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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We wish to thank Prof. Roberts for sharing his valuable knowledge on therapeutic drug monitoring and antimicrobial prescribing, and for his dedicated involvement in this booklet.

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 48 - 51.

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WHAT IS THE RELEVANCE OF DOSE OPTIMIZATION?

1 Antimicrobial resistance

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", devised by David Looke and John Ferguson in 2005. [1]

M	**M**icrobiology guides therapy wherever possible
I	**I**ndications should be evidence based
N	**N**arrowest spectrum required
D	**D**osage appropriate to the site and type of infection
M	**M**inimize duration of therapy
E	**E**nsure monotherapy in most cases

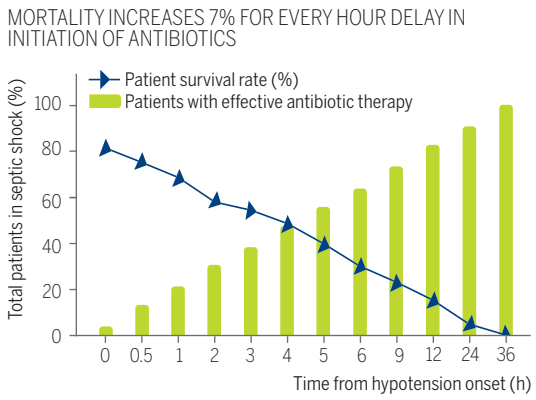
Antimicrobial therapy is based on the selection of the most appropriate antimicrobial combined with an effective dose and duration of therapy.

2 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 1)**

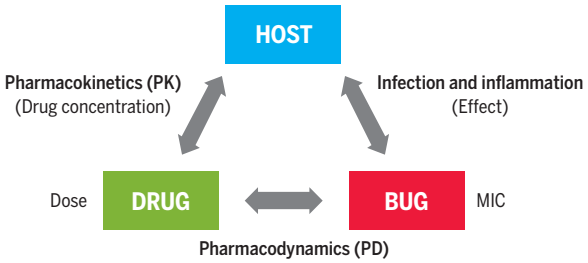
Figure 1: Fast effective antimicrobial therapy increases survival rate
Adapted from Kumar A *et al. Crit Care Med*. 2006;34(6):1589-96 [2]



3 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 2)**

Figure 2: Patient, pathogen and antimicrobial interactions



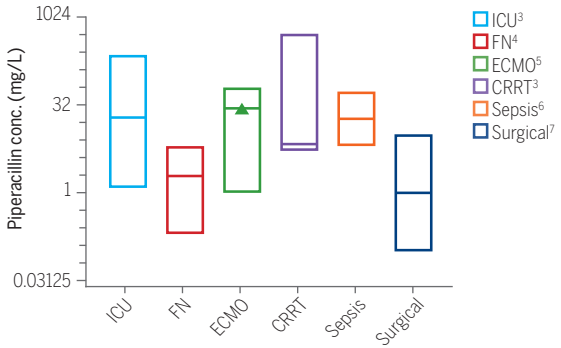
Dosing regimens for a specific drug are defined for minor or moderate infections. However, antimicrobial pharmacokinetics (PK†) can be extremely different in cases of severe infection.

*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.

For example, in **critically ill patients, there is a significant variability of antimicrobial concentrations in serum (organ failure greatly affects PK).**

Figure 3: Piperacillin concentration in different patient cohorts
Median and range are presented. The y-axes are presented on a log2 scale
Figure created from various data [3-7]



*ICU: general intensive care unit cohort, FN: febrile neutropenia, ECMO: extracorporeal membrane oxygenation, CRRT: continuous renal replacement therapy

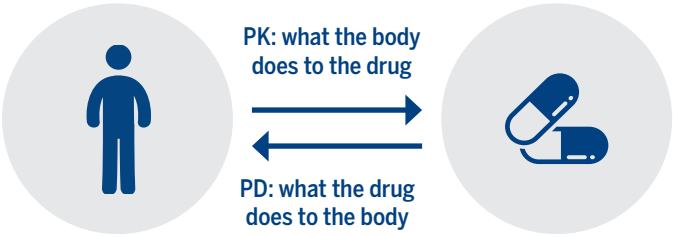
Dosing regimens are developed and licensed in specific patient populations which do not encompass the range of scenarios that the drug may be used in. In **Figure 3**, the different trough concentrations of piperacillin in various patient groups are presented, highlighting the need for population-specific and patient-specific dosing considerations.

