospital setting remains somewhat weak (no randomised clinical trials have been published), the volume of documented evidence in support of this practice is nevertheless considerable.

Infections that can be effectively managed with oral therapy should not involve the use of OPAT. Although intravenous-to-oral stepdown therapy has been traditionally described in the context of treatment in the hospital setting, this practice should also apply to OPAT.

Table I. Infections that have been managed by outpatient parenteral antimicrobial therapy (from Williams et al.,[9] with permission)[a]

System	Infection
Central nervous system	Meningitis, brain and epidural abscesses
Ear, nose, throat	Sinusitis (complicated), chronic otitis/mastoiditis
Cardiovascular	Endocarditis
Respiratory	Cystic fibrosis (infectious exacerbations), pneumonia/severe lower respiratory infections
Intra-abdominal and surrounding	Hepatic abscess, peritonitis, intra-abdominal abscess, tubo-ovarian abscess/pelvic inflammatory disease, splenic abscess
Urinary tract	Pyelonephritis, perinephric abscess and other, complicated urinary tract infections
Dermatological	Cellulitis, soft tissue, wound
Bone and joint	Osteomyelitis, septic arthritis/bursitis, prosthetic joint infections
Other	Intravenous access–associated, vascular graft infections, Lyme disease, neutropenic fever, bacteraemia, fungaemia/systemic mycoses, cytomegalovirus and other viral infections

a Management of an infection may warrant hospitalisation for the initial assessment, commencement of parenteral antimicrobial treatment and potential need for intensive medical intervention. This is particularly important for compromised patients and serious infections in which rapid decompensation may occur.

1.3 Antimicrobials Typically Used for OPAT

The type of antimicrobials employed for OPAT is almost as varied as the infections that have been managed. Antimicrobials used for OPAT typically include those agents that cannot be administered orally and for which there are no suitable oral alternative agents because of infection, microbial susceptibility and/or patient factors.

Although many previously published OPAT series have focused on the use of cephalosporins for outpatient intravenous therapy,[9] we have tended to utilise a broad group of agents in our practice (table II).[8] When multiple antimicrobials are being considered as alternatives for the management of a particular infection, the choice of drug(s) and regimen for OPAT therapy should be based upon sound clinical and microbiological evidence that these agents are safe and effective for the infection(s) involved. Cost and convenience of administration should only be considered after these primary determinants of treatment outcome have been assessed to establish the optimal treatment plan for a patient. When designing the treatment regimen for use in an OPAT setting, the pharmacokinetic and pharmacodynamic characteristics of the individual agents should be considered to maximise the likelihood that the desired outcome can be achieved.

Table II. Antimicrobial utilisation for outpatient parenteral antimicrobial therapy[a]

Agent	Patients (%)
Vancomycin ± other antimicrobials	30
Cloxacillin ± gentamicin	24
Penicillin ± other antimicrobials	10
Ceftriaxone ± gentamicin	8
Ganciclovir	8
Cefazolin	4
Ceftazidime + (tobramycin or gentamicin)	4
Ampicillin ± other antimicrobials	3
Gentamicin	2
Other[b]	7

a Series of 379 patients over 6 years, updated from Stiver et al.[8]

b Includes ceftizoxime, foscarnet, amphotericin B, piperacillin + tobramycin, clindamycin, acyclovir, amikacin, meropenem, aztreonam, imipenem, fluconazole, chloramphenicol, stibogluconate, tobramycin and piperacillin/tazobactam.

2. Pharmacokinetic Properties of Antimicrobials

The pharmacological characteristics of antimicrobials can be stratified into two distinct components, namely pharmacokinetics and pharmacodynamics (table III).[16-26] Pharmacokinetics is the study of the time course of the primary pharmacokinetic processes of absorption, distribution, metabolism, and elimination of antimicrobials, and the overall disposition of drug in the body. The rate and extent of each of these individual processes determines the serum concentration-time profile for the antimicrobial in a given patient. Thus pharmacokinetics reflects 'what the body does to the drug'. Pharmacodynamics is the study of the actions of drugs, and more specifically the relationship between the serum antimicrobial concentration and pharmacological effect. Accordingly, pharmacodynamics reflects 'what the drug does to the body'.

The concentration-response relationship of antimicrobial agents is very complex, and neither pharmacokinetic nor pharmacodynamic characteristics alone can adequately describe the unique interactions between the pathogen, host and antimicrobial agent during an infectious disease process. The antimicrobial activity time course is variable and a result of the complex interplay between these properties. Through the application of our current understanding of these properties, we should be able to optimise antimicrobial killing, improve microbiological eradication, increase clinical cure rates, improve patient outcomes and quality of life, prevent the development of microbial resistance, and reduce the costs and inconvenience of therapy.

The effectiveness of antimicrobial drugs is influenced by the kinetics of microbial growth and the drug concentration in the environment of these microbes. The concentration of an antimicrobial drug at the site of an infection typically changes with time, and rises and falls in a pattern that tends to parallel the changes in serum antimicrobial concentrations resulting from the intermittent administra-

tion of an antimicrobial.[31] Clinicians have used clinical pharmacokinetic monitoring of antimicrobials in an attempt to optimise antimicrobial therapy. An understanding of the pharmacokinetics of antimicrobials enables the clinician to predict and achieve serum antimicrobial concentrations that may be associated with a desired pharmacological effect, and avoid those that are associated with treatment failure or toxicity. Using population-based pharmacokinetic parameters, clinicians routinely initiate standard empirical regimens in an attempt to achieve target serum antimicrobial concentrations. Unfortunately, the administration of standard antimicrobial dosage regimens does not always result in the achievement of desired serum antimicrobial concentrations because of patient-specific variability in absorption, distribution, metabolism and elimination.[32] Thus, for selected antimicrobials (particularly those with narrow therapeutic indices), clinicians have used patient-specific clinical pharmacokinetic monitoring to determine pharmacokinetic parameters, individualise antimicrobial dosage regimens, and achieve predefined target serum antimicrobial concentrations. For those antimicrobials not amenable to patient-specific clinical pharmacokinetic monitoring (e.g. β-lactams), population-based pharmacokinetic parameter estimates must still be applied to design effective antimicrobial regimens.

2.1 Absorption

Drug absorption is affected by the physicochemical properties of the drug, the formulation, gastrointestinal tract motility, transit time, blood flow, gastrointestinal contents and pH, drug-drug or drug-food interactions, gut wall metabolism, hepatic first pass metabolism and other factors. Bioavailability is defined as the extent of drug transfer from the site of administration to the systemic circulation. Many of the newer antimicrobial agents (e.g. fluoroquinolones) can be administered orally, have an excellent bioavailability, and achieve serum antimicrobial concentrations that are almost equivalent to those obtained when the same drug is administered intravenously.[24,27,33] (table IV). Although this is an important consideration for patients who are candidates for oral therapy (e.g. patients with less serious infections, outpatients, and those who meet the criteria for intravenous-to-oral stepdown therapy), OPAT programmes inherently involve the administration of antimicrobials via the intravenous route with the assumption that oral therapy is not clinically feasible.[26,34-38]

2.2 Distribution

The apparent volume of distribution (Vd) is defined as the volume in which the total amount of the drug in the body (A) would have to be uniformly distributed in order to result in the observed serum drug concentration. Simply stated, it reflects the ratio of the amount of drug in the body to the serum drug concentration. The Vd of a drug indicates the tendency of the drug to stay or leave the bloodstream, which in turn is related to the inherent properties of the drug, including polarity, affinity for protein binding and molecular size. Although the Vd of a drug does not correspond to any particular anatomical space, it does provide information as to how widely the drug tends to distribute throughout the body. Most antimicrobials have a Vd of 0.15–0.40 L/kg total bodyweight, although there are a few notable exceptions. Vancomycin has a Vd of approximately 0.7 L/kg, and fluoroquinolones have a Vd of approximately 4 L/kg.[39] The clinical relevance of Vd is that this parameter can be used to estimate the dose of an antimicrobial required to achieve a particular serum concentration. This has clinical utility when determining an initial loading dose for an antimicrobial regimen. When used in combination with other pharmacokinetic parameters (i.e. serum elimination half-life), knowing the Vd of a drug also helps to estimate the maximum (C_{max}) and minimum (C_{min}) serum antimicrobial concentrations that can be achieved with a particular dosage regimen. The ability to estimate a Vd for a patient, along with the knowledge of other pharmacokinetic parameters (e.g. distribution characteristics into body compartments such as cerebrospinal fluid, prostatic fluid, joint fluid, respiratory tissues and other anatomical sites) can assist us in our

