A béta-laktám antibiotikumok gyógyszerszint monitorozás melletti alkalmazása

Háttér, indokoltság, gyakorlati szempontok

Karvaly Gellért Balázs

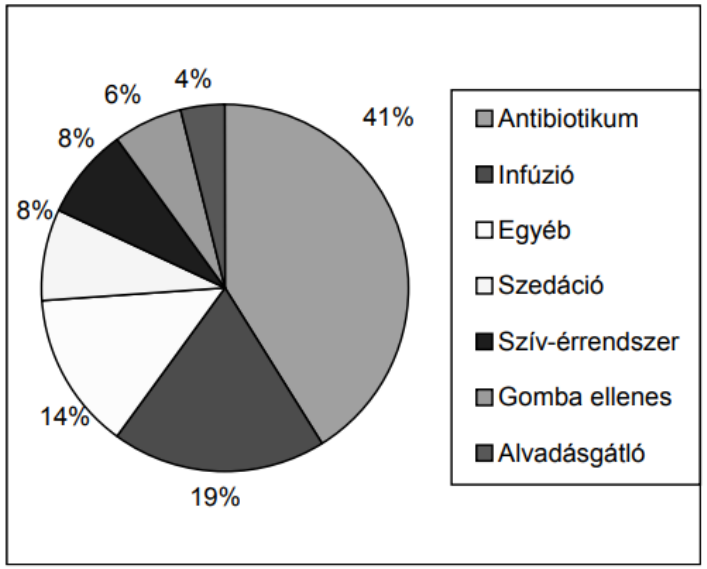
Néhány statisztikai adat

- 1 betegnap költsége az ITO-n: **4300 USD** (USA, 2010); **4200-4400 AUD** (Ausztrália, 2014); **1168-2025 EUR** (EU, 2006-2007)
- A gyógyszerköltség a teljes napi költség 40-50%-át, a laborköltség a teljes napi költség 10-15%-át teszi ki

1 USD = 341,06 HUF
1 AUD = 227,44 HUF
1 EUR = 369,89 HUF

- 88 ország 1150 centrumában végzett felmérés:
  - Az ITO-n kezelt betegek körében a gyanított vagy igazolt infekció prevalenciája kb. 50%, ennek kb. 40%-a nozokomiális eredetű
  - A betegek kb. 70%-a kap legalább egyféle antibiotikumot, **leggyakrabban béta-laktámot**

1. sz. ábra **A Top 10 gyógyszerek eloszlása csoportokra bontva Magyarországon**



https://www.sccm.org/Communications/Critical-Care-Statistics
Hicks P et al. *Med J Aust* **2019**;*211*:324-325.
Tan SS et al. *Value Health* **2012**;*15*:81-86.
Vincent JL et al. *JAMA* **2020**;*323*:1478-1487
Csomós Á: Költségelemzés az intenzív osztályon. Egyetemi doktori (PhD) értekezés (2008)

AMERICAN THORACIC SOCIETY DOCUMENTS

Antibiotic Stewardship in the Intensive Care Unit

An Official American Thoracic Society Workshop Report in Collaboration with the AACN, CHEST, CDC, and SCCM

Richard G. Wunderink, Arjun Srinivasan, Philip S. Barie, Jean Chastre, Charles S. Dela Cruz, Ivor S. Douglas, Margaret Ecklund, Scott E. Evans, Scott R. Evans, Anthony T. Gerlach, Lauri A. Hicks, Michael Howell, Melissa L. Hutchinson, Robert C. Hyzy, Sandra L. Kane-Gill, Erika D. Lease, Mark L. Metersky, Nancy Munro, Michael S. Niederman, Marcos I. Restrepo, Curtis N. Sessler, Steven Q. Simpson, Sandra M. Swoboda, Christina Vazquez Guillamet, Grant W. Waterer, and Curtis H. Weiss; on behalf of the American Thoracic Society, Centers for Disease Control and Prevention, American Association of Critical-Care Nurses, American College of Chest Physicians, and Society of Critical Care Medicine

THIS OFFICIAL WORKSHOP REPORT OF THE AMERICAN THORACIC SOCIETY WAS APPROVED BY THE AMERICAN THORACIC SOCIETY FEBRUARY 2020, AND BY THE AMERICAN ASSOCIATION OF CRITICAL-CARE NURSES, THE AMERICAN COLLEGE OF CHEST PHYSICIANS, THE CENTERS FOR DISEASE CONTROL AND PREVENTION, AND THE SOCIETY OF CRITICAL CARE MEDICINE JANUARY 2020