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.

4 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.

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.

5 Antimicrobial pharmacokinetic characteristics

PK variations may be induced by the **hydrophilic** or **lipophilic** nature of an antimicrobial[8], as well as by organ failure which can result from severe infections.

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.

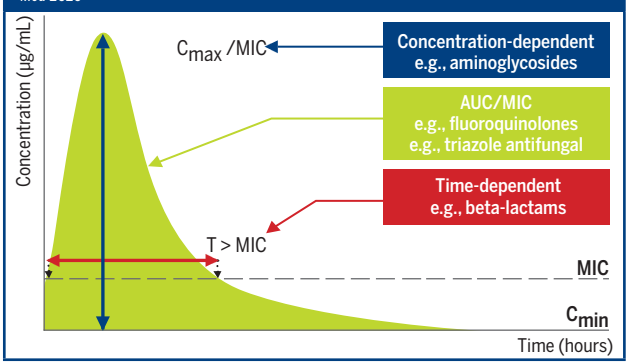
For both hydrophilic and lipophilic drugs, **changes in kidney and/or liver function can affect antimicrobial clearance.** However, the effects appear to be far greater for renally cleared drugs.[15]

6 Antimicrobial pharmacodynamic classifications

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

Figure 4: 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[9] & Roberts and Abdul-Aziz, *Intensive Care Med* 2020[10]



- **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 5: Categorization of antimicrobials according to PD characteristics

Adapted from Roberts and Lipman, *Crit Care Med*.2009[9] & Roberts and Abdul-Aziz, *Intensive Care Med* 2020[10]

Antimicrobials	β-lactams Flucytosine Lincosamides Oxazolidinones	Aminoglycosides Fluoroquinolones Metronidazole	Aminoglycosides Daptomycin Echinocandins Fluoroquinolones Glycopeptides Oxazolidinones Polymyxins Triazoles
PD kill characteristics	Time-dependent	Concentration-dependent	Concentration-dependent with time-dependence
Optimal PD index	T > MIC	C_{max} / MIC	AUC_{0-24} / MIC

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.

Prolonged infusion has been shown to successfully increase the proportion of patients achieving effective concentrations and also reduced hospital mortality in sepsis.[11,12]

7 What is therapeutic drug monitoring (TDM)?

Therapeutic drug monitoring (TDM) refers to the measurement of drugs in biological fluids (e.g., blood or cerebrospinal fluid). 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 non-standard antimicrobial doses to achieve therapeutic exposures that maximize treatment success.

Figure 6: Criteria for using TDM

DRUG FACTORS (must have all of these)	• 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)	• Suspected drug interactions • Suspected drug adverse effects/toxicity • Suspected drug abuse • Unexplained failure of therapy • Suspected noncompliance
PATHOGEN FACTORS	• Multidrug-resistant organisms (or increased MIC for several antimicrobials)[13]

[a] 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.

8 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 who have received high volumes of resuscitation fluids, have renal or liver (modified drug metabolism) injury or multiple therapies (drug interactions) could also have altered drug concentrations.

Figure 7: Main patient populations with altered pharmacokinetics

Source of altered pharmacokinetics	Patient population
Acute pathophysiology	• **Sepsis and septic shock** (frequent organ failure). These patients include those with: **Augmented renal clearance (ARC)**, an elevated creatinine clearance (>130 mL/min) associated with increased renal drug clearances and low antimicrobial concentrations[14] **Renal replacement therapy (RRT)** which is associated with highly variable drug concentrations, both sub- and supra-therapeutic[3] **Extracorporeal membrane oxygenation (ECMO)** which has variable effects on concentrations of different drugs causing them to be commonly sub- or supra-therapeutic[5] • **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	• **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

9 The effect of altered PK on dose requirements

In critical illness, dysfunction in organ systems can lead to significantly altered antibiotic concentrations compared to those in non-critically ill patients. Without appropriate dose adjustments, these variations in drug concentrations can increase the risk of clinical failure, the development of antimicrobial resistance, or other complications.

The effects of altered pathophysiology on PK are summarized in **Figure 8**, which shows that effects on drug clearance and Vd can both lead to altered concentrations and therapeutic effects.

