



BIOMÉRIEUX

ANTIMICROBIAL PRESCRIBING

Optimization through
Drug Dosing and MIC



PIONEERING DIAGNOSTICS

PREFACE



Professor Jason A. Roberts

The objective of this booklet is to provide practical recommendations for healthcare workers to improve antimicrobial prescription and thereby improve patient outcomes.

It aims to highlight how important the antimicrobial susceptibility of a pathogen (described by the minimum inhibitory concentration, MIC) and potential changes in pharmacokinetics can be for antimicrobial choice and dosing. Current practice does not make full use of our knowledge of pharmacokinetics and pharmacodynamics and an increased awareness of the value of knowing pathogen MICs can help with optimizing patient therapy.

Most of the recommendations in this booklet have been extracted from the published literature and have been cited where relevant. The recommendations also assume availability of various resources which may not be available in some countries, or in smaller or regional healthcare institutions.

I hope that this booklet will inform, encourage and support healthcare professionals who wish to improve antimicrobial dosing with the aim of ensuring patients get better faster, and potentially limit the emergence of antimicrobial resistant pathogens.

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INTRODUCTION

The wide use and frequent misuse of antimicrobials in all countries has resulted in the emergence of drug resistance, with 'superbugs' being resistant to most or even all antimicrobials. In addition to a limited arsenal of effective and available antimicrobials, there are also few new antimicrobials under development.

It is therefore essential to optimize the use of antimicrobials which are still effective. This is particularly relevant in the case of critically ill patients and multidrug-resistant infections, which are more difficult to treat.

As a result, the way infections are prevented and treated needs to be improved by:

- **Using antimicrobials only where an evidence-based indication exists;**
- **Optimizing antimicrobial dosing** (antimicrobial administration) enabling patients to be cured faster and to **slow the rate of emerging resistance;**
- **Performance of continuous surveillance** of drug susceptibility profiles and Minimal Inhibitory Concentrations (MICs) by the microbiology laboratory to reliably guide selection of empiric and directed therapies.

THIS BOOKLET WILL FOCUS ON:

- Principles for optimization of antimicrobial prescription and dosing to treat bacterial infections (non-mycobacterial), although the principles apply equally to anti-mycobacterials, antivirals and antifungals.
- The value of determining the MIC in customization of antimicrobial therapy, especially for treating critical patients and drug-resistant bacteria.

It is intended to provide broad information for healthcare staff to support their knowledge of the considerations associated with dose optimization in individual patients.



For easy reading and reference, look for the colored boxes highlighting the key points in each chapter. The Top Ten Key Points can be found on pages 36-39.

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Optimizing Antimicrobial Prescribing through Drug Dosing and MIC

WHAT IS THE RELEVANCE OF DOSE OPTIMIZATION?

Principles of antimicrobial prescribing

Antimicrobials should always be prescribed taking into account the best practices of antimicrobial stewardship. A simple set of reminders is given in the rules known as “MINDME” (Figure 1), devised by David Looke and John Ferguson in 2005. [Therapeutic Guidelines: Antibiotic, 2014]

Figure 1: The Golden Rules of Antimicrobial Prescribing: MINDME
Adapted from Therapeutic Guidelines: Antibiotic. Version 15, 2014

- M** Microbiology guides therapy wherever possible
- I** Indications should be evidence based
- N** Narrowest spectrum required
- D** Dosage appropriate to the site and type of infection
- M** Minimize duration of therapy
- E** Ensure monotherapy in most cases

➤ Antimicrobial therapy is based on the selection of the most appropriate antimicrobial combined with an effective dose and duration of therapy.

Goals of antimicrobial therapy

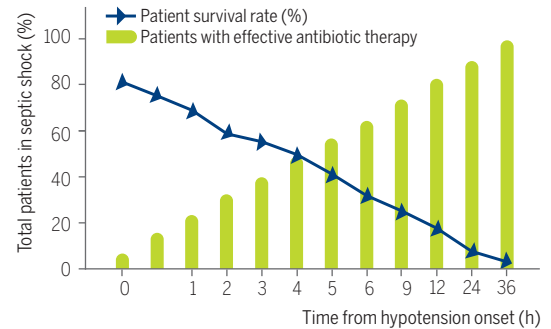
A clinician treating a patient should apply the principles of antimicrobial dosing (MINDME) to try to eradicate the microbial pathogen(s) from the site of infection. However, eradication of the pathogen does not necessarily ensure the patient will be cured.

For instance, in sepsis and septic shock, the patient's inflammatory response can play a key role in defining the outcome of infection. In the case of severe infection, the inflammatory processes drive organ dysfunction and potentially patient death. For this reason, the early initiation of appropriate antimicrobial treatment is essential to **reduce the bacterial burden which drives the inflammatory response.** (Figure 2)

WHAT IS THE RELEVANCE OF DOSE OPTIMIZATION?

Figure 2: Fast effective antimicrobial therapy increases survival rate
Adapted from Kumar A et al. Crit Care Med. 2006;34(6):1589-96

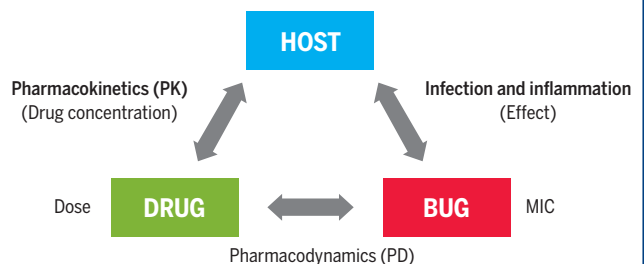
MORTALITY INCREASES 7% FOR EVERY HOUR DELAY IN INITIATION OF ANTIBIOTICS



Principles of antimicrobial dosing

Antimicrobial dosing requires consideration of the interactions between the patient's metabolism (or physiology) (HOST), the susceptibility, or MIC*, of the pathogen (BUG), the microbiological spectrum of activity and chemical properties of the antimicrobial (DRUG). (Figure 3).

Figure 3: Patient, pathogen and antimicrobial interactions



Dosing regimens for a specific drug are defined for minor or moderate infections. However, antimicrobial pharmacokinetics (PK†) can be extremely different in cases of severe infection.

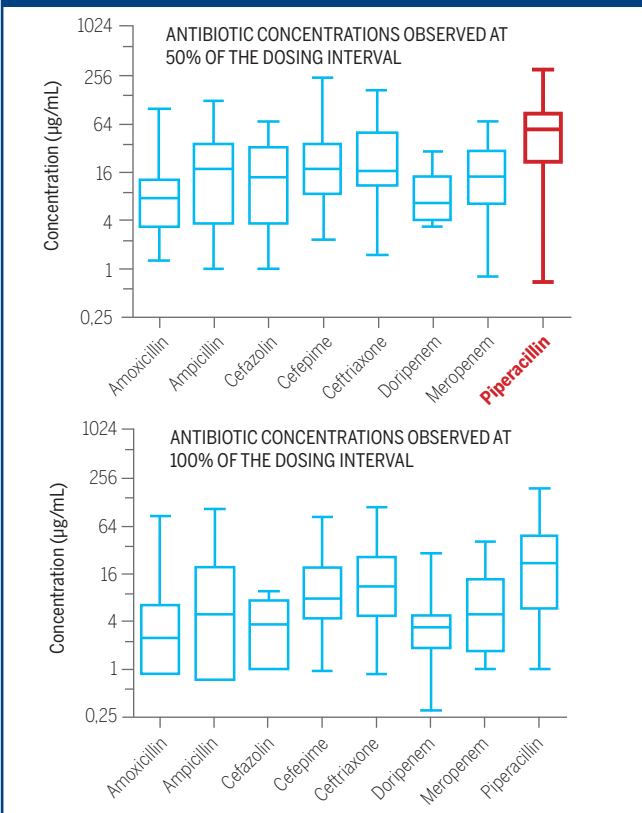
*The MIC is the lowest antimicrobial concentration that inhibits the growth of a microorganism and is a measure of the susceptibility of the pathogen to an antimicrobial.