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Abstract

Intensive care units (ICUs) are an appropriate focus of antibiotic stewardship program efforts because a large proportion of any hospital's use of parenteral antibiotics, especially broad-spectrum, occurs in the ICU. Given the importance of antibiotic stewardship for critically ill patients and the importance of critical care practitioners as the front line for antibiotic stewardship, a workshop was convened to specifically address barriers to antibiotic stewardship in the ICU and discuss tactics to overcome these. The working definition of antibiotic stewardship is "the right drug at the right time and the right dose for the right bug for the right duration." A major emphasis was that antibiotic stewardship should be a core competency of critical care clinicians. Fear of pathogens that are not covered by empirical antibiotics is a major driver of excessively broad-spectrum therapy in critically ill patients. Better diagnostics and outcome data can address this fear and expand efforts to narrow or shorten therapy. Greater awareness of the substantial adverse effects of antibiotics should be emphasized and is an important counterargument to broad-spectrum therapy in individual low-risk patients. Optimal antibiotic stewardship should not focus solely on reducing antibiotic use or ensuring compliance with guidelines. Instead, it should enhance care both for individual patients (by improving and individualizing their choice of antibiotic) and for the ICU population as a whole. Opportunities for antibiotic stewardship in common ICU infections, including community- and hospital-acquired pneumonia and sepsis, are discussed. Intensivists can partner with antibiotic stewardship programs to address barriers and improve patient care.

Keywords: antibiotic stewardship; antibiotic resistance; pneumonia; sepsis

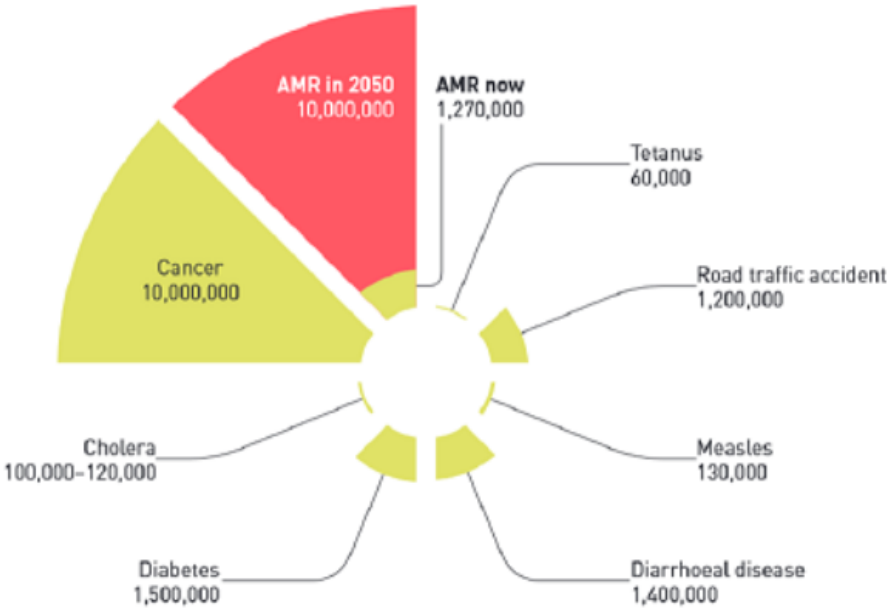
Wunderink RG et al. *Ann Am Thorac Soc* **2020**;*17*:531-540.

Az antimikrobiális rezisztencia probléma jelentősége

What is the impact of AMR?

The World Health Organization (WHO) lists AMR among top 10 threats for global health.

Antimicrobial resistance threatens human and animal health and welfare, the environment, food and nutrition security and safety, economic development, and equity within societies.