Figure 8: Pathophysiological effects on pharmacokinetics in critically ill patients
Adapted from Roberts JA *et al. Lancet Inf Dis.* 2014;14:498-509.[15]

Pathophysiology	Impact on PK	Effect on plasma concentration
RENAL AND/OR HEPATIC DYSFUNCTION	↑ VOLUME OF DISTRIBUTION ↓ CLEARANCE	↑ PLASMA CONCENTRATIONS
ORGAN SUPPORT RTT and/or ECMO	↑ VOLUME OF DISTRIBUTION ? CLEARANCE	↑ OR ↓ PLASMA CONCENTRATIONS
NO ORGAN DYSFUNCTION	UNCHANGED VOLUME OF DISTRIBUTION and CLEARANCE	"NORMAL" PLASMA CONCENTRATIONS
HYPERDYNAMIC ↑ Cardiac output	↑ CLEARANCE	↓ PLASMA CONCENTRATIONS
ALTERED FLUID BALANCE Third spacing and/or altered protein binding	↑ VOLUME OF DISTRIBUTION	↓ PLASMA CONCENTRATIONS

RRT – renal replacement therapy
ECMO – extracorporeal membrane oxygenation
? CLEARANCE – possible increased clearance

WHAT IS THE USEFULNESS OF THE MIC?

1 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**.

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 leading to a higher risk of clinical failure.

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 **Figure 9**.
- **customize antimicrobial dosing** taking into account the pathogen's susceptibility (MIC) as well as the patient's profile and drug exposures (concentrations) through the use of TDM where available. **The MIC helps define the target exposure that an optimized antimicrobial dosing regimen should reach**. Antimicrobial TDM has seen significant growth in clinical use over the past decade, emphasazing the need for accurate susceptibility testing to ensure that patients receive the best possible treatment.[16]

Figure 9 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 10 highlights the increased risk of mortality in the presence of higher MIC pathogens. This supporting the need for a greater PK/PD approach to antimicrobial dosing.

Figure 9: Relationship between MIC and patient outcome
Adapted from Tam V *et al. Clin Infect Dis.* 2008;46:862-7.[17]

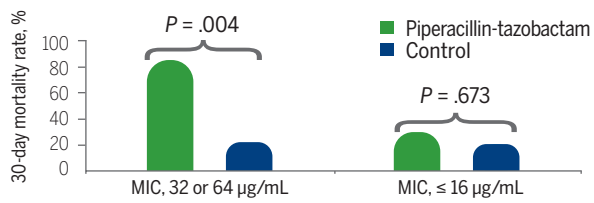


Figure 10: Meta-analysed data describing the effect of pathogen MIC for Enterobacterales and non-fermenters
Adapted from Falagas *et al. Antimicrob Agents Chemother.*2012;56(8):4214–4222.[18]

	High MICs		Low MICs		Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**M-H. Random. 95% CI**
1- Enterobacteriaceae					
Anthony 2008	2	2	0	3	
Goethaert 2006 C	2	3	7	13	
Goethaert 2006 CA	0	4	6	16	
Paterson 2001	3	7	1	11	
Qureshi 2011	1	1	3	15	
Rodriguez-Bano 2012 A/C	2	25	1	12	
Rodriguez-Bano 2012 P/T	3	13	1	22	
Subtotal (95% CI)		**55**		**92**	
Total events	13		19		
Heterogeneity: Tau² = 0.07; Chi² = 6.52, df = 6 (P = 0.37); I² = 8%					
Test for overall effect: Z = 2.11 (P = 0.03)					
2- Non-fermentative					
Anthony 2008	0	2	0	2	
Bhat 2009	9	19	4	17	
Tam 2008	6	7	3	10	
Subtotal (95% CI)		**28**		29	
Total events	15		7		
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.62); I² = 0%					
Test for overall effect: Z = 2.45 (P = 0.01)					

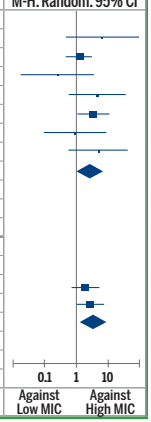
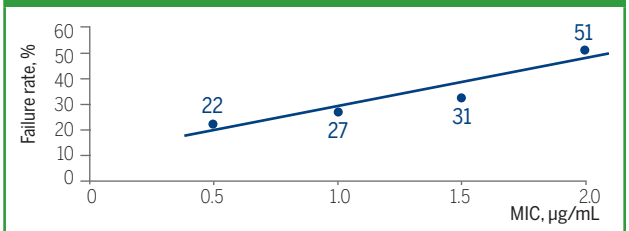


Figure 11 shows a direct relationship between vancomycin MIC and treatment failure rates in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infection.