Table III. Some pharmacokinetic and pharmacodynamic characteristics of selected antimicrobials[16-25,27-30]

Representative agents	Candidate for OPAT[a]	Pharmacokinetic properties[b]				Pharmacodynamic properties			
		F (%)	Vd (L/kg)	$t_{1/2\beta}$ (h)	dosage interval (h)	activity[c]	killing	Gram-negative PAE	PK-PD parameter best correlating with clinical efficacy
β-Lactams									
Benzylpenicillin and phenoxymethylpenicillin (oral)	2	15 (60)	0.29	0.5	4–6	Bactericidal	T	N	t>MIC
Cloxacillin	2	50	0.08–0.11	0.5	4–6	Bactericidal	T	N	t>MIC
Ampicillin and amoxicillin[d]		40 (75)	0.18–0.35	1.0	4–6	Bactericidal	T	N	t>MIC
Piperacillin[d]	1		0.15–0.21	1.3	4–6	Bactericidal	T	N	t>MIC
Ticarcillin[d]	1		0.17–0.25	1.2	4–6	Bactericidal	T	N	t>MIC
Cefazolin	1		0.10–0.18	1.8	8	Bactericidal	T	N	t>MIC
Cefuroxime (axetil)	2	52	0.16–0.24	1.3	8	Bactericidal	T	N	t>MIC
Ceftriaxone	1		0.13–0.19	8.0	12–24	Bactericidal	T	N	t>MIC
Ceftazidime	1		0.21–0.25	1.8	8	Bactericidal	T	N	t>MIC
Imipenem	1		0.18–0.28	1.0	6	Bactericidal	T	Y	t>MIC
Meropenem	1		0.37–0.49	1.0	8	Bactericidal	T	Y	t>MIC
Aztreonam	1		0.14–0.18	2.0	8	Bactericidal	T	N	t>MIC
Glycopeptides									
Vancomycin	1		0.7–0.9	6–8	12	Bactericidal	T	N	t>MIC, AUC/MIC
Fluoroquinolones									
Ciprofloxacin	2	70–85	1.7–3.7	2.5–5.3	12	Bactericidal	C	Y	C_{max}/MIC, AUC/MIC
Levofloxacin	2	85–95	1.2–1.5	6.5–7.4	12–24	Bactericidal	C	Y	C_{max}/MIC, AUC/MIC
Gatifloxacin	2	95	1.5–2.2	6.5–8.4	24	Bactericidal	C	Y	C_{max}/MIC, AUC/MIC
Moxifloxacin	2	85	2.1–3.5	9.1–15.6	24	Bactericidal	C	Y	C_{max}/MIC, AUC/MIC
Aminoglycosides									
Gentamicin	1		0.21–0.41	2.5	8–24	Bactericidal	C	Y	C_{max}/MIC, AUC/MIC
Tobramycin	1		0.25–0.41	2.5	8–24	Bactericidal	C	Y	C_{max}/MIC, AUC/MIC
Amikacin	1		0.21–0.33	2.5	8–24	Bactericidal	C	Y	C_{max}/MIC, AUC/MIC
Macrolides									
Erythromycin	2	18–45	0.34–1.2	2–4	6	Bacteriostatic	T	N	t>MIC
Clarithromycin	4	50	2.1–3.1	5–7	12	Bacteriostatic	T	N	t>MIC
Azithromycin	2	37	31		24	Bacteriostatic	T	N	AUC/MIC
Lincosamides									
Clindamycin	3	90	0.8–1.4	2.4	8	Bacteriostatic	T	N	t>MIC

Continued next page

Table III. Contd

Representative agents	Candidate for OPAT[a]	Pharmacokinetic properties[b]				Pharmacodynamic properties			
		F (%)	Vd (L/kg)	$t_{1/2}\beta$ (h)	dosage interval (h)	activity[c]	killing	Gram-negative PAE	PK-PD parameter best correlating with clinical efficacy
Streptogramins									
Quinupristin/dalfopristin	1		0.45/0.24	1.5	8	Bactericidal	C	N	AUC/MIC, AUC/MBC
Oxazolidinones									
Linezolid	2	100	0.57–0.71	5	12	Bacteriostatic	T	N	t>MIC
Other									
Metronidazole	3	95	0.64–0.84	6–14	12	Bactericidal	C	N	C_{max}/MIC, AUC/MIC

a 1 = suitable agent for OPAT as no oral dosage form exists; 2 = potential agent for OPAT if bioavailability may be impaired due to drug interactions and/or access and/or gut problems; 3 = unsuitable agent for OPAT for most clinical situations; 4 = no intravenous preparation is available.

b In adults with normal renal and hepatic function.

c Against pathogens for which the agent it typically used; activity may be bacteriostatic only against some pathogens.

d Available in combination with a β-lactamase inhibitor.

AUC = area under the concentration-time curve; **C** = concentration-dependent killing; **C_{max}** = peak plasma concentration; **F** = oral bioavailability; **MBC** = minimum bactericidal concentration; **MIC** = minimum inhibitory concentration; **N** = no; **OPAT** = outpatient parenteral antimicrobial therapy; **PAE** = post-antibiotic effect; **PK-PD** = pharmacokinetic-pharmacodynamic; **T** = time-dependent killing; **$t_{1/2}\beta$** = elimination half-life; **t>MIC** = duration of time for which antimicrobial concentrations exceed the MIC; **Vd** = volume of distribution; **Y** = yes.

attempts to estimate the antimicrobial concentration at the site of an infection. Many antimicrobials do not distribute well into all body tissues and fluids, and this is an important consideration when choosing antimicrobial therapy for deep-seated infections such as endocarditis, osteomyelitis and meningitis.

2.3 Metabolism

Antimicrobials are typically metabolised hepatically or eliminated unchanged in the urine or faeces. Agents that undergo hepatic metabolism may be broken down in phase I reactions via the cytochrome P450 system, and then conjugated during phase II reactions. Liver blood flow, the fraction of unbound drug, the intrinsic hepatic metabolic activity, and liver disease such as alcoholic cirrhosis can alter the metabolism of drugs cleared by the liver. Dosage reductions are usually recommended for hepatically cleared antimicrobials (e.g. macrolides, cotrixomazole [trimethoprim-sulfamethoxazole]) in patients with serious liver dysfunction or disease.[31] A more common problem for these drugs, however, is the impact of drug-drug interactions involving antimicrobials and other drugs that act as cytochrome P450 system enzyme inhibitors or inducers.[40-44] When administered concurrently with antimicrobial agents, some cytochrome P450 system enzyme inhibitors (e.g. cimetidine) can cause clinically important increases in serum drug concentrations, resulting in concentration-related drug effects including gastrointestinal and CNS toxicities, QTc prolongation and other complications.[40-44] Conversely, some drug interactions may lead to subtherapeutic antimicrobial concentrations and clinical failures (e.g. itraconazole plus phenytoin).[45-47] Some antimicrobials themselves are potent enzyme inhibitors or inducers (e.g. erythromycin, ketoconazole, ciprofloxacin, rifampicin [rifampin]) and thus can affect the pharmacokinetic profiles of other medications, leading to adverse drug effects and/or clinical failures.[45-49]

2.4 Elimination

The serum elimination half-life ($t_{1/2}\beta$) of an antimicrobial drug is defined as the time required for the

Table IV. Oral bioavailability of antimicrobial agents

Average bioavailability (%)[a]	Agent	Variable bioavailability[b]
>80	Amoxicillin	Yes
	Cefaclor	No
	Cefadroxil	No
	Cefalexin	No
	Clindamycin[c]	No
	Cotrimoxazole (trimethoprim-sulfamethoxazole)[c]	No
	Doxycycline	Yes
	Fluconazole[c]	No
	Gatifloxacin[c]	Yes
	Levofloxacin[c]	Yes
	Metronidazole[c]	No
	Moxifloxacin[c]	Yes
	Ofloxacin	Yes
	Rifampicin	No
51–80	Ampicillin[c]	Yes
	Ciprofloxacin[c]	Yes
	Clarithromycin	No
	Cloxacillin[c]	Yes
	Phenoxymethylpenicillin	No
	Tetracycline[c]	Yes
	Valaciclovir	No
<50	Acyclovir[c]	No
	Azithromycin[c]	Yes
	Benzylpenicillin[c]	Yes
	Cefixime	Yes
	Cefuroxime axetil[c]	Yes
	Erythromycin[c]	Yes
	Norfloxacin	Yes

a Typical reported unimpeded bioavailability (oral AUC/intravenous AUC) in adult patients.[26]

b Bioavailability is highly variable (range varies by ≥20%) when the drug is administered under conditions in which the presence of food or other drug products (e.g. antacids) may interfere with absorption from the gastrointestinal tract.

c Available in a parenteral dosage form.