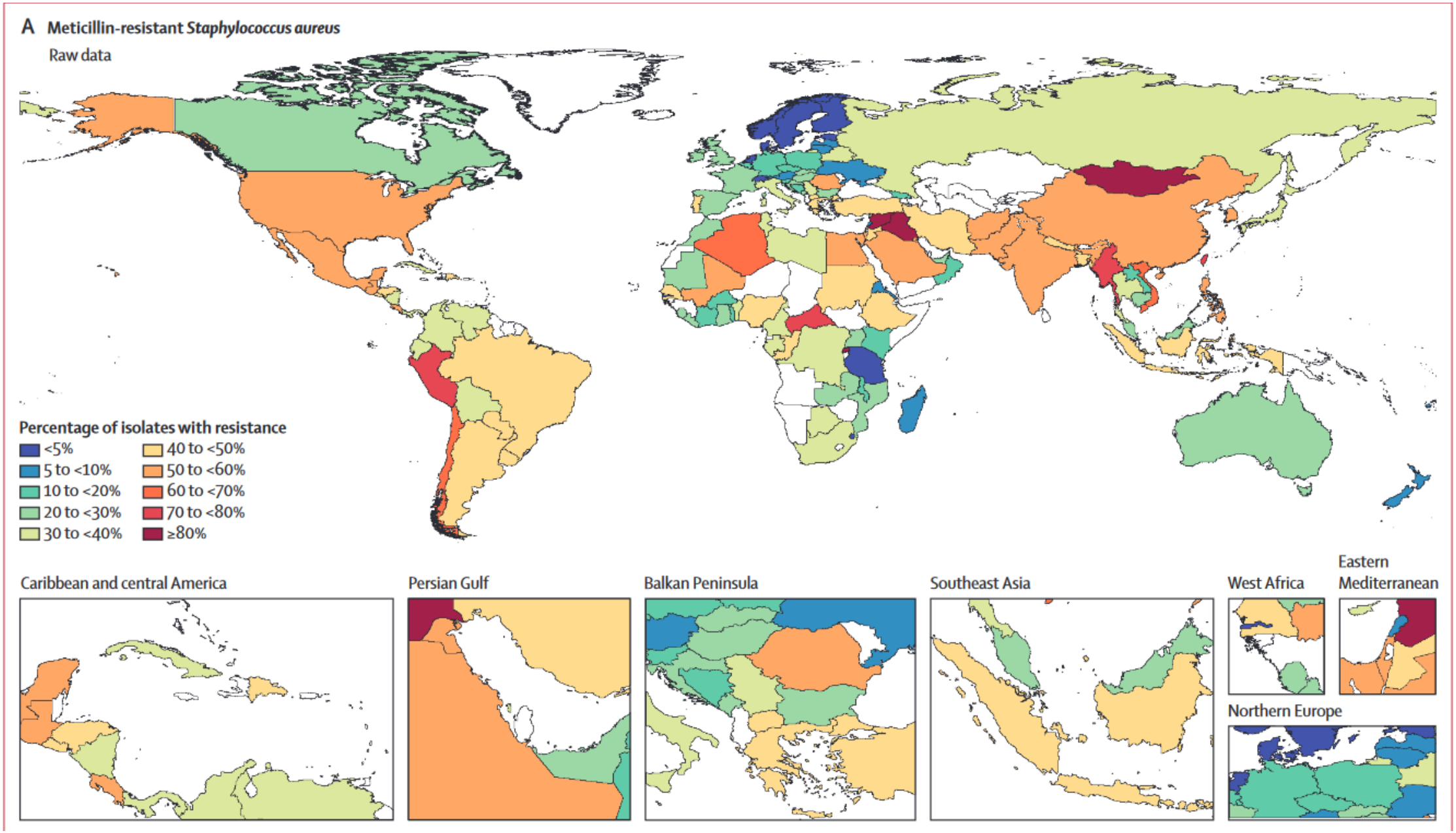
Predicted mortality from AMR compared to common causes of death today (adapted from O'Neill 2016; Murray et al. 2022)

According to recent estimates, in 2019, 1.27 million deaths were directly attributed to drug-resistant infections globally. By 2050, up to 10 million deaths could occur annually.