Figure 11: Relationship of MIC to vancomycin treatment failure in patients with MRSA infections
Adapted from Stevens DL. Clin Infect Dis. 2006;42:S51–7.[19]



2 Methods for measuring MICs and Antimicrobial Susceptibility Testing (AST)

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

Antimicrobial activity can be measured using a wide variety of different *in vitro* methods and commonly generates **a quantitative estimate of antimicrobial activity**, MICs. The measurement units for MICs are micrograms per milliliter (µg/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 (ETEST®)

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 µg/mL that shows the conventional doubling dilutions as well as values in between these two-fold dilutions (e.g., 0.75 µg/mL). MIC ranges for ETEST® products span 15 two-fold dilutions. Strips containing 3 different concentration ranges are also available (0.016-256 µg/mL,0.002-32 µg/mL, and 0.064-1024 µg/mL) depending on the agent. These ranges cover the clinically significant MIC values of most antimicrobial agents and organism groups.

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.**

Automated AST systems

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

Recent developments are providing laboratories with more timely AST results. These have been most frequently developed for use on positive blood culture broths.

One such example (VITEK® REVEAL™, bioMérieux) uses small molecule sensors to detect volatiles released by bacteria as they grow. By assessing presence or absence of growth in different concentrations of antibiotics, a MIC can be determined within 6 hours on average.[20]

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 automated AST results may not be reliable for certain bacterial species (e.g., *Pseudomonas, Burkholderia*...)

3 The epidemiological cut-off values

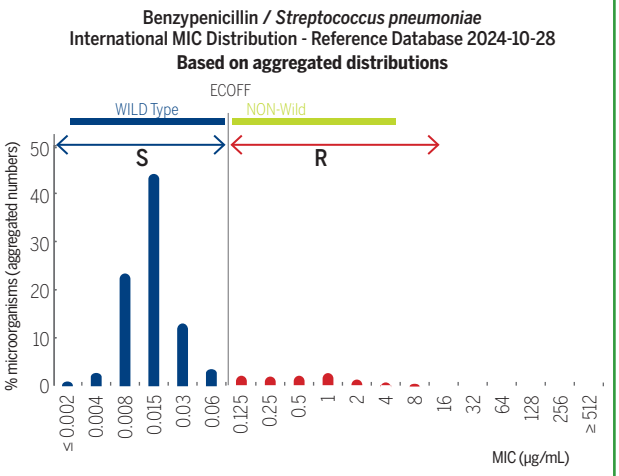
The epidemiological cut-off allows the differentiation of two populations according to MIC values as "wild type" and "non-wild type".

Bacterial phenotypes can be segregated into two types based on their antimicrobial resistance characteristics.

- **The "wild type" or intrinsic resistance phenotype (or inherent or innate or natural resistance)** refers to the bacterial species in the 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.[21]
- **The "non-wild type"** isolates have **acquired resistance** and therefore reduced susceptibility to antimicrobial agents.

Figure 12: Example of Epidemiological Cut-off 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/][22]



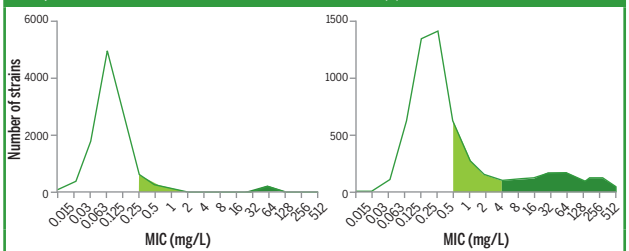
Breakpoints	ECOFF
S ≤ 0.06 and R > 0.06	0.06