AUC = area under the concentration-time curve.

drug to fall to 50% of its former concentration in the serum as a result of elimination from the body. This reduction in concentration parallels the reduction of total drug in the body, and is usually calculated once drug absorption and distribution have been completed. The $t_{1/2}\beta$ helps to determine how long it will take to achieve steady-state serum antimicrobial concentrations, and may help to determine if an initial loading dose is required to rapidly achieve therapeutic serum concentrations. The $t_{1/2}\beta$ is determined by the volume of distribution and the sum of clearance by all organs independently contributing to overall drug clearance. Thus, the $t_{1/2}\beta$ of the antimicrobial is influenced by changes in clinical factors that affect the volume of distribution of the drug (e.g. albumin concentration, hydration status or concomitant medical conditions such as malnutrition, pregnancy, heart failure, thermal injury, critical illness or organ failure) and/or the organ systems responsible for elimination (e.g. drug or disease-altered renal or hepatic function). All of these factors must be considered when choosing an antimicrobial agent and determining an appropriate dosage regimen.

The reported serum $t_{1/2}\beta$ range of commonly employed antimicrobial drugs in the average adult patient is quite wide (figure 1, table III).[26] Inter- and intrapatient variability can also be significant. Most β-lactam drugs have a serum $t_{1/2}\beta$ of less than 2 hours (with a few notable exceptions that will be discussed later), aminoglycosides tend to exhibit serum $t_{1/2}\beta$ in the range of 2–4 hours, and vancomycin usually has a serum $t_{1/2}\beta$ of 6–8 hours. In the face of renal impairment, some antimicrobial agents may further aggravate organ dysfunction (e.g. aminoglycosides), and safer alternatives may have to be used. Moreover, the serum $t_{1/2}\beta$ of agents such as aminoglycosides may vary unpredictably in the presence of fluctuating organ function, which may also make an agent with a broader therapeutic index or an alternative route of elimination more attractive. Conversely, if the use of an antimicrobial in the presence of organ dysfunction is considered safe, a dosage modification enabling the use of lower doses (e.g. vancomycin every 24–36 hours) may be an advantage for convenience of administration and may be less costly.

2.5 Area Under the Concentration-Time Curve

Area under the concentration-time curve (AUC) is a pharmacokinetic parameter that can be calculated as bioavailability (F) times dose (D) divided by total body clearance (CL). The AUC can be thought

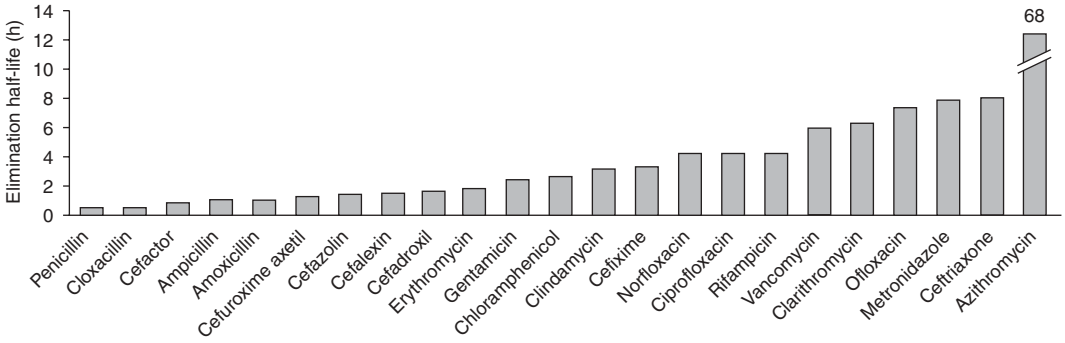

Fig. 1. Serum elimination half-lives of various antimicrobials (modified from Jewesson,[26] with permission).

of as the overall exposure over time of the host (and infecting microorganism) to the antimicrobial agent, as it takes into account both the magnitude and duration of drug exposure. Accordingly, for antimicrobial agents administered via the oral route, bioavailability is an important determinant of the exposure of the host and microorganism to the antimicrobial agent. Since some antimicrobial agents can demonstrate significant interpatient (and intrapatient) bioavailability (table IV), this route of administration may not be clinically feasible when designing a treatment course for some infections. For intravenous antimicrobials, this concern is minimised as only changes in dose or clearance will affect the AUC, and the overall exposure over time of the host and microorganism to the antimicrobial agent.

3. Pharmacodynamic Properties of Antimicrobials

The time course of antimicrobial activity is variable, and is the result of the complex interplay between antimicrobial pharmacokinetics and pharmacodynamics. From a clinical perspective, pharmacodynamics can be described as the relationship between drug concentration and patient response. Drugs generally demonstrate a predictable *in vitro* dose-response relationship that can be explained by the interactions between the drug and receptor sites. In the case of antimicrobials however, the receptor sites of interest are not situated in the patient receiving the drug, but are located in the pathogens that have assaulted the host tissues (figure 2).[50] This adds a third dimension to an existing complex set of interactions between the drug and the patient. The interplay between these three components of antimicrobial pharmacology is very important, because dose-concentration relationships are only useful if a certain concentration produces the desired pharmacological response.

Our knowledge of the clinical pharmacodynamics of anti-infective agents has increased substantially over the past decade. Traditionally, *in vitro* susceptibility testing using Kirbey Bauer or microtitre techniques have been used to quantify the intrinsic activity of antimicrobial agents by determining the minimum inhibitory concentration (MIC) or minimum bactericidal concentration (MBC) for the antimicrobial against a given inoculum of a bacterium.[32] These methods have been used to characterise the lethality of antimicrobials as bacteriostatic or bactericidal agents. Unfortunately,

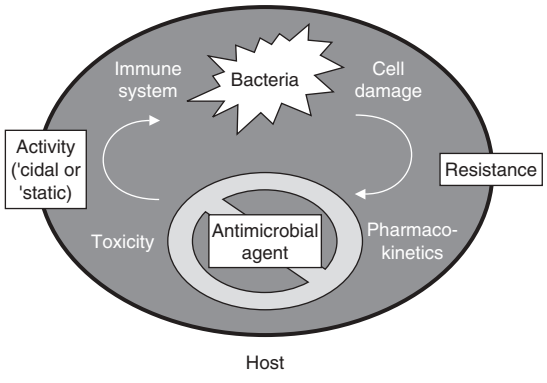

Fig. 2. Drug-pathogen-host relationship (from Jewesson,[50] with permission).

there are limitations to this procedure, and researchers have adopted time-kill curves to better delineate the time course of antimicrobial activity. Time-kill curves are employed to determine whether antimicrobials possess concentration-dependent or time-dependent killing profiles, and also to enable the identification of antimicrobial effects that may persist once antimicrobial concentrations have fallen to negligible levels.[51,52] Moreover, time-kill curves enable us to examine the pharmacodynamics of antimicrobials both alone and in combination.[53] *In vitro* models have been developed that attempt to more closely simulate the fluctuations in antimicrobial concentrations in the human host at the site of infection.[54] *In vitro* models appear to be able to predict the pharmacokinetic/pharmacodynamic parameters associated with efficacy in *in vivo* studies.[54,55] *In vivo* animal models are used to characterise the activity of antimicrobials in the setting of a host immune system, and have highlighted how the presence of a host immune system is an important contributor to the interaction between the antimicrobial and microorganism.[52] Data from *in vitro* and animal models have enabled us to identify integrated pharmacokinetic-pharmacodynamic parameters that predict *in vitro* antimicrobial activity as well as *in vivo* microbiological eradication and clinical cures.[32,52,55-62] Although our understanding is far from complete, some human studies have already shown that achieving certain magnitudes of these integrated pharmacokinetic-pharmacodynamic parameters may lead to faster bacterial eradication, higher clinical cure rates and a reduction in the development of resistance.[61,63]

3.1 Susceptibility Testing

Although MIC susceptibility testing is an accepted standard for quantifying antimicrobial activity, it does not always predict clinical success, and has some inherent limitations. Artificial growth conditions are employed with organisms usually in the growth phase and in the setting of an ideal temperature and pH, abundant nutrient and oxygen supply, and unique cation content.[51,52] The inoculum size may be much lower than that present for many infections, and the ability of antimicrobials may be overestimated (inoculum effect) because of the presence of a large number of high-MIC organisms in the *in vivo* setting. This *in vitro* testing procedure is devoid of immune cells and complement that contribute to antimicrobial activity, and of plasma proteins, which may decrease antimicrobial activity in the host by reducing the concentration of free, active drug. Moreover, as this method tests static concentrations of antimicrobial agents, it cannot delineate the time-course of antimicrobial activity and it cannot provide any information on the effect of antimicrobial concentrations above or below the MIC. Finally, reporting susceptibility results nominally as sensitive or resistant implies an all-or-none response, which is not the case because *in vitro* susceptibility is only one factor contributing to the success of an antimicrobial regimen.