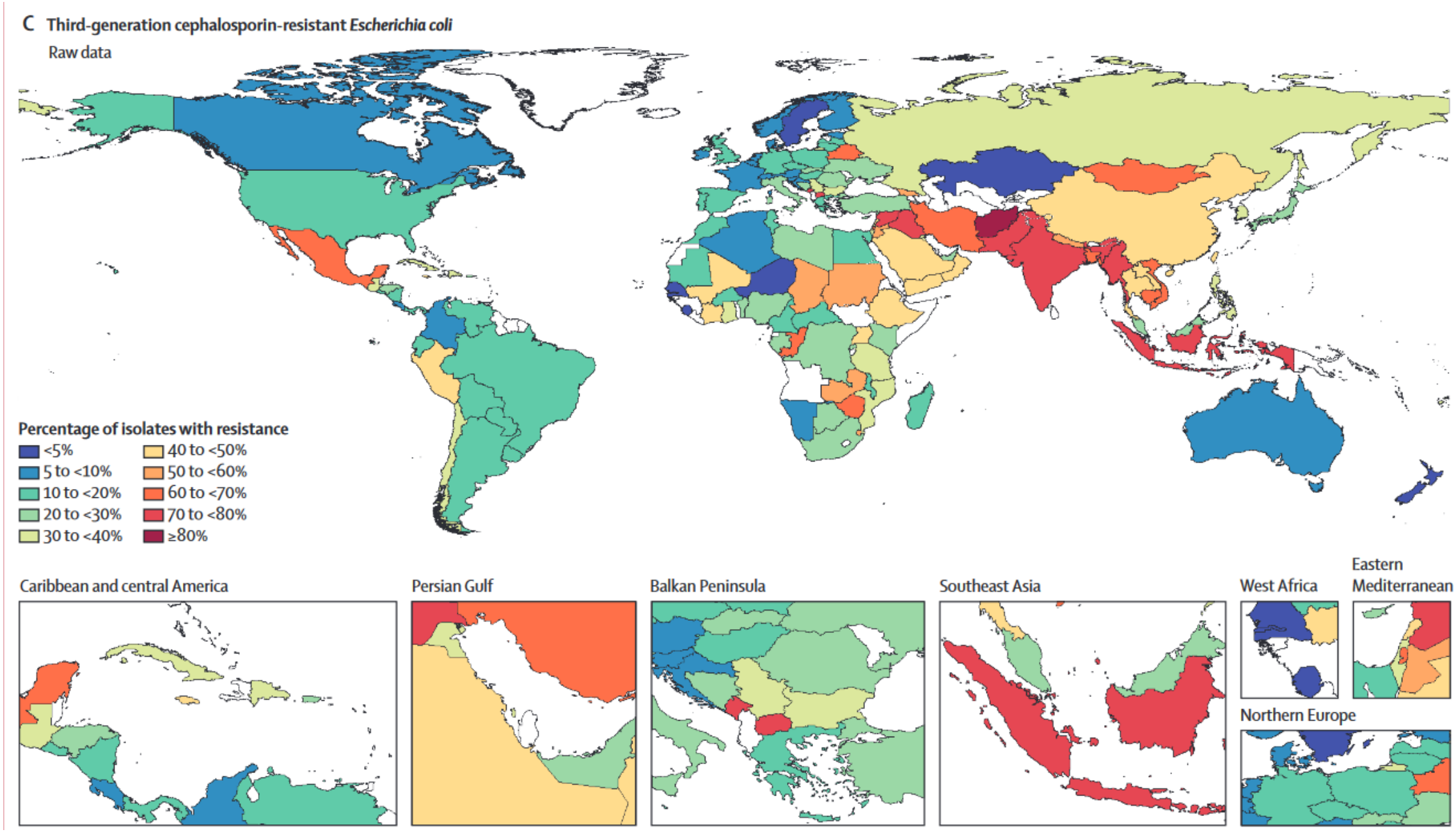
If unchecked, AMR could shave US$ 3.4 trillion off GDP annually and push 24 million more people into extreme poverty in the next decade.