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

The epidemiological cut-off value, referred to as "ECOFF" by EUCAST or "ECV" by CLSI, assists in the establishment of clinical breakpoints (see next chapter). In the absence of a clinical breakpoint, these values may serve as a useful surrogate. However, **they should be used with caution in clinical practice, as they only differentiate bacterial subpopulations and do not account for drug dosing levels or clinical outcome data.**

Figure 13: Interpreting ECOFFs given different MIC distributions

Adapted from Mouton *et al. J Antimicrob Chemother.* 2018;73(3):564-568.[23]



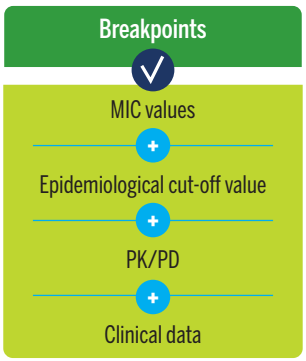
Schematic MIC distributions. White area, MICs with a wild-type phenotype as defined by EUCAST:
MICs with a low-level resistance phenotype
MICs with a high-level resistance phenotype
(left) ECOFF = 0.25 mg/L, resistance rare.
(right) ECOFF = 0.5 mg/L, resistance common.

The left panel shows a predominant low-level resistance with an epidemiological cut-off value that would correspond to 0.25 µg/mL. The right hand panel has more resistance present, including a high-level resistance phenotype, with an associated epidemiological cut-off value of 0.5 µg/mL.

4 What are clinical MIC breakpoints?

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

Clinical breakpoints are determined based on pathogen susceptibility, clinical outcome data, and pharmacokinetics, including antimicrobial concentrations at the infection site. Consequently, where available, they provide a more reliable guide for selecting antimicrobials because they incorporate all these critical factors.



Agencies such as **EUCAST** and **CLSI** (depending on the region) have defined breakpoints categories as follows:

EUCAST breakpoints categories:

S: Susceptible (high likelihood of therapeutic success using a standard dosing regimen of the agent)

I: Susceptible, increased exposure (high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection)

R: Resistant (high likelihood of therapeutic failure even when there is increased exposure)

ATU: Area of technical uncertainty (when breakpoint is in a place where reproducible interpretation cannot be achieved)

CLSI breakpoints categories (CLSI M100 2024):[24]

S: Susceptible (isolates are inhibited by the usually achievable concentrations of antimicrobial agent when the dosage recommended to treat the site of infection is used)

I: Intermediate (a buffer zone for technical uncertainty)

I^: Intermediate^ (zone to highlight those antimicrobial agents that concentrate in urine and the likelihood of treatment success when the agent is prescribed for uncomplicated urinary tract infections)

SDD: Susceptible dose-dependent (isolates are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and/or that demonstrate MIC that fall in the range in which specific microbial resistance mechanisms are likely)

R: Resistant (the minimum MIC of the antimicrobial is above a specific threshold, meaning that the organism is unlikely to be inhibited by standard doses of the drug used in therapy)

NS: Non-susceptible (isolate for which only a susceptible breakpoint is designated because of the absence or rare occurrence of resistant strains, or for which the MICs are above the value indicated for the susceptible breakpoint)

Referring back to **Figure 13**, the clinical breakpoint may be defined, but in this case, depends on the site of infection. Therefore, the clinical breakpoint aligns with the ECOFFs for meningitis and non-meningitis indications. The meningitis indication accounts for reduced antimicrobial concentrations distributing into the site of infection.

Breakpoints are not always available for different infection scenarios, in which case individual MIC testing is recommended.

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

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

5 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.

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 likley to be.

CASE EXAMPLE

A 56-year-old female (95 kg; history of insulin-dependent diabetes and hypertension) is admitted to the Emergency Department and diagnosed with healthcare associated pneumonia (recent hospital visit within 30 days).

She is empirically given piperacillin-tazobactam 4.5 g intravenously (IV) every 6 hours and a one-time dose of gentamicin (IV 340 mg). *Pseudomonas aeruginosa* is identified in blood and sputum as the causative pathogen. Piperacillin-tazobactam treatment is maintained, although on day 3 of therapy her symptoms deteriorate with an increasing oxygen requirement and need for fluid boluses (but not vasopressors) for blood pressure support.

MIC for piperacillin-tazobactam is found to be 16 µg/mL (other MICs, ciprofloxacin 0.125 µg/mL; meropenem 1 µg/mL; cefotaxime 8 µg/mL). A measured creatinine clearance was obtained, indicating a value of 183 mL/min.