3.2 Bacteriostatic Versus Bactericidal Activity

In vitro susceptibility testing has enabled the clinician to categorise antimicrobial agents based on the lethality of their killing. Bacteriostatic agents are those that inhibit growth of microorganisms, but require a much higher concentration to kill the organisms. That is, they have MBC values much higher than their MIC for a given organism. Most bacteriostatic agents are inhibitors of protein synthesis (table III). Bactericidal agents are able to kill microorganisms at similar concentrations to those that inhibit them. That is, their *in vitro* MBC values are similar to their MIC values. Most bactericidal agents inhibit cell wall or DNA synthesis. Bactericidal agents should be used wherever possible for serious infections, particularly in immunocompromised patients. Although classification of antimicrobials as bacteriostatic or bactericidal does describe their lethality, it does not describe the relationship between antimicrobial concentration and the time course of killing.

3.3 Antimicrobial Killing Characteristics

Time-kill studies are conducted to examine the interaction between an antimicrobial with a standard

inoculum of bacteria over time. These studies involve the assessment of the relationship of time versus the log CFU/mL of the bacterial inoculum, and can be used to determine the rate and extent of bactericidal killing, and characterise the antimicrobial as a concentration-dependent or time-dependent kill agent (figure 3).[64,65]

For antimicrobials with concentration-dependent killing characteristics, increasing concentrations of the antimicrobial leads to a greater rate and extent of bactericidal activity across a wide range of antimicrobial concentrations. Agents exhibiting concentration-dependent killing classically include the fluoroquinolones, aminoglycosides, metronidazole and rifampicin (table III). Antimicrobial regimens for concentration-dependent kill agents are typically designed to take advantage of this property and involve the administration of larger doses less frequently. This has been the pharmacodynamic impetus behind the administration of high-dose extended-interval aminoglycoside therapy.

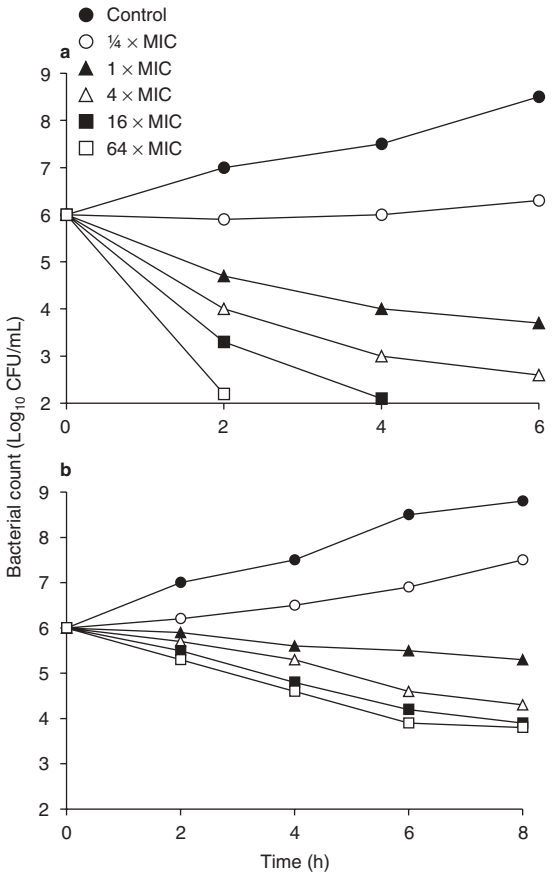

Fig. 3. Time-kill curve (time versus bacterial colony count) showing (**a**) concentration-dependent killing and (**b**) time-dependent killing (reproduced from Craig & Ebert,[64,65] with permission). **CFU** = colony-forming units; **MIC** = minimum inhibitory concentration.

Antimicrobials with time-dependent killing also exhibit a greater rate and extent of bactericidal activity with increasing antimicrobial concentrations, however only up to a certain multiple of the MIC. That is, they have saturable killing characteristics that tend to plateau at about 4–5 times the MIC.[32] Thus, the extent of killing is largely dependent on the duration of antimicrobial-pathogen exposure. Serum concentrations (as a reflection of drug concentration at the site of infection) should ideally be maintained above some multiple of the MIC. Agents exhibiting time-dependent killing classically include β-lactams (penicillins, cephalosporins, monobactams, carbapenems), macrolides and clindamycin (table III). Antimicrobial regimens designed to administer smaller doses more frequently exploit the killing characteristics of time-dependent antimicrobials, and this has been the pharmacodynamic impetus driving the investigation of continuous infusion β-lactam and vancomycin therapy.

3.4 Post-Antibiotic Effect

Time-kill studies have also enabled us to characterise the persistence effect, or post-antibiotic effect (PAE), of antimicrobial agents.[32] The PAE can be described as the period during which bacterial growth continues to be suppressed subsequent to discontinuing the exposure of that pathogen to an antimicrobial drug. The PAE reflects bacterial recovery time and is probably the result of several mechanisms, including non-lethal damage (i.e. morphological changes) caused by the antimicrobial, continued persistence of the drug at the bacterial drug-receptor binding sites after concentrations of the drug are no longer detectable, and an increased susceptibility of bacteria to intracellular killing or phagocytosis by leucocytes.[32,52,66] The PAE is in-

fluenced by several factors, including the type of microorganism, inoculum, the concentration, duration and type of antimicrobial agent, and the presence of immune cells. Almost all antimicrobials exhibit *in vitro* PAE of about 1–2 hours duration against susceptible Gram-positive organisms, such as staphylococci and streptococci.[63] Inhibitors of protein and nucleic acid synthesis (e.g. aminoglycosides, fluoroquinolones, tetracyclines, macrolides, chloramphenicol, rifampicin) have a prolonged *in vitro* PAE against Gram-negative bacteria for up to 4 hours. In contrast, most β-lactams tend to exhibit no significant PAE against Gram-negative organisms.[65] Carbapenems (e.g. imipenem, meropenem), are an exception and tend to exhibit a prolonged PAE against Gram-negative bacteria.[32] The duration of the *in vitro* PAE can be concentration-dependent, and synergistic with certain antimicrobial combinations. The duration of the *in vitro* PAE, however, is not always predictive of the *in vivo* PAE. For example, penicillins exhibit a significant *in vitro* PAE against streptococci, but no *in vivo* PAE can be demonstrated.[63] In most cases, the *in vitro* PAE underestimates the *in vivo* PAE, and this may be explained, in part, by a post-antimicrobial leucocyte-enhancing effect. Studies have shown that the presence of neutrophils may actually double the duration of PAE against Gram-negative organisms for aminoglycosides and fluoroquinolones, but may have no major effect for β-lactams.[32] This enhanced *in vivo* effect partially explains why we can effectively administer antimicrobials with short serum elimination half-lives at reasonable dosage intervals (e.g. benzylpenicillin every 6 hours). Finally, we must remember that for most patients, the antimicrobial rarely cures the infection outright. Rather, the antimicrobial usually buys us precious time to permit the patient's own host defences to recover.[50,67]

4. Integrated Pharmacokinetic-Pharmacodynamic Parameters

The complex inter-relationship of pharmacokinetics and pharmacodynamics between the host, antimicrobial agent, and organism is what determines the ultimate effect from antimicrobial therapy. The pharmacokinetic characteristics of an antimicrobial (e.g. C_{max}, AUC, C_{min}) determine the dosage requirements necessary to achieve target drug concentrations, whereas its pharmacodynamic and susceptibility characteristics (e.g. MIC) determine the ultimate clinical effect. When considered independently, neither the pharmacokinetic nor pharmacodynamic parameters of a drug can adequately predict antimicrobial clinical efficacy.

Determining patient-specific pharmacokinetic and pharmacodynamic data has been proposed to achieve 'dual individualisation' of a drug regimen.[35,68-70] Proponents of this approach argue that population estimates of pharmacokinetic parameters do not accurately predict actual drug disposition for an individual patient due to significant inter- and intra-patient variability. Similarly, literature-derived MIC data for a particular pathogen may not accurately reflect the actual susceptibility patterns of the pathogen(s) responsible for a specific infection. It stands to reason, therefore, that if we were able to determine patient-specific pharmacokinetic and pharmacodynamic parameters, we would be able to apply known pharmacokinetic-pharmacodynamic characteristics for a drug and individualise (and optimise) the dosage regimen employed. Although this method appears attractive, there are some practical drawbacks that currently impede routine clinical application.