†PK describes the relationship between the dose of drug given and the resulting concentration in the body.

WHAT IS THE RELEVANCE OF DOSE OPTIMIZATION?

For example, in critically ill patients, there is a significant variability of antimicrobial concentrations in serum (organ failure greatly affects PK) as shown in Figure 4 below for beta-lactam antimicrobials in ICU patients. [Roberts, 2014] The highest variability is observed for piperacillin.

Figure 4. Defining beta-lactam Antibiotic Levels in Intensive care patients (DALI)
Adapted from Roberts JA et al. *Crit Care Med.* 2014;58:1072-1083
Median, interquartile range, and range are presented. The y-axes are presented on a log₂ scale.



Furthermore, given that dosing regimens are defined when the antibiotics are relatively new to clinical practice, the pathogens being treated are commonly highly susceptible. However, over time susceptibility may decrease (increasing MICs), reducing the probability of clinical success with the recommended dosing regimens.

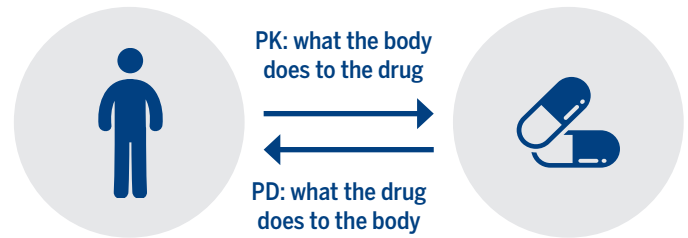
Knowledge of local MICs is very important for clinicians to guide empiric treatment (choice and dose of antimicrobial) in both critically ill and non-critically ill patients.

WHAT IS THE RELEVANCE OF DOSE OPTIMIZATION?

Definition of pharmacokinetics (PK) and pharmacodynamics (PD)

Pharmacokinetics (PK) describes the relationship between the dose of drug given and the resulting concentration in the body. PK includes the physiological processes of absorption, distribution, metabolism and elimination.

Pharmacodynamics (PD) describes the interaction between drug concentration and pharmacological effect. It relates the concentration of the drug to its ability to kill or inhibit the growth of the pathogen and is mostly described by MIC.



PK/PD evaluates the “dose-concentration-effect” relationship and predicts the effect time-course resulting from administration of a drug dose.

PK-PD Relationship

dose $\xrightarrow{\text{PK}}$ concentration $\xrightarrow{\text{PD}}$ effect

Changing the way the drug is administered (dose, route, frequency and speed of administration) helps to ensure **maximal antimicrobial effect and minimize toxic effects**, taking into account the way the drug is eliminated from the body. If sufficient doses are used, this can decrease the probability of emergence of antimicrobial resistance.

Antimicrobial pharmacokinetic characteristics

PK variations may be induced by the **hydrophilic** or **lipophilic** nature of an antimicrobial (Pea, 2005) (Figure 5), as well as by organ failure which can result from severe infections (as seen in ICU patients).

Dramatically altered PK is more likely to occur in hydrophilic renally cleared drugs. For example, **volume distribution (Vd)**, which is the theoretical volume of fluid into which a drug appears to distribute in order to give a concentration equal to that measured in plasma, increases with renal failure due to fluid retention and liver failure. With hydrophilic drugs, Vd is commonly increased and as a result there is a need to use higher initial antimicrobial doses to ensure therapeutic concentrations at the site of infection.

For both hydrophilic and lipophilic drugs, **changes in kidney and/or liver function can affect antimicrobial clearance**. However, the effects appear to be far greater for renally cleared drugs.

Figure 5: Effects of severe infection and inflammation on pharmacokinetics, according to physicochemical properties of antimicrobials
Adapted from Roberts and Lipman, *Crit Care Med.* 2009;37(3):840-51.

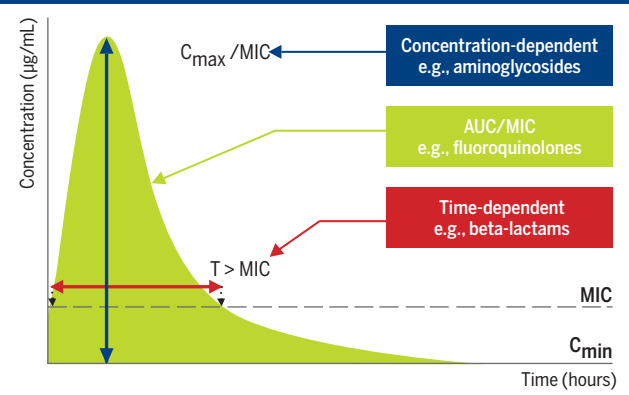
	HYDROPHILIC ANTIBIOTICS	LIPOPHILIC ANTIBIOTICS
General PK	<ul style="list-style-type: none"> • Low Vd • Predominant renal CL • Low intracellular penetration 	<ul style="list-style-type: none"> • High Vd • Predominant hepatic CL • Good intracellular penetration
Altered ICU PK	<ul style="list-style-type: none"> • \uparrowVd • CL\uparrow or \downarrow dependent on renal function 	<ul style="list-style-type: none"> • Vd largely unchanged • CL\uparrow or \downarrow dependent on hepatic function
Examples	<ul style="list-style-type: none"> • Beta-lactams • Aminoglycosides • Glycopeptides • Linezolid • Colistin 	<ul style="list-style-type: none"> • Fluoroquinolones • Macrolides • Lincosamides • Tigecycline
Antimicrobial adaptation	INCREASE INITIAL ANTIMICROBIAL DOSE	INITIAL ANTIMICROBIAL DOSE UNCHANGED

Vd - Volume of distribution; CL - clearance

Antimicrobial pharmacodynamic classifications

Different antimicrobial profiles over a dosing interval (or 24-hour period) are associated with maximal PD effects.

Figure 6: Description of the three different pharmacodynamics classifications of antimicrobials; time-dependent; concentration-dependent and those with a combination of both time- and concentration-dependent effects.
Adapted from Roberts and Lipman, *Crit Care Med.* 2009;37(3): 840-5



- **Time-dependent antimicrobials** have maximal microbiological effects when their concentrations are maintained above MIC for as long as possible throughout the dosing interval.
- **Concentration-dependent antimicrobials** have maximal effects driven by the magnitude of the peak antimicrobial concentration relative to the MIC of the pathogen.
- Other antimicrobials have a combination of both **time and concentration dependent** characteristics.

Figure 7: Categorization of antimicrobials according to PD characteristics
Adapted from Roberts and Lipman, *Crit Care Med.* 2009; 37(3):840-51.

Antibiotics	Beta-lactams Carbapenems Linezolid Erythromycin Clarithromycin Lincosamides	Aminoglycosides Metronidazole Fluoroquinolones Telithromycin Quinupristin/ dalfopristin	Fluoroquinolones Aminoglycosides Azithromycin Tetracyclines Glycopeptides Tigecycline Quinupristin/ dalfopristin Linezolid
PD kill characteristics	Time-dependent	Concentration-dependent	Concentration-dependent with time-dependence
Optimal PD index	T > MIC	C _{max} / MIC	AUC ₀₋₂₄ / MIC

WHAT IS THE RELEVANCE OF DOSE OPTIMIZATION?

In the case of a high MIC (exceeding the susceptible range), dosing may need to be modified or the antimicrobial selection may need to be changed. If the MIC is slightly elevated, dose modulation can still enable successful treatment.

For instance, in the presence of a slightly higher MIC (e.g., one dilution higher than the susceptible breakpoint (concentration) of an antimicrobial which defines whether a bacterial species is susceptible or resistant to the antimicrobial), an aminoglycoside would achieve best effects with a higher once daily dose to increase the magnitude of the peak concentration.