Antimicrobial resistance in

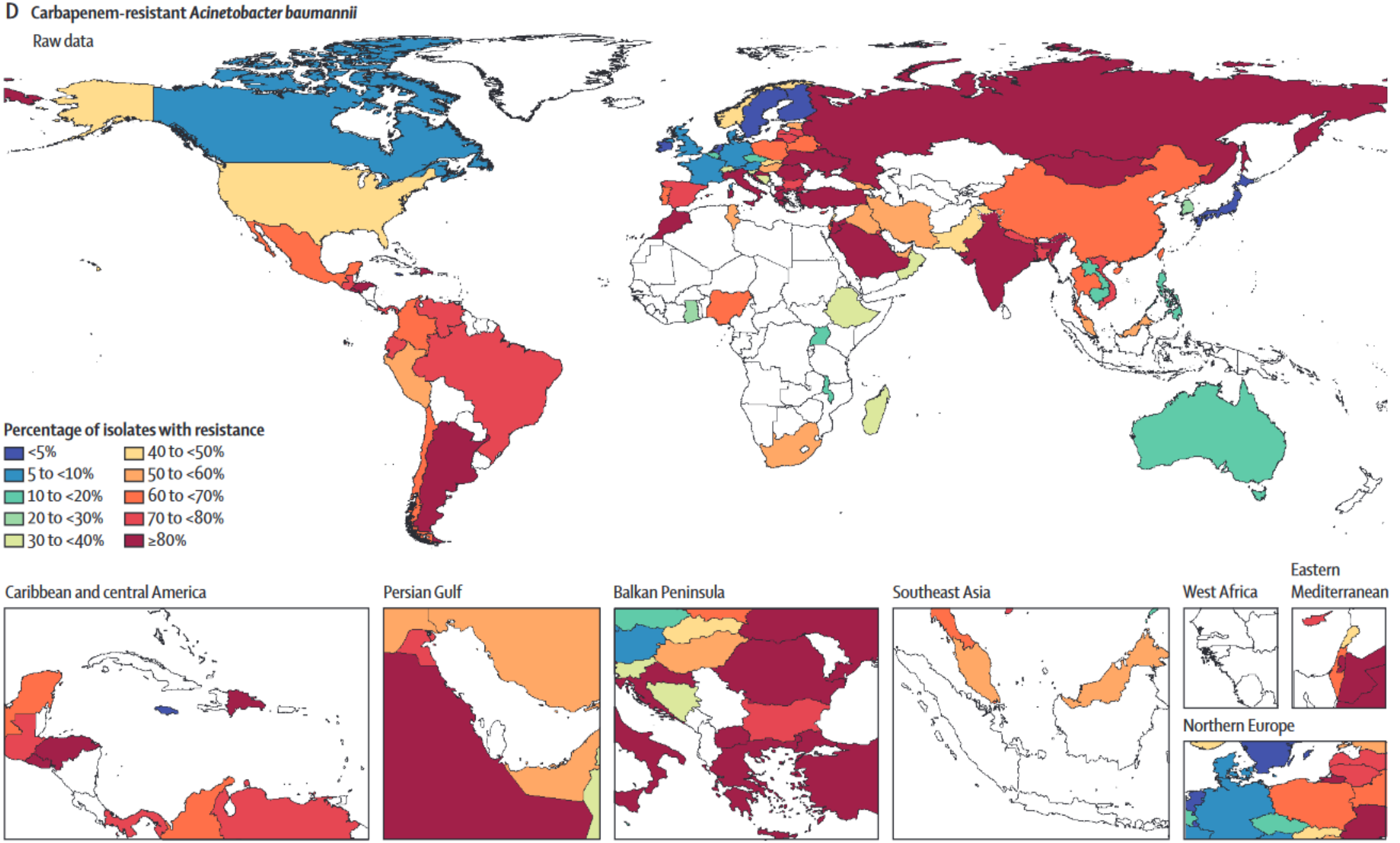
https://www.unep.org/



Antimicrobial Resistance Collaborators. *Lancet* **2022**;*399*:629-655.



Antimicrobial Resistance Collaborators. *Lancet* **2022**;*399*:629-655.



Antimicrobial Resistance Collaborators. *Lancet* **2022**;*399*:629-655.

Surviving sepsis campaign

History

Initiated in 2002 at the ESICM's annual meeting with the Barcelona Declaration, the campaign progressed in phases that have expanded the scope and reach of publication of four editions of evidence-based guidelines, implementation of a performance improvement program, and analysis and publication of data from more than 30,000 patient charts collected from around the world.

- **Phase I: Development of Awareness of Scope of the Problem**
- **Phase II: Development and Publication of Guidelines**
- **Phase III: Guideline Implementation, Behavior Change, and Data Collection**

https://www.sccm.org/SurvivingSepsisCampaign/About-SSC/History

ONLINE SPECIAL ARTICLE

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021

KEY WORDS: adults; evidence-based medicine; guidelines; sepsis; septic shock

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TABLE 3.
Guidance for PK/PD-Based Dosing for Specific Drug Classes