WHAT SHOULD YOU DO?

16 µg/mL is above the MIC that piperacillin-tazobactam is likely to be able to cover. Your options are the following:

- **increase the dose** to 4.5 g IV every 4 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.

Given the severe symptoms, 400 mg IV every 8 hours is recommended and would likely lead to sufficient ciprofloxacin concentrations in this case.

The high c†/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**.

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	c/MIC Index
		Breakpoints EUCAST (≤)	
Ciprofloxacin	**0.125**	**0.5**	**4**
Cefotaxime	8	8	1
Meropenem	1	2	2
Piperacillin-tazobactam	16	16	0.5

Calculation of c/MIC index - CLSI

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

6 The importance of the MIC to define optimal drug dosing regimens

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 - S29, 2019):

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 12h.**
- **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**

However, reports of toxicity with higher cefepime exposures have been reported numerous times in recent years, therefore, its use in renal dysfunction must be cautious.

* 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.[25] For example, a German study of predominantly Gram negative pathogens (e.g., *E. coli*, *Klebsiella* spp.) found that the MIC_{90} for carbapenem antimicrobials was 4-8 times higher in the ICU compared with patients based in other wards.[26]

Measuring MICs in special patient groups is useful for detecting pathogens with higher MICs.[27] 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 and the need for this may be strengthened if high drug clearance is suspected in the patient.

Dosing information is available in pharmacokinetic guides (e.g., 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.

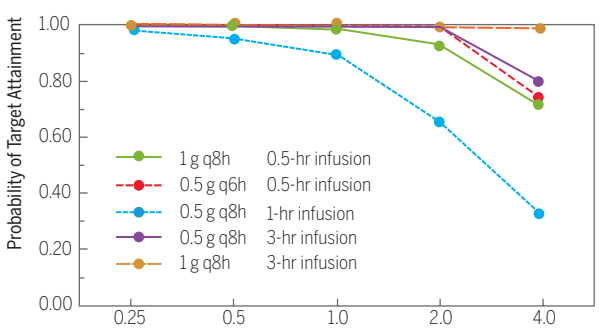
WHAT SHOULD YOU DO?

- 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 trough concentration of **4 µg/mL** is required, which would indicate 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 **2 g every 8 hours** is sufficient to achieve the target exposure in this patient. If a continuous infusion is used rather than an intermittent infusion, a dose of 2 g given as an 8-hour infusion every 8 hours (equivalent to 6 g per day continuous infusion – 250 mg/hour infusion rate) would give a steady-state concentration of 9 µg/mL.

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 (Figure 14):

- **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).

Figure 14: Medication Administration: Extended-Infusion Meropenem Protocol
Adapted from Stanford Hospital and Clinics Pharmacy Department Policies and Procedures (02/2016)



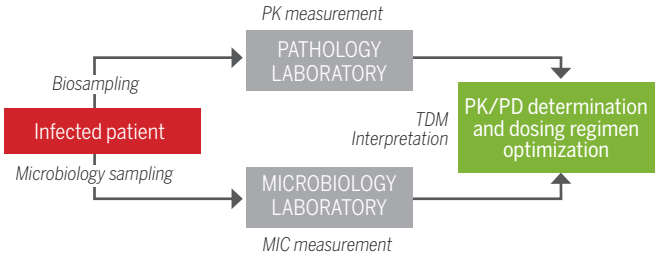
The lower the MIC, the better the probability of PK/PD target attainment:

- **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 1 g every 8 hours during a 3-hr infusion will reach the targeted concentration.

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).



1 Importance of accurate biological sampling and drug assays

Sampling of biological fluids for measurement of antimicrobial concentrations or the causative pathogen must be performed at an appropriate time in the dosing interval and results returned 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, reducing the likelihood of the pathogen identification or its susceptibility 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 appropriate time(s), relevant to the PK/PD index, 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.

Accurate 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 or harmful therapy.

2 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 (targets may vary depending on site of infection),**
- **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 36-year-old male (76 kg; normal serum creatinine concentration) with a history of epilepsy (treated with valproate) develops febrile neutropenia post allogeneic bone marrow transplant. The patient is started empirically on cefepime. He has a previous history of *Pseudomonas aeruginosa* pneumonia caused by an isolate resistant to piperacillin-tazobactam. 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 with MIC gradient test performed **(ciprofloxacin MIC = 0.125 µg/mL, gentamicin MIC = 1 µg/mL)**.