However, a beta-lactam should be administered in more frequent doses or by prolonged infusion to maintain a concentration above the slightly higher MIC.

What is therapeutic drug monitoring (TDM)?

Therapeutic drug monitoring (TDM) refers to the measurement of drugs in biological fluids (e.g., blood or plasma).

TDM is used to personalize dosing (dose, route, frequency) and ensures a high probability of therapeutic success, with low toxicity.

Although most commonly used for **drugs with a narrow therapeutic range** (e.g., aminoglycosides, glycopeptides), the use of TDM is expanding due to:

- **the increasing number of patients for whom PK cannot be predicted** (e.g., critically ill, significant comorbidities, elderly and extremes of body size),
- **the decreasing susceptibility of pathogens**, which may require higher antimicrobial doses to achieve therapeutic exposures that maximize treatment success.

Figure 8: Criteria for using TDM

Drug factors (must have all of these):	<ul style="list-style-type: none"> • Large variability between subjects • Small therapeutic index^a • An established concentration–effect (or toxicity) relationship (or both) • Therapeutic response that is not obvious
Patient factors (any of these):	<ul style="list-style-type: none"> • Suspected drug interactions • Suspected drug adverse effects/toxicity • Suspected drug abuse • Unexplained failure of therapy • Suspected noncompliance
Pathogen factors	<ul style="list-style-type: none"> • Multidrug-resistant organisms (or increased MIC for several antimicrobials) [Magiorakos, 2012]

^aTherapeutic index: The ratio between the toxic dose and the therapeutic dose of a drug, used as a measure of the relative safety of the drug for a particular treatment.

WHAT IS THE RELEVANCE OF DOSE OPTIMIZATION?

Patient populations likely to have altered PK

Some patient groups commonly experience **pathophysiological changes that may lead to very low and sub-therapeutic drug concentrations** and are therefore much harder to treat. These are typically critically ill patients with sepsis or septic shock, organ dysfunction, immunosuppression or debilitated patients. Patients that have received high volumes of resuscitation fluids, renal or liver (modified drug metabolism) injury or with multiple therapies (drug interactions) could also have altered drug concentrations.

Figure 9: Main patient populations with altered pharmacokinetics

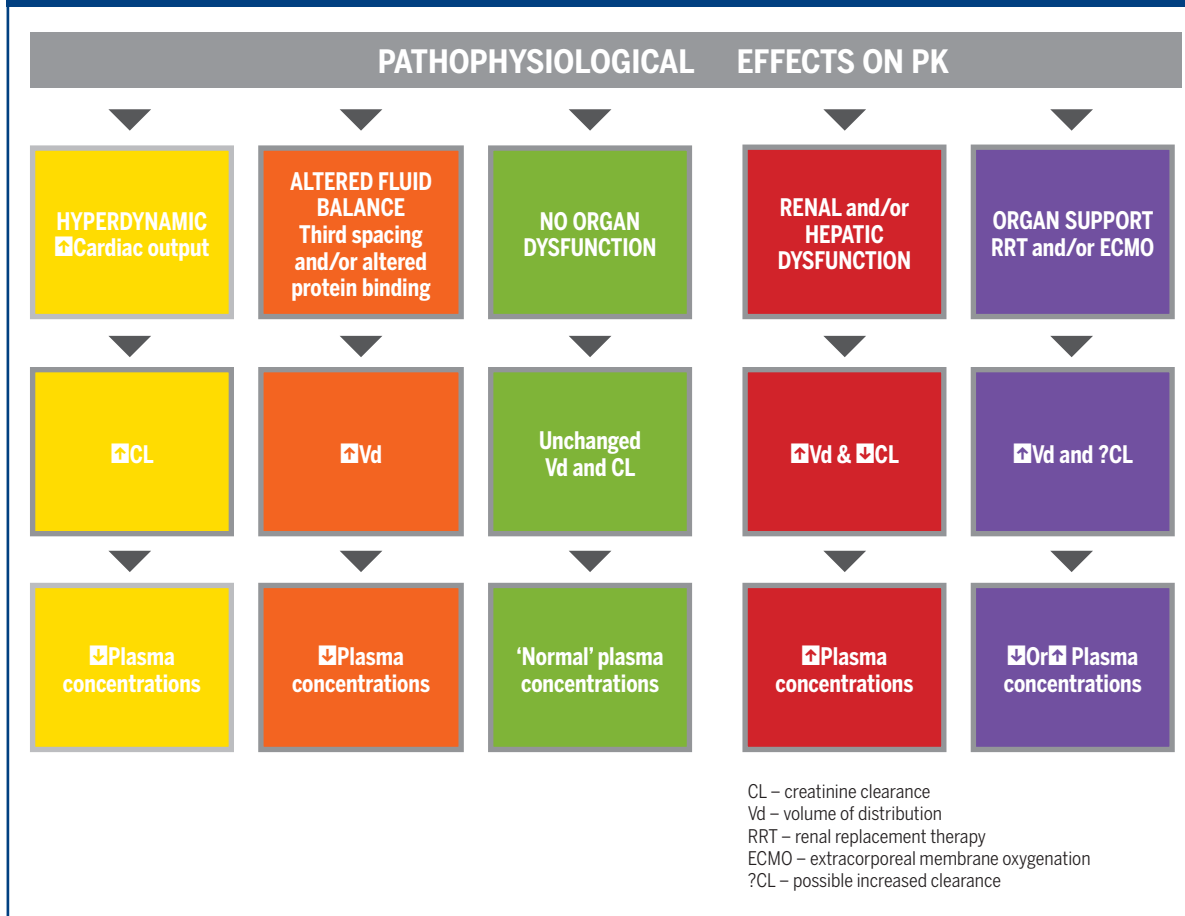
Source of altered pharmacokinetics	Patient Population
Acute pathophysiology	<ul style="list-style-type: none"> • Sepsis and septic shock (frequent organ failure). These patients include those with: <ul style="list-style-type: none"> • Augmented renal clearance (ARC), an elevated creatinine clearance (>130 mL/min) associated with increased renal drug clearances and low antimicrobial concentrations; [Udy, 2012] • Renal replacement therapy (RRT) which is associated with highly variable drug concentrations, both sub- and supra-therapeutic [Jamal, 2015] • Extracorporeal membrane oxygenation (ECMO) which has variable effects on concentrations of different drugs causing them to be commonly sub- or supra-therapeutic [Shekar, 2014] • Immunosuppression: transplant febrile neutropenia. These patients can have altered pharmacokinetics and infections by pathogens with higher MICs • Trauma • Neurosurgery • Burns • Acute kidney or liver failure • Endocarditis • Bone and joint infections: antimicrobial penetration may be low
Baseline physiology	<ul style="list-style-type: none"> • Obesity • Elderly • Cystic fibrosis: patients could have altered pharmacokinetics and infections by pathogens that may have higher MICs • Pediatric • Pre-existing organ dysfunction (e.g., chronic kidney disease) • Limited blood perfusion of peripheral tissues

The effect of altered PK on dose requirements

The effects of altered pathophysiology on PK are summarized in **Figure 10**, which shows that effects on drug clearance and Vd can both lead to altered concentrations and therapeutic effects.

Figure 10: Pathophysiological effects on pharmacokinetics in critically ill patients

Adapted from Roberts JA et al. *Lancet Inf Dis.* 2014;14:498-509.



WHAT IS THE USEFULNESS OF THE MIC?

What is an MIC ?

The MIC is a key component of the relationship between antimicrobials and microorganisms. It is defined as the **lowest antimicrobial concentration that inhibits the growth of bacteria/fungi** and is a **measure of the susceptibility of the pathogen to an antimicrobial**.

MICs are used to measure the susceptibility of a pathogen to a possible antimicrobial therapy *in vitro*.

- A low MIC indicates higher susceptibility to the antimicrobial,
- A high MIC indicates lower susceptibility and potential resistance to the antimicrobial.