Currently, only three quantifiable pharmacokinetic-pharmacodynamic parameters have been thoroughly investigated as surrogate predictors of antimicrobial efficacy. The first is the ratio of the maximum serum antimicrobial concentration under steady-state conditions (C_{max}) to the minimum inhibitory concentration (C_{max}/MIC). The second predictor of efficacy is the duration of time for which antimicrobial concentrations exceed the minimum inhibitory concentration (t>MIC) The third predictor is the ratio of the area under the concentration-time curve during a 24-hour administration interval to the minimum inhibitory concentration (AUC_{24}/MIC). This last measure is sometimes called area under the inhibitory curve (AUIC), although techni-

cally AUIC is the area under the curve of the inverse serum inhibitory titre versus time ($SIT^{-1} \bullet h$) over a 24-hour period.[70] In general, C_{max}/MIC or AUC_{24}/MIC appear to correlate best with clinical efficacy for antimicrobials that exhibit concentration-dependent killing, whereas t>MIC correlates best for drugs with time-dependent kill characteristics.[32,52,55-63] Unfortunately, since there is a direct relationship between all three of these pharmacokinetic-pharmacodynamic parameters, there is considerable covariance when dosage regimens are adjusted solely by dose or interval in pharmacodynamic studies. This has led to conflicting data in the literature as to which parameters most accurately predict efficacy and the development of resistance. Schentag et al. have proposed AUIC as a universal surrogate end-point for different classes of antimicrobials,[53,70,71] with a critical threshold of 125. This parameter takes into account the degree and extent of antimicrobial exposure over time. Although a universal surrogate threshold would be desirable, there is some controversy regarding its universality and the applicability of this parameter threshold to clinical situations such as the outpatient management of Gram-positive infections.[60,62]

5. Pharmacodynamic Properties of Select Antimicrobials

5.1 β-Lactams

β-Lactams exhibit time-dependent killing, and data from *in vitro* and animal models suggest that t>MIC is the pharmacokinetic-pharmacodynamic parameter that best correlates with bactericidal activity and clinical efficacy.[32,52,55,63,72] Although clinical response to β-lactams has also been shown to correlate with AUC_{24}/MIC, t>MIC appears to be a better predictor.[63,73] Data from *in vitro* and animal models also suggest that t>MIC of ≥40–50% of the administration interval is required to achieve survival rates of 90–100% for infections involving Gram-positive organisms.[32] For infections caused by Gram-negative organisms, animal studies suggest that a t>MIC of ≥60–70% may be required.[63,73,74] Extrapolation of animal data suggests that, for neutropenic hosts, t>MIC should be ≥50–60% and ≥90–100% for β-lactam agents with and without a PAE for the designated pathogen, respectively.[61] In a retrospective study involving paediatric patients with *Streptococcus pneumoniae*- or *Haemophilus influenzae*-associated otitis media, Craig & Andes found a significant correlation between t>MIC of >40% and bacteriological cure rates.[75] Schentag et al. examined prospective, dual-individualised, dosage adjustments to standard therapy and found a significant correlation between t>MIC and AUC_{24}/MIC in patients with Gram-negative nosocomial pneumonia. Patients who achieved an AUC_{24}/MIC ratio of >140 had more rapid microbiological eradication of the pathogen, and a shorter duration of antimicrobial treatment.[68]

A logical extension of the pharmacodynamic principles of β-lactam agents would be to administer short elimination half-life agents via a continuous infusion to exploit their time-dependent pharmacodynamic properties and maximise t>MIC. In addition to being able to achieve a greater t>MIC at the site of infection and thus theoretically an improved clinical response rates, other potential benefits of continuous infusion β-lactam regimens could include fewer concentration-dependent adverse drug effects and the convenience associated with the once-daily set up and delivery of the drug. If lower daily doses could be employed to achieve the same clinical response, drug acquisition cost savings would also be possible.

Unfortunately, there are some realised limitations of continuous infusion β-lactams, including drug stability and compatibility problems, the risk of delayed tissue equilibration at the site of infection (which can be avoided with the use of an initial loading dose), susceptibility to an inoculum effect, the lack of a well-defined goal steady-state concentration/MIC ratio, and the potential need to monitor serum concentrations (if lower total daily doses are used) to ensure adequate concentrations are maintained in the presence of pharmacokinetic variability.[76,77]

There is a relatively large body of evidence examining the use of continuous infusion β-lactams in

unique clinical situations and patient populations. Data from neutropenic cancer patients has suggested a benefit in some studies, but the results are inconsistent.[78,79] Data from healthy volunteers suggest that equivalent total daily doses of cefepime or ceftazidime in healthy volunteers does result in a longer t>MIC.[80,81] Data from several small open-label trials in critically ill patients suggest that in the presence of a concomitant aminoglycoside, continuous infusion ceftazidime 3–4g/day results in a greater t>MIC, similar microbiological eradication rates, clinical cure rates and adverse drug effects, and lower treatment costs, than intermittent ceftazidime 2g intravenously every 8 hours.[82-85] Two studies involving the use of cefuroxime or piperacillin-tazobactam in immunocompetent patients with selected infections suggest that continuous infusion regimens can be used with similar clinical outcomes, lower total daily antimicrobial doses and lower costs as compared with intermittent administration.[86,87]

Despite the promising results of these preliminary studies, there are no adequately powered, properly controlled randomised double-blind clinical trials to support the use of continuous infusion β-lactam treatment regimens for most infections. Accordingly, this method of administration should probably be reserved as second-line therapy for use in patients failing to respond to treatment with conventional intermittent regimens involving short elimination half-life antimicrobials. Comparative studies in the OPAT setting have also yet to be undertaken, although these investigations would certainly be justified for some drug and infection scenarios.

5.2 Glycopeptides

Similar to β-lactams, vancomycin also exhibits time-dependent killing, with a PAE of about 2–3 hours against many Gram-positive bacteria.[32,52,88] Data from *in vitro* studies and animal models, and limited human data, suggest that t>MIC, and possibly AUC_{24}/MIC, are the pharmacokinetic-pharmacodynamic parameters that correlate best with the bactericidal activity of glycopeptides. As with β-lactams, the pharmacodynamic properties of vancomycin have led to the investigation of continuous infusion administration in an attempt to improve efficacy, reduce toxicity or reduce the costs associated with vancomycin therapy.

Using an *in vitro* pharmacodynamic model, Larsson et al. showed that despite increasing vancomycin concentrations of vancomycin of 5, 10, 20, and 40 mg/L, time-kill curves were not significantly different from one another ($p = 0.20$), and increasing vancomycin concentrations did not increase the time to kill 99.9% of the population of *Staphylococcus aureus* or the rate of kill.[89] Duffull et al. used an *in vitro* continuous bacterial culture model to assess four different vancomycin regimens against *S. aureus*.[90] Despite regimens that achieved concentrations of 8–48 mg/L and various C_{max}, C_{min} and AUC values, there was no difference in the degree or rate of *S. aureus* killing. Interestingly, all of the regimens achieved t>MIC values of 100%. Cantoni et al. used a rat endocarditis model infected with *S. aureus* to evaluate the difference in efficacy between vancomycin regimens of 30 mg/kg every 12 hours and 30 mg/kg every 6 hours.[91] Vancomycin serum concentrations were undetectable 6 hours after vancomycin administration. Reducing the administration interval to 6 hours resulted in a decreased number of bacteria recovered from aortic valve vegetations. Taken together, the data from *in vitro* and animal studies suggest that t>MIC may be the pharmacokinetic-pharmacodynamic parameter correlating best with activity.