Meropenem was not selected because of a drug interaction with valproate. The treating team requests 3-days of dose-optimized **gentamicin therapy** combined with a 7-10 day course of dose **optimized ciprofloxacin**.

GENTAMICIN

- Therapeutic Drug Monitoring Targets (TDM), (desired PK/PD):
  Peak concentration target >20 µg/mL and $AUC_{0\text{-}24}$ target 80 µg.h/mL.
  Predefined toxic concentrations to avoid: trough concentration >5 µg/mL or $AUC_{0\text{-}24}$ >120 µg.h/mL
- Treatment:
  Gentamicin is initially dosed at 7 mg/kg (560 mg)
  Therapeutics Drug Monitoring results: peak concentration = 22 µg/mL; $AUC_{0\text{-}24}$ = 55 µg.h/mL.

How do you adjust the dose?

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 an $AUC_{0\text{-}24}$ of 80 µg.h/mL.

CIPROFLOXACIN

- Therapeutic Drug Monitoring targets (TDM)(desired PK/PD: $AUC_{0\text{-}24}$/MIC of 125 – $AUC_{0\text{-}24}$ of 10 given MIC is 0.125 µg/mL.
- Treatment:
  Ciprofloxacin is initially dosed at 400 mg Intra-Venous (IV) every 12 hours (60-minute infusion).
  On day 2, two samples being taken at 2 and 6 hours (post-commencement of infusion) with an $AUC_{0\text{-}12}$ calculated by the ward pharmacist as 3.8 µg.h/mL ($AUC_{0\text{-}24}$ of 7.6).

How do you adjust the dose?

For ciprofloxacin, the patient should receive a higher daily dose as either 600 mg IV every 12 hours or 400 mg IV every 8 hours.

ON FOLLOWING DAYS

- **On day 3**, you change the dose to 600 mg IV every 12 hours (60-minute infusion) with two TDM samples being taken at 2 and 6 hours (post-commencement of infusion) with an $AUC_{0\text{-}12}$ calculated by the ward pharmacist as 7.1 µg.h/mL ($AUC_{0\text{-}24}$ of 14.2 = $AUC_{0\text{-}24}$/MIC of 142 which exceeds the efficacy target of 125).
- **On day 5**, the patient develops an acute kidney injury with an eGFR of 34 mL/min. TDM is requested and two TDM samples are taken at 2 and 6 hours (post-commencement of infusion) with an $AUC_{0\text{-}12}$ calculated by the ward pharmacist as 26.1 µg.h/mL ($AUC_{0\text{-}24}$ of 52.2 = $AUC_{0\text{-}24}$/MIC of 522 which exceeds the efficacy target of 125 and a possible toxicity threshold of 500).

  In response you decrease the dose to 200 mg IV every 12 hours.
- **On day 8**, due to the slow progression to pharmacokinetic steady-state with the patients persisting acute kidney injury. You repeat TDM on day 8 and request two TDM samples to be taken at 2 and 6 hours (post-commencement of infusion) with an $AUC_{0\text{-}12}$ calculated by the ward pharmacist as 8.8 µg.h/mL ($AUC_{0\text{-}24}$ of 17.6 = $AUC_{0\text{-}24}$/MIC of 176 which exceeds the efficacy target of 125 and is below a possible toxicity threshold of 500).

  The dose is maintained and the patient completes a 10-day course.

3 Optimizing drug dosing with the main antimicrobial classes in daily practice

Antimicrobial class	Pharmaco-dynamic classification	Optimal pharmacodynamics parameter and usual values considered
Aminoglycosides	Concentration dependent	Cmax/MIC between 8 and 12.
Beta-lactams	Time dependent	For non-severe infections, *f*T>MIC between 40 and 100%*, 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. Cmax/MIC > 10.
Glycopeptides (e.g., vancomycin)	Concentration with time dependence	AUC/MIC 400-600.

*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. In critical illness, a 100% *f*T>MIC is recommended as a minimum exposure.[10]

4 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.**

For many antimicrobials, **MIC determination is useful** because where a highly susceptible pathogen is present, the likelihood of underdosing is very low, meaning that the value of TDM in those cases lies in avoidance of drug toxicity.