However, the interpretation of the MIC value is highly dependent on both the antimicrobial and the pathogen (for example, in the treatment of a cerebral spinal fluid infection, a low MIC for *Streptococcus pneumoniae* and ceftriaxone can still be considered as resistant because of likely reduced antimicrobial penetration of the brain barrier).

The aim of susceptibility testing and MIC measurement is to predict the likely treatment success or failure of a chosen therapy

The MIC value allows the clinician to:

- **select the most appropriate antimicrobial:** a direct relationship between MIC and patient outcome has been demonstrated in many studies, as shown in **Figures 11 and 12** opposite.
- **customize antimicrobial dosing** taking into account the susceptibility of the pathogen (MIC) combined with patient profile and the PK parameters of the drug through use of TDM. **The MIC helps to define the target exposure that an optimized antimicrobial dosing regimen should reach.**

Figure 11 shows the thirty-day mortality rate for patients with bacteremia according to piperacillin-tazobactam MIC. Patients infected with *Pseudomonas aeruginosa* having a high piperacillin/tazobactam MIC are more likely to have a high mortality after 30 days.

Figure 11: Relationship between MIC and patient outcome

Adapted from Tam V et al. *Clin Infect Dis*. 2008;46:862-7.

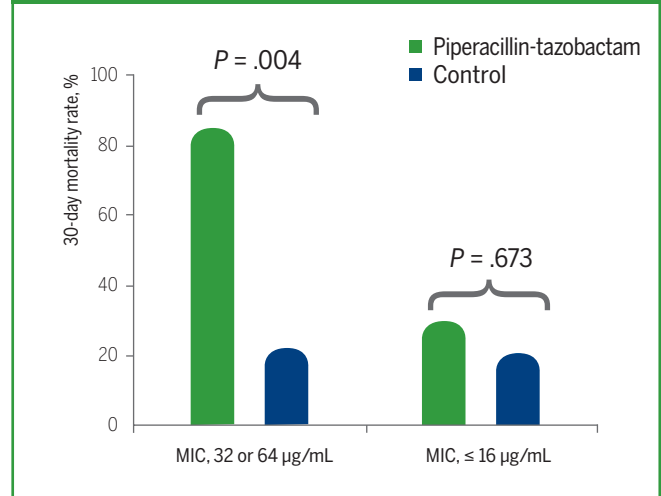
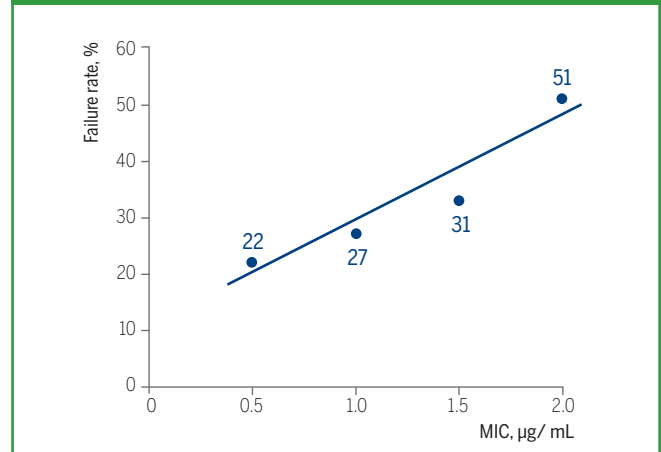


Figure 12 shows a direct relationship between vancomycin MIC and treatment failure rates in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infection.

Figure 12: Relationship of MIC to vancomycin treatment failure in patients with MRSA infections.

Adapted from Stevens DL. *Clin Infect Dis*. 2006;42:S51-7.



Methods for measuring MICs and Antimicrobial Susceptibility Testing (AST)

Antimicrobial activity can be measured using a wide variety of different *in vitro* methods.

Depending on the method employed, results are expressed in the form of:

- either **susceptibility categories** (susceptible [S], intermediate [I], or resistant [R])

The **Susceptible Dose Dependent (SDD)** interpretation is a new category for antimicrobial susceptibility testing. It implies that the susceptibility of a pathogen is dependent on the dosing regimen used in the patient. To achieve concentrations that are likely to be clinically effective against isolates in the SDD category, it is necessary to achieve a higher drug exposure (i.e., use higher doses, more frequent doses or both), giving a highest probability of adequate coverage (*CLSI M100-S27, 2017*).

The “**Nonsusceptible**” (NS) category applies to strains for which only a susceptible breakpoint is designed because of the absence or rare occurrence of resistant strains.

- and/or **quantitative estimates of antimicrobial activity, MICs**. The measurement units for MICs are micrograms per milliliter ($\mu\text{g/mL}$). **MICs currently represent the most refined estimate of *in vitro* antimicrobial effect.**

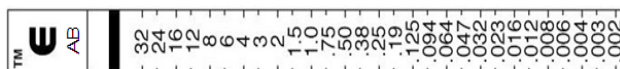
MIC values depend on the method used, the type of antimicrobial, the microbial species and isolate.

■ Broth macro/micro dilution or agar dilution

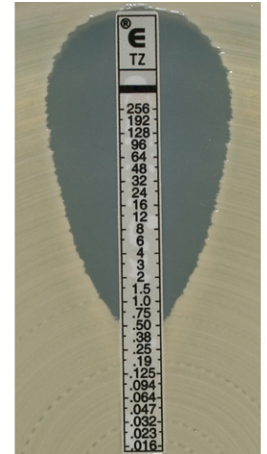
These are the reference methods for measuring MICs. The procedure involves preparing 2-fold dilutions of an antimicrobial in liquid or solid growth medium. The medium containing decreasing concentrations of the antimicrobial is inoculated with a standardized bacterial suspension, incubated overnight, then examined for visible bacterial growth. The MIC is the lowest antimicrobial concentration that prevents growth.

■ MIC gradient strip (E-test®)

These are “ready-to-use” reagent strips comprised of a preformed gradient of an antimicrobial agent as shown below:



The upper surface of the plastic strip is pre-calibrated with a continuous MIC scale in $\mu\text{g/mL}$ that shows the conventional doubling dilutions as well as values in between these two-fold dilutions (e.g., 0.75 $\mu\text{g/mL}$). MIC ranges for ETEST products span 15 two-fold dilutions. Strips containing 3 different concentration ranges are also available (0.016-256 $\mu\text{g/mL}$, 0.002-32 $\mu\text{g/mL}$, and 0.064-1024 $\mu\text{g/mL}$) depending on the agent. These ranges cover the clinically significant MIC values of most antimicrobial agents and organism groups.



■ Automated AST systems

Various AST methods are commercially available. Most provide results within 18-24 hours. More rapid automated systems, such as the VITEK® 2, are capable of providing same-day results for most clinically significant organisms (8-24 hours).

The majority of automated systems are designed to accommodate many drugs on a single panel or card and they generally cover clinically relevant concentrations. In some cases, automated systems may not provide sufficient data for dosing considerations and further MIC testing may be required. For certain patients (e.g., cystic fibrosis) automated AST results may not be reliable for certain bacterial species (e.g., *Pseudomonas*, *Burkholderia*...)

■ Disk diffusion (Kirby Bauer)

Disk diffusion is also used, but does not determine the actual MIC. This method involves placing antimicrobial-impregnated filter paper disks on an agar plate inoculated with a standardized suspension of microorganism. The plate is incubated overnight. The antimicrobial diffuses into the medium and if an antimicrobial kills or inhibits bacterial growth, there will be an area around the disk where no bacteria have grown. The size of this zone is proportional to the effectiveness of the antimicrobial and the zone diameter is correlated to a S, I or R category.

Disk diffusion is only capable of providing S, I or R category results and **cannot generate MIC values**.

What are clinical MIC breakpoints ?