There are limited data suggesting a relationship between vancomycin serum concentrations and clinical outcomes. Schadd et al. performed a cohort study of 20 paediatric patients with heterogeneous staphylococcal infections treated with vancomycin.[92] Sixteen patients (80%) who were successfully treated with vancomycin all achieved peak serum bactericidal titres of > 1 : 8, which corresponded to a serum vancomycin concentration >12 mg/L. In a retrospective review of 273 consecutive patients with Gram-positive infections, Zimmerman et al. studied the relationship between serum vancomycin concentrations and the duration of fever and abnormal white cell count, serum creatinine, length of

hospital stay and overall mortality.[93] In an evaluable subgroup of 31 patients, significantly more patients had resolution of fever and elevated white cell count within 72 hours if trough serum vancomycin concentrations remained above 10 mg/L ($p < 0.01$). An unpublished preliminary report of a multicentre study in patients with Gram-positive infections suggested that serum vancomycin C_{min} >10 mg/L was associated with an increased rate of bacterial eradication.[94] Finally, in another study published in abstract form only, Rybak et al. prospectively randomised 104 patients with heterogeneous Gram-positive infections to target vancomycin serum C_{min} of 5–10, 10–15 or 15–25 mg/L.[95] There was no difference between any of the groups in number of febrile days or clinical outcome. Due to the limited and conflicting data correlating vancomycin serum concentrations to clinical effect, the utility of obtaining routine serum vancomycin concentrations has been debated in the literature.[23,96-105]

There are also no published human studies to identify which pharmacokinetic-pharmacodynamic parameter may be the most predictive of vancomycin activity, or what magnitude of that parameter must be achieved to improve clinical outcomes. Schentag et al. performed a retrospective analysis on 84 patients with microbiologically confirmed Gram-positive infections in patients receiving vancomycin, and found that patients infected with organisms with an MIC of > 1 mg/L or those with an AUC_{24}/MIC ratio of <125 had a higher probability of clinical failure.[52] The correlation between t>MIC and clinical outcomes was not reported. More data correlating pharmacokinetic-pharmacodynamic parameters with clinical efficacy is required.

Due to their pharmacodynamic similarity to β-lactams, continuous infusions of vancomycin have been investigated in both healthy volunteers and in patients with Gram-positive infections[106-111] The influence of a continuous infusion vancomycin regimen on serum bactericidal activity against isolates of methicillin-sensitive *S. aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA), methicillin-resistant *S. epidermidis* (MSSE) and *Enterococcus faecalis* has been assessed in two studies involving healthy volunteers. James et al. demonstrated that continuous infusion administration of vancomycin resulted in serum bactericidal titres >1 : 8 for 100% of the administration interval, compared with 60% of the administration interval for intermittent administration (statistical significance not reported).[106] In a study involving one isolate of *E. faecalis*, Klepser et al. found that continuous infusion of vancomycin 2000 mg/day provided bactericidal activity for a greater portion of the administration interval than that achieved with 1000mg every 12 hours when either were combined with gentamicin (97% vs 75%, $p < 0.001$).[107] Unfortunately, all patients receiving continuous infusion vancomycin in this study suffered thrombophlebitis, ranging from injection site pain to redness along the length of the vein. None of the patients in the intermittent group reported this adverse effect. The clinical impact of a slightly longer bactericidal activity with continuous infusion vancomycin is debatable, and studies examining the continuous infusion of vancomycin in patients infected with Gram-positive bacteria have failed to show a clinically important difference to intermittent administration regimens on microbiological eradication and clinical cures. Although more data are required on continuous infusion administration of vancomycin, its long $t_{½}β$ (compared with β-lactam agents) and Gram-positive PAE appear to make continuous infusion unnecessary for most patients.

5.3 Fluoroquinolones

Fluoroquinolones classically exhibit concentration-dependent killing, and data from *in vitro* and animal models suggest that C_{max}/MIC or AUC_{24}/MIC correlates best with their bactericidal activity, clinical efficacy and the development of resistance. *In vitro* data suggest that C_{max}/MIC ratios of ≥3 are bactericidal,[112] although ratios of 8 appear to be required to prevent regrowth and the emergence of resistant isolates.[112,113] Animal data have suggested that despite similar AUC_{24}/MIC values, survival is increased with increased C_{max}/MIC ratios of 20.[112,114] Although this suggested that C_{max}/MIC is

more closely correlated with fluoroquinolone activity, if C_{max}/MIC was <10, AUC_{24}/MIC was just as good a predictor of outcome.[32,115] Because of covariance with fixed administration intervals or doses, different views exist as to which pharmacokinetic-pharmacodynamic parameter best correlates with fluoroquinolone activity. It may be that if C_{max}/MIC is >10, then it is the most predictive parameter, whereas if C_{max}/MIC is <10, AUC_{24}/MIC may correlate better with outcome.[61,63] In general, animal data suggest that AUC_{24}/MIC ratios <30 are associated with >50% mortality, whereas AUC_{24}/MIC ratios ≥100 confer almost 100% survival.[32,116] Interestingly, fluoroquinolones may be active against Gram-positive organisms at lower AUC_{24}/MIC ratios than are required for Gram-negative organisms.[60] Thus, the activity of fluoroquinolones may be pathogen-dependent, and AUC_{24}/MIC ratios as low as 30–50 may have at least bacteriostatic activity against *S. pneumoniae* and *Bacteroides* sp.[60] This has led some to suggest that AUC_{24}/MIC ratios should be ≥25 for less severe infections or in immunocompetent hosts, whereas AUC_{24}/MIC ratios of ≥100 should be achieved in more severe infections or in immunocompromised hosts.[55] Others have suggested that acceptance of lower AUC_{24}/MIC ratios of 30–50 may lead to incomplete bacterial eradication, selection of isolates with higher MICs, and potentially promote antimicrobial resistance that could lead to clinical failures and cross-resistance with other fluoroquinolones.[62]

The majority of studies evaluating the pharmacodynamics of fluoroquinolones in humans have been in patients with nosocomial Gram-negative infections. In a prospective, observational study, Peloquin et al. evaluated 50 patients receiving ciprofloxacin for ventilator-associated pneumonia at a fixed interval, and found that bacterial eradication was correlated with C_{max}/MIC and t>MIC, but not AUC>MIC. A post-hoc analysis suggested that a C_{max}/MIC ratio of ≥8 was needed to achieve cure rates of ≥80%.[117] Forrest et al. performed a retrospective study in 74 patients receiving ciprofloxacin for moderate to severe respiratory tract infections, and found AUC_{24}/MIC to be the most important predictor of activity. An AUC_{24}/MIC ratio of ≥125 was required to achieve microbiological eradication and clinical cure rates of >80%.[118] Interestingly, only about 50% of patients in this study achieved C_{max}/MIC ratios of ≥10, which may explain why AUC_{24}/MIC was a better predictor of activity. Forrest et al. also studied 76 patients receiving grepafloxacin for acute exacerbations of chronic bronchitis infected with mostly Gram-negative organisms, and some *S. pneumoniae*.[119] Patients achieving higher AUC_{24}/MIC ratios had faster bacterial eradication (2.5 days with <75 vs 0.5 days with 75–190), higher microbiological cures (57% with <70 vs 90% with ≥70) and higher clinical cures (71% with <75, 80% with 75–175 and 90% with >175). The relationship between C_{max}/MIC and outcome was not studied in this trial. Preston et al. studied 116 patients receiving levofloxacin for respiratory tract, skin or urinary tract infections, and found that C_{max}/MIC was the best predictor of outcome.[120] Patients who achieved C_{max}/MIC ratios of ≥12.2 had higher microbiological (100% vs 80.8%) and clinical (99.0% vs 83.3%) cures than those with ratios <12.2. The AUC_{24}/MIC ratio was also predictive of activity, and patients with AUC_{24}/MIC ratios of >100, 25–100 and <25 had clinical failure rates of 1%, 12% and 43%, respectively.[55] Interestingly, a small subgroup of patients with *S. pneumoniae* had microbiological cure rates of 87.5% with an AUC_{24}/MIC of 0–92.[60] Other recent work has evaluated the optimal AUC_{24}/MIC ratio for fluoroquinolones against *S. pneumoniae*. Zhanel et al. used an *in vitro* pharmacodynamic model to simulate achievable peak serum concentrations and AUC of ciprofloxacin, grepafloxacin, trovafloxacin, levofloxacin, gatifloxacin and moxifloxacin against multidrug-resistant strains of *S. pneumoniae*. Except for ciprofloxacin, all of the agents reduced the inoculum below the level of detection by 48 hours with no resistant mutants. The estimated free AUC_{24}/MIC ratios for these agents ranged from 35–63.[121] Ambrose et al.[122] evaluated 58 ambulatory patients with pneumonia or bronchitis from phase III trials using levofloxacin and gatifloxacin. All patients who achieved an estimated free AUC_{24}/MIC of at least 33.7 had a microbiological response, whereas those

with a free AUC_{24}/MIC of less than 33.7 had a 64% response rate ($p = 0.013$). These data have prompted some clinicians to advocate lower AUC_{24}/MIC values for fluoroquinolones for respiratory tract infections caused by *S. pneumoniae*.[121-123] However, others argue that higher AUC_{24}/MIC ratios should still be attempted, especially in critically-ill patients admitted to hospital, and that clinically important differences exist in achievable AUC_{24}/MIC ratios between various fluoroquinolones. Thus, they suggest the use of lower potency agents may lead to clinical failures and ultimately increase fluoroquinolone resistance.[62]

The pharmacodynamics of fluoroquinolones are predictive for clinically important resistance. Thomas et al. studied the relationship between AUC_{24}/MIC ratios and the development of resistance in 143 patients from four nosocomial pneumonia trials involving five antimicrobial regimens (including ciprofloxacin).[124] Patients who achieved an AUC_{24}/MIC ratio of ≥100 had a 9% probability of developing resistance, whereas patients with an AUC_{24}/MIC of <100 had an 82.4% probability of developing resistance.