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

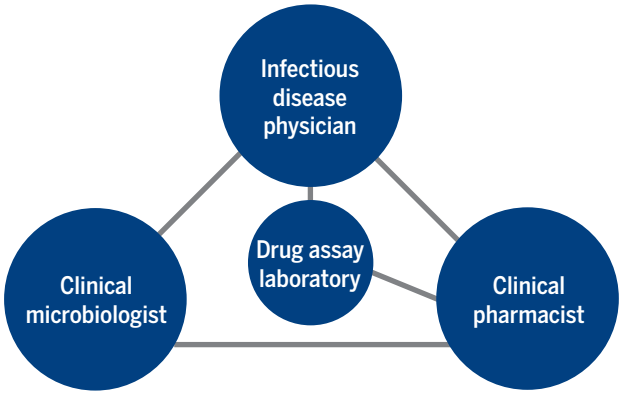
- Trauma
- Sepsis and septic shock
- Meningitis
- Burns
- Neurosurgery
- Pancreatitis
- Obesity
- Cystic fibrosis
- Pediatrics
- Renal failure requiring renal replacement therapy
- Severe liver failure

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.

5 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.

They require support from the laboratory bioanalysis team, which measures drug concentrations, to communicate any assay considerations.

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. There is clear evidence that optimized antimicrobial dosing can save lives in critically ill patient populations, such as those with sepsis.

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.

ANTIMICROBIAL SUSCEPTIBILITY TESTING (AST)
In vitro measure of bacterial response to an antimicrobial agent that predicts therapeutic efficacy.

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 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.

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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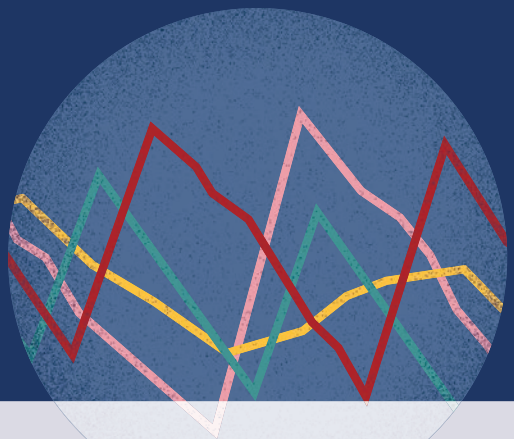
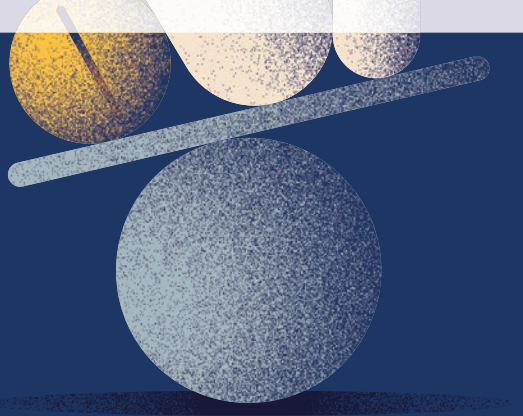


10 KEY POINTS

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 ARE S, I, R SUSCEPTIBILITY TESTING RESULTS SUFFICIENT?

An S, I, R result is acceptable in most routine cases:

- For outpatients
- For body sites where antimicrobial concentrations easily exceed the MIC (i.e., urine)
- For orally treated patients
- For non-immunocompromised patients
- When treatment failure is unlikely to be life-threatening

4 WHEN TO PERFORM MIC TESTING?

When S, I, R are not sufficient:

- Multi-resistant micro-organisms including extended spectrum beta-lactamases (ESBLs)
- Immuno-compromised 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

5 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.

6 WHAT IS THERAPEUTIC DRUG MONITORING (TDM)?

- TDM refers to the measurement of drugs in biological fluids.
- **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.

7 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.

8 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 (fT>MIC)**

Concentration-dependent antimicrobials (e.g., amino-glycosides) optimal index to consider is **Maximum serum concentration (Cmax/MIC)**

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

9 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.

10 WHO SHOULD BENEFIT FROM TDM AND MIC DETERMINATION?

- **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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