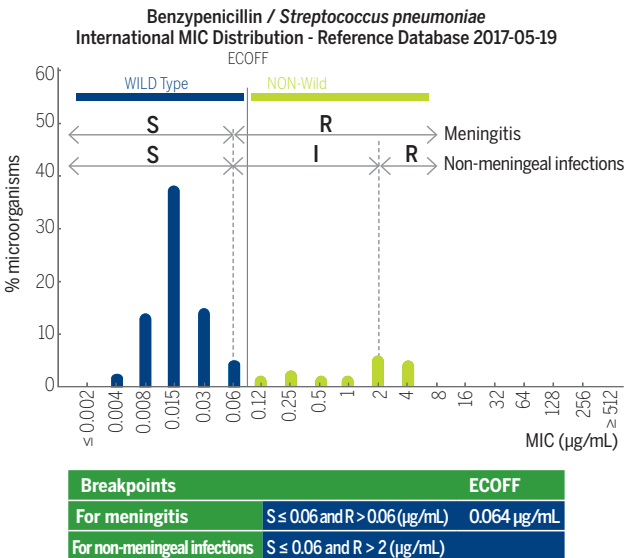
➤ A clinical breakpoint is a concentration of an antimicrobial which defines whether a bacterial species is susceptible or resistant to a particular antimicrobial.

Clinical breakpoints refer to the MICs that separate strains where there is a high likelihood of treatment success from those bacteria where treatment is more likely to fail.

- The “wild type” or **intrinsic resistance phenotype (or inherent or innate or natural resistance)** refers to the bacterial species in the naive or wild type state. It does not harbor any acquired and mutational mechanisms of resistance to antibacterial(s). When intrinsic resistance is found in all “wild type” strains, susceptibility testing is unnecessary for that particular drug class [Turnidge and Paterson, 2007].
- The “non-wild type” isolates have **acquired resistance** and therefore reduced susceptibility to antimicrobial agents.

Figure 13: Example of Epidemiological Cutoff for Wild and Non-Wild Types and Breakpoints for Meningeal and Non-meningeal Infections as defined by EUCAST for Benzylpenicillin and *S. pneumoniae*

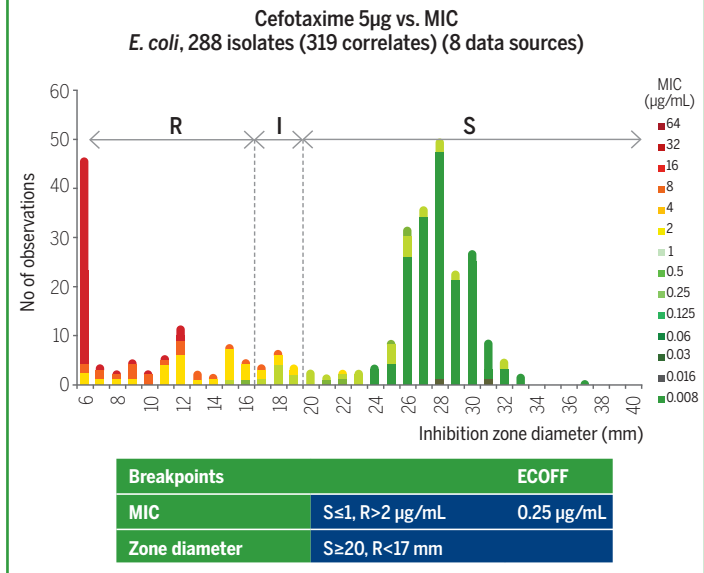
Adapted from EUCAST MIC distributions and ECOFFs [http://www.eucast.org/mic_distributions_and_ecoffs/]



➤ The epidemiological cut-off (ECOFF) allows the differentiation of two populations according to MIC values as “wild type” and “non-wild type”.

Figure 14: Example of breakpoints defined by EUCAST for Cefotaxime and *Escherichia coli*

Adapted from EUCAST, Development and Validation of EUCAST Disk Diffusion breakpoints. [http://www.eucast.org/ast_of_bacteria/calibration_and_validation/#c7263].



Where the MIC is less than or equal to the susceptible breakpoint, the bacterial species is considered **susceptible**, and when greater than this concentration, the bacteria is considered **intermediately-susceptible** or **resistant** to the antimicrobial.

The classification “intermediate” indicates that the bacterial strain is inhibited *in vitro* by a concentration of an antimicrobial that is associated with an **uncertain therapeutic effect**, and therefore a higher dosing regimen may be required. The intermediate category is also used because of the inherent variability in MIC testing (+/- a dilution).

However, the process of setting these breakpoints mostly assumes normal patient PK and does not always account for special patient populations.

As shown in the example above, some heterogeneity of MIC within the categories can exist. This shows that susceptibility testing that provides category-based interpretation only may not always be sufficient and there may be a need to determine the actual MIC.

➤ In patients where the PK changes dramatically, S, I, R breakpoints may not always be appropriate and knowledge of the MIC is required for optimal antimicrobial selection and dosing.

The importance of the MIC for antimicrobial selection

In combination with knowledge of the likely exposures achieved with different antimicrobials and doses, the MIC helps in the selection of the most appropriate antimicrobial.

- A **low MIC** (lower than the susceptible breakpoint) indicates that an antimicrobial will most likely be effective and is therefore an appropriate choice for treatment.
- A **high MIC** (higher than the susceptible breakpoint i.e., intermediate or resistant) means that an antimicrobial may have limited or no effectiveness for treatment.

Antimicrobial susceptibility testing results are interpreted using the laboratory standard methods recommended by the guidelines. The most common guidelines are Committee of Laboratory Standard Institute (CLSI) and European Committee of Antimicrobial Susceptibility Testing guidelines (EUCAST). These guidelines are updated very regularly with the most recent information for drug selection according to the bacteria, MIC interpretive standards with relevant comments on resistance mechanisms, drug dosage or intended use, susceptibility testing interpretation rules and quality control using standardized procedures.

Antimicrobials with low MICs compared to the susceptibility breakpoint should be preferred. The closer the MIC matches the MIC ranges of the wild type population of the species, the more effective the therapy is likely to be.

➔ CASE EXAMPLE

A 23-year-old female (60 kg; no significant related medical or surgical history) is admitted to the Emergency Department and diagnosed with urosepsis.

She is empirically given ampicillin 1 g intravenously (IV) every 6 hours and a one-time dose of gentamicin (IV 340 mg). *E. coli* is identified as the causative pathogen. Ampicillin treatment, is maintained although on day 3 of therapy, her symptoms have continued to deteriorate.

MIC for ampicillin is found to be 8 µg/mL (other MICs, ciprofloxacin <0.064 µg/mL; cefotaxime 0.25 µg/mL; meropenem 0.125 µg/mL; piperacillin-tazobactam 8 µg/mL).

WHAT DO YOU DO?

8 µg/mL is the highest MIC that ampicillin is likely to be able to cover. Your options are the following:

- **increasing the dose** to 2 g IV every 4-6 hours (maximum dose in package insert) which may achieve therapeutic concentrations,
- **change to another antimicrobial** with a lower MIC below the susceptible breakpoint.

Given the other MIC data, ciprofloxacin is highly susceptible and can also be used as either IV or oral therapy (po*) enabling completion of the treatment course with the same antimicrobial after hospital discharge.

Dosing at **400 mg IV every 12 hours** or **500 mg po every 12 hours** would lead to sufficient ciprofloxacin concentrations in this case.

The high c^{\dagger}/MIC index of ciprofloxacin, as shown below indicates that this molecule is **one of the most active, avoiding other more broad spectrum antimicrobials** such as meropenem and **is therefore the preferred choice**. The MIC result also means that maximum dosing (400 mg IV every 8 hours or 750 mg po every 12 hours) is not necessary.

This case example shows that knowledge of the MIC assists choice of therapy and dosage.