5.4 Aminoglycosides

Like fluoroquinolones, aminoglycosides exhibit rapid, concentration-dependent killing, although when used as adjunctive therapy for *S. aureus* or enterococci their activity may be concentration-independent.[60,61] Aminoglycosides also have a concentration-dependent PAE against Gram-negative organisms.[60,61] Aminoglycosides are subject to adaptive resistance – a short-term decrease or down-regulation in drug uptake and subsequent reduction in bactericidal activity after prolonged exposure to low drug concentrations.[32,61] *In vitro* data has shown that C_{max}/MIC ratios of ≥8 are required to prevent regrowth and the emergence of resistant isolates.[112] Both C_{max}/MIC and AUC_{24}/MIC may predict the efficacy of aminoglycosides; however, animal models have shown AUC_{24}/MIC to be more predictive of efficacy.[32,116,125,126] Data from animal models with Gram-negative organisms indicates that aminoglycosides may have a 2–10-hour concentration-dependent PAE.[52,127]

Maximum aminoglycoside concentrations have been closely linked to outcomes in human studies. Noone et al. studied 65 patients with Gram-negative sepsis and reported higher cure rates (84% vs 23%) for patients with 'adequate' gentamicin C_{max} values (≥5 mg/L for sepsis, urinary tract or wound infections, and ≥8 mg/L for pneumonia).[128] Moore et al. analysed data from four clinical trials in 84 patients with sepsis, and reported higher survival rates (97.6% vs 79.1%) in patients with 'therapeutic' gentamicin, tobramycin (>5 mg/L) or amikacin (>20 mg/L) serum concentrations.[129] In a similar study in 36 patients with Gram-negative pneumonia, Moore et al. reported higher cure rates (70% vs 32%) in patients with 'adequate' gentamicin (>7 mg/L) or amikacin (>28 mg/L) serum concentrations.[130]

Unlike in animal models, C_{max}/MIC is the pharmacokinetic-pharmacodynamic parameter most closely linked to outcomes in human studies, despite issues with covariance in studies with fixed administration regimens.[131] In an analysis of four clinical trials of patients with sepsis, Moore et al. found that maximal and mean C_{max}/MIC were significantly higher in responders than in nonresponders (8.5 vs 5.0 mg/L and 5.5 vs 4.6 mg/L, respectively).[132] Clinical cure rates approached 90% with C_{max}/MIC ratios of ≥8–10. In patients with nosocomial Gram-negative pneumonia, these same authors demonstrated that achieving a C_{max}/MIC ratio of ≥10 within the first 48 hours on aminoglycoside therapy was associated with a 90% probability of therapeutic response by day 7.[133] Resolution of temperature and leucocyte count on day 7 was also more likely if a C_{max}/MIC ratio of >4.7 was achieved within 48 hours of therapy.[134] Thus, based on the pharmacodynamic properties of aminoglycosides determined from *in vitro*, animal and human studies, the theoretical goal of aminoglycoside administration regimens may be give higher doses less frequently to take advantage of their concentration-dependent killing and PAE, and to prevent adaptive resistance. This concept has led to the development of the high-dose

extended-interval administration regimens that have been used clinically.

To our knowledge, there have been no published studies comparing extended-interval administration versus conventional regimens using individualised administration. Moreover, there have been no published studies of individualised extended-interval administration regimens attempting to incorporate individual pharmacokinetic and antimicrobial susceptibility data to design or optimise administration regimens. Numerous clinical trials have evaluated the efficacy and toxicity of conventional versus extended-interval administration regimens, but the results have been inconclusive because of lack of methodological rigour or design flaws. These clinical trials have been pooled using meta-analytic techniques by several authors.[135-143] Although some meta-analyses have shown either statistically significant increases in microbiological efficacy,[136] clinical efficacy[136,138,142] and overall response,[143] or statistically significant reductions in nephrotoxicity,[137,141] there appears to be no clinically important differences between aminoglycosides administered using conventional or extended-interval regimens.

5.5 Other Antimicrobials

There are limited data available to characterise the pharmacodynamics of macrolides/azalides, lincosamides, metronidazole, streptogramins and oxazolidinones.

5.5.1 Macrolides

In general, the macrolides and azalides are bacteriostatic agents with time-dependent kill characteristics and a variable PAE.[32,60] It is difficult for an integrated pharmacokinetic-pharmacodynamic parameter to strongly predict their activity, because of their intracellular activity that is not accounted for by reported MICs.[60,144] Moreover, due to variable pharmacokinetic differences between macrolides, there are differences between the agents with respect to which pharmacokinetic-pharmacodynamic parameters predict their activity in animal models.

Animal models have shown that for erythromycin and clarithromycin, t>MIC is the pharmacokinetic-pharmacodynamic parameter predictive of activity.[55,126,145] In a neutropenic murine thigh infection model, stepwise regression analysis showed that the best predictor of the activity of erythromycin against *S. pneumoniae* was t>MIC ($r^2 = 0.73$, $p < 0.05$).[126] A similar study evaluating clarithromycin in a neutropenic murine thigh infection model with *S. pneumoniae* found a highly significant correlation between bacterial counts and t>MIC ($p < 0.05$)[145] Standard doses of erythromycin and clarithromycin produce serum concentrations that generally exceed the MIC for susceptible strains of *S. pneumoniae* for 88–100% of the administration interval,[75] with associated bacteriological cures in 93–100% of children with otitis media.[32]

The difficulty of selecting pharmacokinetic-pharmacodynamic parameters to explain the intracellular activities of the newer macrolides is highlighted in a study by Nightingale et al.[146] Although both clarithromycin and azithromycin exceeded the MIC values for *S. pneumoniae* throughout the administration interval, neither reached their respective MIC levels of 4–8 mg/L and 0.5–2 mg/L for *H. influenzae*, despite being clinically effective agents for this organism.

Unlike the newer macrolides, the activity of the azalide azithromycin is best correlated with AUC_{24}/MIC in the neutropenic murine thigh infection model.[60,147] The explanation for this has been the prolonged *in vivo* PAE of azithromycin that correlates with its AUC.[32,55,61] There are no human studies that correlate pharmacokinetic-pharmacodynamic parameters with clinical outcomes for macrolides or azalides.

5.5.2 Clindamycin

Clindamycin is a lincosamide antimicrobial with bacteriostatic activity against most organisms. There are limited data available to characterise its pharmacodynamic properties.[32,58,60] An *in vitro* pharmacodynamic model against *S. aureus* and *S. pneumoniae* tested administration regimens that maintained t>MIC for the entire administration interval, but varied C_{max}/MIC and AUC_{24}/MIC.[148] Regimens that resulted in lower C_{max}/MIC and AUC_{24}/MIC ratios did not correlate with a loss of antimicrobial efficacy.[60,148] There are no human

studies that correlate pharmacokinetic-pharmacodynamic parameters with clinical outcomes for clindamycin.

5.5.3 Metronidazole

Metronidazole is an anti-anaerobic antimicrobial with concentration-dependent bactericidal activity. An *in vitro* study was performed under anaerobic conditions to characterise the activity of metronidazole against *Trichomonas vaginalis*.[149] Metronidazole exhibited concentration-dependent killing against *T. vaginalis* at concentrations from 0.1 to >10 times the minimum lethal concentration, and maximal kill rates were at 10–25 times the minimum lethal concentrations. The authors suggest that C_{max}/MIC or AUC_{24}/MIC are the important pharmacokinetic-pharmacodynamic parameters that should be optimised. The concentration-dependent effect of metronidazole was the impetus behind the investigation of a high single-dose regimen for the treatment of *T. vaginalis*, and data from randomised trials show higher cure rates with doses of at least 1.5g as a single oral dose.[150] Unfortunately, there are no human studies that correlate pharmacokinetic-pharmacodynamic parameters with clinical outcomes for metronidazole.