*po = per os

† c = low (susceptible) breakpoint

➔ Calculation of c/MIC index - EUCAST

	MIC (µg/mL)	Low susceptible Breakpoints EUCAST (≤)	c/MIC Index
Ampicillin	8	8	1
Ciprofloxacin	< 0.064	0.5	7.8
Cefotaxime	0.25	1	4
Meropenem	0.125	2	16
Piperacillin-tazobactam	8	8	1

➔ Calculation of c/MIC index - CLSI

	MIC (µg/mL)	Low susceptible Breakpoints CLSI (≤)	c/MIC Index
Ampicillin	8	8	1
Ciprofloxacin	< 0.064	0.5	7.8
Cefotaxime	0.25	1	4
Meropenem	0.125	1	8
Piperacillin-tazobactam	8	16	2

The importance of the MIC to define optimal drug dosing regimens

i. Prevent underdosing

Based on the MIC value the dosing may be adjusted:

- **regular dose** if MIC corresponds to the susceptible profile of the wild-type population
- **higher dose** if the MIC falls in the non-wild type population range but is still in the susceptible range
- **maximum dose** if the MIC is in the susceptible range but borderline or intermediate range

In some cases, susceptibility testing guidelines recommend to adjust dosing according to MIC.

CASE EXAMPLE

Considering **CEFEPIME** for *Enterobacteriaceae* and according to CLSI recommendations (CLSI M100-S27, 2017):

Cefepime breakpoints:

- S < 2 µg/mL
- SDD*: 4 - 8 µg/mL
- R > 16 µg/mL

According to the MIC value, there are 3 therapeutic possibilities:

- **For susceptible strains:** the recommended dosage is 1 g every 12 h
- **For SDD strains:** dosage depends on MIC:
 - If MIC = 4, the recommended dosage is 1 g every 8 h or 2 g every 12 h
 - If MIC = 8, the recommended dosage is 2 g every 8 h

* SDD: Susceptible Dose Dependent

The MIC is centrally important for effective antibiotic dosing.

It defines how much antibiotic exposure is necessary to achieve the PK/PD target that is associated with maximum effectiveness.

Infections in special patient populations (i.e., ICU or cystic fibrosis) are often caused by less susceptible pathogens than in the community or other wards. [Rhomberg, 2006] For example, a German study of predominantly Gram negative pathogens (e.g., *E. coli*, *Klebsiella spp.*) found that the MIC₉₀ for carbapenem antimicrobials was 4-8 times higher in the ICU compared with patients based in other wards. [Valenza, 2012]

Measuring MICs in special patient groups is useful for detecting pathogens with higher MICs. [Huttner, 2015] Higher antimicrobial doses may be needed to reach PK/PD targets.

A higher dose of antimicrobial may be required for a pathogen with a borderline susceptible or intermediate AST classification.

Dosing information is available in pharmacokinetic guides (i.e., Stanford Hospital and Clinics Pharmacy Department Policies and Procedures)

CASE EXAMPLE

For **MEROPENEM**, a PK/PD target of a mid-dosing interval concentration four-times greater than the MIC may be required.

A 19-year-old male in the ICU admitted initially with trauma develops a ventilator-associated pneumonia and has a measured creatinine clearance of 170 mL/min indicating likely high meropenem clearance and a need for increased dosing.

WHAT DO YOU DO?

- If the pathogen has a MIC of 0.25 µg/mL (susceptible), then a mid-dosing interval concentration of 1 µg/mL is required and this could be achieved with a 1 g IV dose every 8 hours.
- If the MIC is 4 µg/mL (intermediately-susceptible), then a mid-dosing interval concentration of 16 µg/mL is required which would require a 2 g IV meropenem dose every 6 hours. If a 3-hour infusion is used rather than a 30-min short infusion, a dose of 1 g every 8 hours is sufficient to achieve the target exposure in this patient.

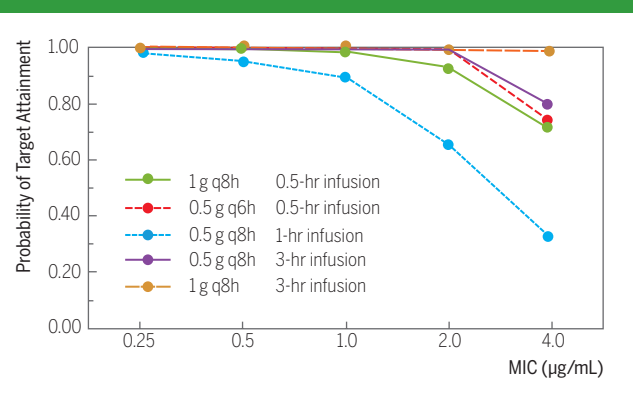
In this case example, dose optimization of meropenem can be used to achieve the target concentration: MIC ratio using three different dose adjustments because meropenem is a time-dependent antimicrobial:

- **higher dosing** (1 g increased to 2 g),
- **more frequent dosing** (8-hourly to 6-hourly dosing),
- **prolonged infusion** (30 minute infusion changed to 3-hour infusion),

See Figure 15 on page 26.

WHAT IS THE USEFULNESS OF THE MIC?

Figure 15: Medication Administration: Extended-Infusion Meropenem Protocol
Adapted from Stanford Hospital and Clinics Pharmacy Department Policies and Procedures (02/2016)



The lower the MIC, the better the probability of PK/PD target attainment:

- with an MIC = 0.25 µg/mL, all therapeutic schemes will reach the targeted concentration. The lower dose will be preferred.
- with an MIC = 4 µg/mL, only 1g every 8 hours during a 3-hr infusion will reach the targeted concentration.

ii. Minimize high dosing for cost savings

In patients with infections caused by highly susceptible organisms, a lower antimicrobial dose could be used, thereby reducing drug costs.

➤ CASE EXAMPLE

If vancomycin is prescribed for a 65-year-old female with normal renal function for treatment of a methicillin-resistant *Staphylococcus aureus* (MRSA) healthcare-associated pneumonia, a PK/PD target of an AUC/MIC ratio of 400 is suggested for clinical efficacy. [Moise-Broder, 2004]

When the MIC has a value of 1.5 µg/mL, a vancomycin dose of 1.5 g IV 12-hourly is needed to achieve the AUC target of 600 (AUC 600/1.5 µg/mL gives target AUC/MIC ratio of 400).

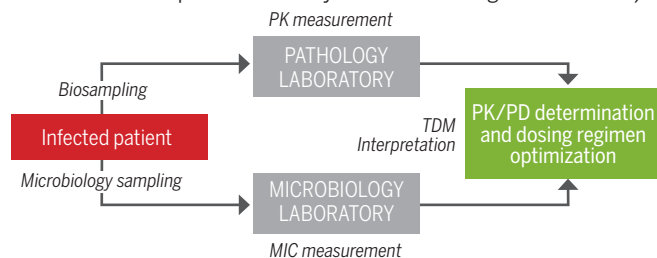
However, if the MIC was determined to be 0.5 µg/mL, then a dose of 500 mg IV 12-hourly is required to achieve the AUC target of 200 (AUC 200/0.5 µg/mL gives target AUC/MIC ratio of 400).

In this case example, one-third of the dose of antimicrobial is required to achieve the same AUC/MIC ratio, which if applied, can reduce drug costs.

IMPLEMENTING THERAPEUTIC DRUG MONITORING INTO DAILY PRACTICE

➤ Therapeutic drug monitoring (TDM) is the measurement of drugs in biological fluids (e.g., blood or plasma) to determine achievement of therapeutic exposure during treatment.

Involvement of the clinical microbiologist to measure MICs is equally as important as the pathology laboratory that measures drug concentrations, since **the MIC is essential in establishing the PK/PD relationship** (i.e., the MIC is the denominator used to help define the desired PK exposure necessary to achieve the target PK/PD index).



Importance of accurate biological sampling and drug assays

Sampling of biological fluids for determination of antimicrobial concentrations or the causative pathogen must be performed in a timely manner.

- If **microbiological sampling** occurs after the initial dose of the antimicrobial is administered, the presence of antimicrobial in the sampled biological fluid can inhibit growth of the pathogen, preventing identification and MIC determination. This could result in the unnecessarily prolonged use of empirical broad-spectrum antimicrobials.
- If **biological fluid sampling for TDM measurement** does not occur at the pre-specified time(s), incorrect interpretations can result. For instance, if targeted sampling of a beta-lactam antimicrobial is a trough concentration with the aim of achieving a concentration above the MIC, but sampling occurs post-dosing and results in a high concentration, this may incorrectly suggest a dose decrease is required.

Drug assays are very important to ensure the accuracy of any dose modifications. Inaccuracy of a concentration result could lead to inappropriate dose modification, which exposes the patient to risks of ineffective therapy.

Determining what new dose and administration mode should be used

Dose modification should be performed based on:

- the PK/PD characteristics of the antimicrobial,
- the chosen PK/PD target,
- the concentration and MIC data that are available.

- If an antimicrobial has **concentration-dependent PD**, then increasing the dose rather than the dosing frequency is appropriate (provided the toxicity level is not reached).
- For an antimicrobial with **time-dependency**, increasing the infusion duration or the frequency of dosing is suggested.

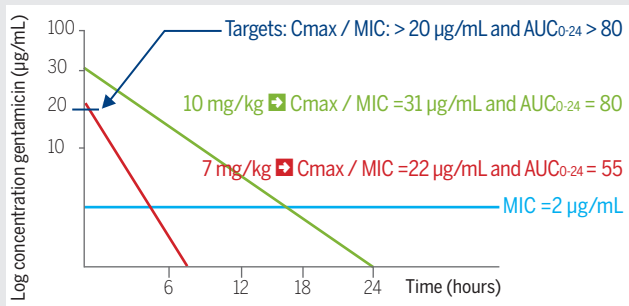
☞ CASE EXAMPLE

A 26-year-old male (80 kg; normal serum creatinine concentration) with febrile neutropenia post allogeneic bone marrow transplant is started empirically on cefepime. His clinical condition rapidly deteriorates with hypotension requiring moderate doses of noradrenaline in the ICU to maintain a targeted mean arterial pressure. Blood culture results are rapidly returned and identify a *Pseudomonas aeruginosa* blood stream infection (cefepime MIC = 8 µg/mL; gentamicin MIC = 2 µg/mL). The treating team requests 3-days of dose-optimized gentamicin therapy combined with a 10-14 day course of dose optimized cefepime.

► **GENTAMICIN** (desired PK/PD targets: peak concentration target >20 µg/mL and AUC₀₋₂₄ target 80 µg.h/mL). Gentamicin is initially dosed at 7 mg/kg (560 mg) and the peak concentration is measured at 22 µg/mL but the AUC₀₋₂₄ is only 55 µg.h/mL.

HOW DO YOU ADJUST THE DOSE?

Answer: for gentamicin, the patient should receive a higher once daily dose to adhere to the concentration-dependent PD. Gentamicin has almost linear PK and so in this case a dose of 10 mg/kg resulted in a peak concentration of 31 µg/mL and a AUC₀₋₂₄ of 80 µg.h/mL.



► **FOR GENTAMICIN:** A dosing with 10 mg/kg allows to be above the targets (C_{max}/MIC and AUC).

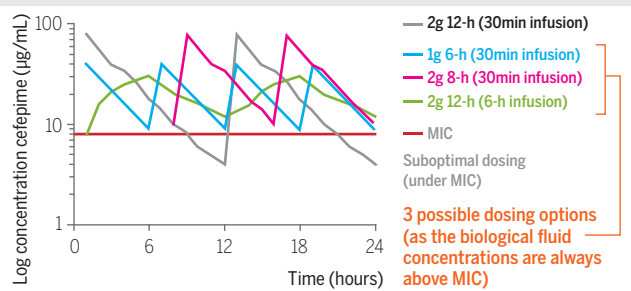
► **CEFEPIME** (desired PK/PD target 100% f_{T>MIC}* – i.e., trough concentration of 8 µg/mL). Cefepime is initially dosed at 2 g every 12 hours (30-minute infusion) and the trough concentration is measured to be 4 µg/mL.

* f_{T>MIC}: percentage of time the free concentration of antibiotic is above the MIC.

HOW DO YOU ADJUST THE DOSE?

Answer: for cefepime, the patient should receive either more frequent dosing or administration by prolonged infusion to adhere to the time-dependent PD. Although different concentration results are possible in different patients, illustrative concentrations that may result in different doses are:

- a more frequent dose of 1 g every 6 hours (30-minute infusion) resulted in a trough concentration of 9 µg/mL;
- a 2 g dose every 8 hours (30-minute infusion) resulted in a trough concentration of 10 µg/mL; and
- a 2 g dose every 12 hours (6-hour infusion) resulted in a trough concentration of 12 µg/mL.



In this case, except for the 2 g dosing in 12 hours, associated with suboptimal dosing (under MIC between 9 and 12 hours), all the 3 other dosing administration modes could be used for a **time-dependent antimicrobial like cefepime**: either lower dose more frequently injected or higher dose... either with continuous infusion or with repeated infusion). **The choice will depend on the infection site, the microorganism and the patient.**

Optimizing drug dosing with the main antimicrobial classes in daily practice

Antimicrobial class	Pharmacodynamic classification	Optimal pharmacodynamics parameter and usual values considered
Aminoglycosides	Concentration dependent	C_{max}/MIC between 8 and 12
Beta lactams	Time dependent	For non-severe infections, $T > MIC$ between 40 and 80%*, Blood concentration > the MIC and preferably >4 times the MIC value for 100% of the dosing interval.
Fluoroquinolones (e.g., ciprofloxacin)	Concentration with time dependence	$AUC/MIC > 30$ for Gram + bacteria and > 125 for Gram - bacteria. $C_{max}/MIC > 10$.
Glycopeptides (e.g., vancomycin)	Concentration with time dependence	$AUC/MIC > 400$

* depending on the microorganism and the antimicrobial: i.e., 40-50% for Gram positive; 60-80% for Gram negative; 50-70% for cephalosporins; 50% for penicillins and 40% for carbapenems

For which patients/drugs should TDM be used?

When a clinician is not confident that a standard dosing regimen will achieve a PK/PD target for a particular patient, **TDM should be considered and supplemented by MIC determination.**

Both are required because they contribute to the numerator (antimicrobial concentration) and to the denominator (MIC) for the PK/PD ratio. Significant variability in one or both of these can lead to **sub-therapeutic antimicrobial exposures.**

Patients in whom antimicrobial concentrations may be difficult to predict for some drugs include:

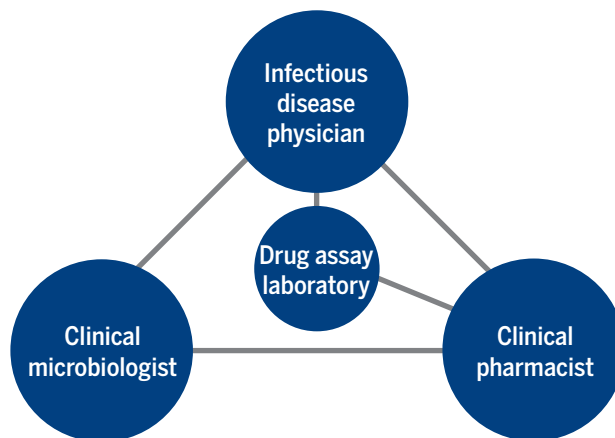
- Trauma
- Sepsis and septic shock
- Meningitis
- Burns
- Neurosurgery
- Pancreatitis
- Obesity
- Cystic fibrosis
- Pediatrics
- Renal failure requiring renal replacement therapy
- Severe liver failure

The most relevant drugs for TDM.

- aminoglycosides
- vancomycin
- teicoplanin
- beta-lactams
- quinolones
- linezolid
- daptomycin
- colistin

However, this list can be expanded to any antimicrobial where a high MIC is present, in order to dramatically increase the likelihood of achieving the PK/PD target.