5.5.4 Quinupristin-Dalfopristin

Quinupristin-dalfopristin, the first marketed streptogramin, is a 30/70 mixture of these two semisynthetic pristinamycin derivatives.[151] Quinupristin-dalfopristin has bactericidal activity against staphylococci and streptococci, and bacteriostatic activity against *E. faecium*. *In vitro* studies suggest that quinupristin-dalfopristin has concentration-dependent activity, and is rapidly bactericidal against staphylococci at 2–4 times MIC, but has little or no activity at the MIC. Quinupristin-dalfopristin possesses a prolonged PAE against Gram-positive bacteria at concentrations above the MIC, and drug concentration is a more important parameter for determining the duration of the PAE than exposure time.[151] *In vitro* PAEs vary based on the bacterial species studied: *S. aureus* 2–8 hours, coagulase-negative staphylococci 2.5–7.5 hours, *S. pneumoniae* 7.5–9.5 hours, *S. pyogenes* 18 hours, vancomycin-sensitive *E. faecium* 8.4–8.6 hours and vancomycin-resistant *E. faecium* (VREF) 0.2–3.2 hours.[151,152] The presence of such a long PAE allows extended administration intervals of 8 hours despite half-lives of 0.6–1.0 hour for quinupristin and 0.3–0.4 hours for dalfopristin.[151,152]

There are relatively few data to define the pharmacokinetic-pharmacodynamic parameter that predicts activity for quinupristin-dalfopristin. An *in vitro* study using a fibrin-clot model studied isolates of *S. aureus* sensitive and resistant to methicillin and erythromycin.[153] AUC was significantly correlated with the reduction in bacterial density over 72 hours, but only for the methicillin-erythromycin resistant isolates ($r^2 = 0.55$, $p = 0.04$). *In vivo* data using the neutropenic thigh model against *S. aureus* and *S. pneumoniae* showed AUC_{24}/MIC to be the best predictor of response.[154] An *in vivo* endocarditis model with *S. aureus* showed both AUC_{24}/MIC ($r^2 = 0.14$, $p = 0.02$) and AUC_{24}/MBC ($r^2 = 0.30$, $p = 0.0001$) to be correlated with outcome.[155] Another *in vitro* study using the concentration-time-kill curve method evaluated quinupristin-dalfopristin against VREF under static conditions, and found a strong correlation between the quinupristin-dalfopristin concentration/MBC ratio and bacterial kill rate ($r^2 = 0.34$, $p = 0.02$).[156] Thus, although relationships between AUC and the MIC or MBC appear promising, there are no human studies that correlate pharmacokinetic-pharmacodynamic parameters with clinical outcomes for quinupristin-dalfopristin.

5.5.5 Linezolid

Linezolid is the first marketed oxazolidinone, with bacteriostatic activity against most susceptible Gram-positive organisms and bactericidal activity against some streptococci (*S. pneumoniae* and *S. pyogenes*). Linezolid has activity against MSSA, MRSA, MSSE, methicillin-resistant *S. epidermidis*, penicillin- and cephalosporin-resistant *S. pneumoniae*, vancomycin-resistant *E. faecalis* and vancomycin-resistant *E. faecium*.[157-159] *In vitro* and animal models suggest that linezolid has time-dependent killing, with increasing doses producing minimal concentration-dependent killing.[160] *In vitro* time-kill experiments have demonstrated a PAE

that is more prolonged at four times the MIC (0.1–1.4 hours) compared with at the MIC (<0.1–0.8 hours) against all organisms tested.[161] In contrast, *in vivo* data from a murine thigh infection model showed that linezolid doses of 20 mg/kg and 80 mg/kg produced similar PAEs of 3.6 and 3.8 hours with penicillin-sensitive *S. pneumoniae* and 3.9 and 3.7 hours with MSSA.[160] *In vivo* data has shown that t>MIC is the major pharmacokinetic-pharmacodynamic parameter determining the efficacy of linezolid (r^2 = 84%) versus AUC_{24}/MIC (r^2 = 42%) and C_{max}/MIC (r^2 = 39%) [statistical significance not reported]. Andes et al. also reported that, based on a t>MIC goal of 40%, linezolid at a dosage of 500mg orally or intravenously twice daily should achieve success against organisms with MIC values as high as 4 mg/L.[160] Thus, although t>MIC appears to predict efficacy in animal models, there are no published human studies that correlate pharmacokinetic-pharmacodynamic parameters with clinical outcomes for linezolid.

6. General Considerations for OPAT

OPAT should be initiated according to an appropriate decision-making plan (figure 4). The choice of drug(s) and drug regimen for OPAT should be based upon a thorough consideration of patient, infection, pathogen, drug, economic resources and psychosocial and environmental conditions under which the treatment course will be implemented. Several antimicrobials are available in both intravenous and oral dosage forms. Many of these agents have good, or at least clinically acceptable, oral bioavailability and thus can be considered alternatives to the parenteral formulations at the commencement of therapy, or as a component of an

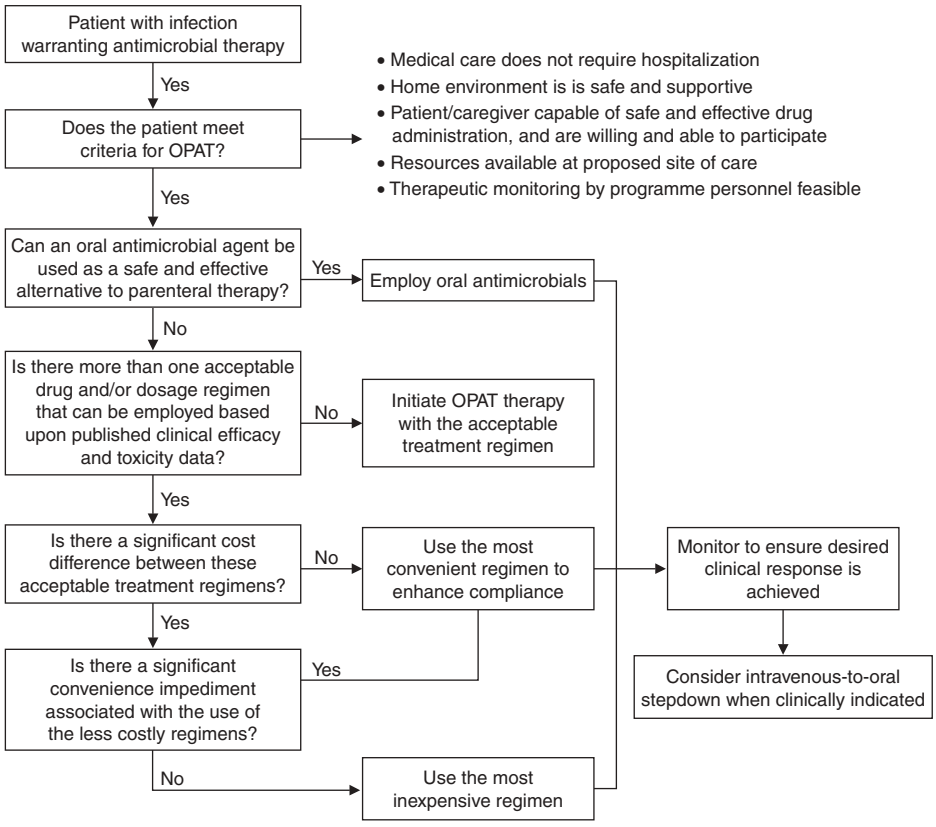

Fig. 4. Decision-making algorithm for outpatient parenteral antimicrobial therapy (OPAT). Criteria for OPAT are from Williams et al.[9]

intravenous-oral stepdown treatment regimen[26] (table IV).

As parenteral fluoroquinolones, lincosamides, metronidazole, macrolides and linezolid are available in oral dosage forms with generally adequate and predictable bioavailability, they should only be used in OPAT under special circumstances. Only patients who are unable to take oral medications due to intolerance or absorption problems should receive parenteral antimicrobials when treatment with one of these oral agents could be employed.

Although some may advocate the use of continuous infusion vancomycin and selected β-lactams, we believe there is neither sufficient rigorous clinical data nor adequate experience at this time to support the routine use of these regimens.[20] In consideration of the evidence and experience to support the use of extended-interval aminoglycoside regimens, we believe this could be considered an alternative administration scheme for the OPAT management of select infections. Although these once-daily aminoglycoside regimens may be attractive alternatives as they can be convenient and less costly than alternative antimicrobials (e.g. intermittent administration ceftazidime), it is important to ensure that final choice is based upon therapeutic appropriateness, not convenience. The primary determinant of drug selection should be made based upon published clinical data and the principles of antimicrobial stewardship.

In summary, OPAT has become an important treatment option for the management of many types of infection in the community setting. When designing a therapeutic regimen for use in OPAT, clinicians should consider the pharmacokinetic and pharmacodynamic properties of their therapeutic armamentarium to ensure optimal outcomes for their patients.

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