TDM dose optimization team



Infectious disease physicians, clinical microbiologists and clinical pharmacists are the cornerstones of the TDM team, ensuring appropriate initiation (and completion) of treatment.

The **clinical microbiologist** is a core member of the dose optimization team, since the MIC plays a key role in the adjustment of dosing regimens. In patients with significantly altered PK, dose adjustment may not be needed if the MIC is low. A close relationship with the local clinical microbiologist can facilitate obtaining this information as well as interpreting MIC results relative to MIC breakpoints.

According to the hospital organization, other team members may include nursing or medical staff, pathology laboratory staff and antimicrobial stewardship physicians.

CONCLUSION

The decreasing susceptibility of pathogens worldwide, combined with increasing sickness severity of critically ill patients in particular, presents significant challenges for healthcare providers.

This booklet has provided guidance on how MICs and PK/PD can be used to guide and optimize antimicrobial therapy, which should increase the likelihood of successful patient treatment, and may even reduce the emergence of resistant superbugs.

PK/PD is central to antimicrobial dosing optimization. Predicting altered PK is vital to determine if target concentration/MIC ratios can be achieved in patients, thereby maximizing the chances of clinical cure.

The MIC plays a most important role in choosing the most effective therapy. The MIC can help healthcare providers determine:

- if they should choose a different antimicrobial because of potentially inadequate therapy;
- whether the same antimicrobial can be used, but at a higher dose;
- or whether the same antimicrobial can be used, but at a lower dose to reduce the likelihood of drug toxicity.

In an era of increasingly difficult-to-treat patients, implementation of antimicrobial stewardship programs, combined with a knowledge and understanding of MICs, altered PK and PK/PD can help optimize therapies and dramatically improve patient outcomes.

GLOSSARY

Area under the Curve (AUC)

Area defined by the plasma drug concentration versus time. It describes and quantifies the plasma concentration-time profile of an administered drug.

AST

Antimicrobial Susceptibility Testing.

Breakpoint

A chosen concentration of an antimicrobial which defines whether a microorganism species is susceptible or resistant to the antimicrobial.

Concentration

The amount of a specified substance in a unit amount of another substance.

Dose

Amount of a medicine, drug.

Dosing

Specified quantity of a therapeutic agent, such as medicine, prescribed to be taken at one time or at stated intervals.

Minimum Bactericidal Concentration (MBC)

The lowest concentration of an antimicrobial that kills a microorganism (decreases initial inoculum by at least 99.9%).

Minimum Inhibitory Concentration (MIC)

The lowest antimicrobial concentration that inhibits the growth of bacteria/fungi. It is used to measure the susceptibility of the pathogen to an antimicrobial.

Minimum Inhibitory Concentration 50 (MIC 50)

The lowest antimicrobial concentration that inhibits the growth of 50% of the strains of a particular bacterial/fungal species, marker of natural susceptibility of the species to an antimicrobial

Minimum Inhibitory Concentration 90 (MIC 90)

The lowest antimicrobial concentration that inhibits the growth of 90% of the strains of a particular bacterial/fungal species, marker of acquired resistance of the species to an antimicrobial.

Pharmacokinetics (PK)

The relationship between the dose of drug given and the resulting concentration in the host.

Pharmacodynamics (PD)

The interaction between drug concentration and the pharmacological effect.

Pharmacokinetics/ Pharmacodynamics (PK/PD)

The relationship between the dose of drug given and the pharmacological effect - with the concentration of the drug being the intermediary determinant factor of effect.

Susceptible Dose Dependent (SDD)

A new category for antimicrobial susceptibility testing. It implies that the susceptibility of a pathogen is dependent on the dosing regimen used in the patient.

Therapeutic drug monitoring (TDM)

The measurement of drugs in biological fluids (e.g., blood or plasma).

Therapeutic index

The ratio between the toxic dose and the therapeutic dose of a drug, used as a measure of the relative safety of the drug for a particular treatment.

Volume distribution (Vd)

The theoretical volume of fluid into which a drug appears to distribute in order to give the concentration equal to that measured in plasma.

Wild Type (WT)

A microorganism is defined as wild type for a species by the absence of acquired and mutational mechanisms of resistance to the antimicrobial. The wild type includes species with or without intrinsic resistance.

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9 KEY POINTS

Optimizing Antimicrobial Prescribing through Drug Dosing and MIC

1

What is a Minimum Inhibitory Concentration (MIC)?

- The MIC is the lowest antimicrobial concentration that inhibits the growth of the microorganisms. The lower the MIC, the higher the chance of therapeutic success.
- It is a quantitative measure which depends on method used (need for standardization), type of antimicrobial, microbial genus, species and isolate.

2

Why measure MIC?

- Measuring MIC helps to characterize the strains as susceptible (S), intermediate (I) or resistant (R).
- It allows the healthcare provider to predict *in vivo* (patient) response based on *in vitro* (laboratory) results.
- Knowledge of the MIC is important for guiding the choice of drug and to personalize antimicrobial dosing, taking into account the susceptibility of the pathogen, combined with patient and drug parameters.

3

When to perform MIC testing?

- Multi-resistant microorganisms including extended spectrum beta-lactamases (ESBLs)
- Immunocompromised and critically ill patients
- Challenging pathogens (i.e., *P. aeruginosa*, *A. baumannii*)
- When the susceptibility testing method used is not accurate enough
- When personalization of antimicrobial prescription is needed

4

How to optimize antimicrobial prescription?

- By simultaneously measuring the antimicrobial concentration and determining the microorganism's MIC to the antimicrobial.
- These two pieces of information will enable personalized dosing for the patient, to reach the fixed target and optimally treat the patient.

5 What is Therapeutic Drug Monitoring (TDM)?

- TDM refers to the measurement of drugs in biological fluids (e.g., blood or plasma).

The antimicrobial dose depends on multiple parameters:

- **the patient** (e.g., clinical pathology, infection site(s), comorbidities).
- **the antimicrobial** (e.g., activity spectrum and PK).
- **the pathogen** (e.g., antimicrobial resistance).
A key parameter related to the pathogen is the MIC.

6 Why use an optimized antimicrobial prescription?

- Personalized antimicrobial dosing enables optimization of antimicrobial administration.
- It also helps ensure a high probability of therapeutic success with limited toxicity and helps reduce emergence of resistance.

7 How to adapt dosing?

- Dosing adaptation is made either by modifying the dose (i.e., increasing antimicrobial concentration) or the frequency of administration or the administration mode (continuous infusion vs intermittent infusion).
- It requires simultaneous antimicrobial serum (or other body fluid) concentrations through TDM and measurement of the microorganism MIC to the antimicrobial.

➤ **Time-dependent antimicrobials** (e.g., beta-lactams)
 ➤ preferred index to consider is **Time the unbound (free) serum concentration exceeds MIC ($f T > MIC$)**

➤ **Concentration-dependent antimicrobials** (e.g., aminoglycosides) optimal index to consider is **Maximum serum concentration (C_{max}/MIC)**

➤ **Time-and concentration-dependent antimicrobials** (e.g., glycopeptides, fluoroquinolones, linezolid) → optimal index to consider is **Area Under the Curve (AUC/MIC)**

8 When to perform TDM and MIC determination?

- Drugs with narrow therapeutic index (e.g., vancomycin, aminoglycosides), therapeutic response not obvious or if PK is strongly altered.
- Decreasing susceptibility of pathogens, which may require higher antimicrobial doses to achieve therapeutic exposures that optimize their effect.

9 Who should benefit from TDM and MIC determination?

Patients with:

- **Acute pathophysiological alterations** (i.e., patients in ICU, with sepsis and septic shock, transplant, febrile neutropenia, trauma, burns, acute kidney or liver failure).
- **Modified baseline physiology** (i.e., obesity, cystic fibrosis, elderly or pediatric patients).



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