Drug or Drug Class	PK/PD Index Associated With Bacterial Killing or Efficacy	Drug Concentration Target	Considerations for Optimized Dosing*	Reference Number
Antibacterials				
Aminoglycosides	AUC_{0-24}/MIC; C_{max}/MIC	AUC 70–100 C_{max}/MIC 8–10	Use extended interval dosing with patient weight and kidney function	237
Beta-lactams	$fT_{>MIC}$	C_{min} > MIC	Use prolonged infusions, consider patient weight and kidney function	253
Colistin	AUC_{0-24}/MIC	Unspecified	Use patient weight and kidney function	259
Daptomycin	AUC_{0-24}/MIC; C_{max}/MIC	AUC_{0-24}/MIC > 200	Use patient weight and kidney function	237
Fluoroquinolones	AUC_{0-24}/MIC; C_{max}/MIC	AUC_{0-24}/MIC 80–125	Use kidney function	237
Vancomycin	AUC_{0-24}/MIC	AUC_{0-24}/MIC 400	Use patient weight and kidney function	260
Antifungals				
Fluconazole	AUC_{0-24}/MIC	AUC_{0-24}/MIC 100	Use patient weight and kidney function	261
Posaconazole	AUC_{0-24}/MIC	C_{min} 1–4 mg/L	Use formulation-specific dose	261
Voriconazole	AUC_{0-24}/MIC	C_{min} 2–6 mg/L	Use patient weight	261

*Other considerations than those listed may have been listed in studies in critically ill patient subpopulations.
AUC_{0-24}–ratio of area under the concentration-time curve from 0–24 hours; MIC–minimum inhibitory concentration; $fT_{>MIC}$–time over-dosing interval that free (unbound) drug is maintained above the MIC; C_{max}–maximum concentration in a dosing interval; C_{min}–minimum concentration in a dosing interval.
Note: use of therapeutic drug monitoring has been described for all drugs, although it is not widely available for most.

Pharmacokinetics and Pharmacodynamics

Recommendation

26. For adults with sepsis or septic shock, we **recommend** optimizing dosing strategies of antimicrobials based on accepted pharmacokinetic/pharmacodynamic (PK/PD) principles and specific drug properties.

Best practice statement.

- augmented renal clearance
- acute kidney injury
- renal replacement therapy
- ECMO
- hypoalbuminaemia

Applying a PK/PD approach to antibiotic dosing requires support from knowledgeable clinician team members, use of a patient population-specific guideline document, ***use of therapeutic drug monitoring, and/or use of dosing software.***

Evans LE et al. *Crit Care Med* 2021;**49**:e1063-e1143

TABLE 1.

Organizations Endorsing the 2021 Surviving Sepsis Guidelines

Society of Critical Care Medicine
European Society of Intensive Care Medicine
American Association of Critical Care Nurses
American College of Chest Physicians
American College of Emergency Physicians
American Thoracic Society
African Sepsis Alliance
Asia and Pacific Sepsis Alliance
Association De Medicina Intensiva Brasileira
Australian and New Zealand Intensive Care Society
Canadian Critical Care Society
Chinese Society of Critical Care Medicine
European Respiratory Society
European Society of Clinical Microbiology and Infectious Diseases
Indian Society of Critical Care Medicine
Infectious Diseases Society of North America
Japanese Society of Intensive Care Medicine
Latin American Sepsis Institute
Society for Academic Emergency Medicine
Scandinavian Critical Care Trials Group

Dellinger RP et al. *Crit Care Med* 2023;**51**:431-444

Idézetek a parenterális infúzió formájában leggyakrabban alkalmazott béta-laktámok Alkalmazási előirataiból (spc)

A hatásosság főként attól függ, hogy az **ampicillin** szintje mennyi ideig marad a mikroorganizmus minimális gátló koncentrációja (MIC) felett.

Cefazolin: A cefalosporinoknál az *in vivo* hatásossággal összefüggést mutató legfontosabb farmakokinetikai-farmakodinámiás paraméter az adagolási intervallum azon részének százalékos aránya, amely során a szabad hatóanyag koncentrációja a célfajra vonatkozó minimális gátlási koncentráció (MIC) felett marad (azaz %T>MIC).

Cefepim: A hatásosság leginkább azon időtartam függvénye, amely alatt a gyógyszerkoncentráció meghaladja a szóban forgó kórokozó mikroorganizmus minimális gátló koncentrációját (MIC).

Ceftazidim: Kimutatták, hogy cefalosporinok esetében az *in vivo* hatásossággal összefüggő legfontosabb farmakokinetikai-farmakodinámiás index az adagolási intervallum azon százaléka, melynél a szabad ceftazidim-koncentráció az egyes célpont fajokra meghatározott minimális gátló koncentráció (MIC) fölött van (vagyis %T > MIC).

A többi béta-laktámhoz hasonlóan az *in vivo* hatásossággal korreláló legfontosabb farmakokinetikai-farmakodinámiás mutató az adagolási intervallum azon részének százalékos aránya, melynek során a meg nem kötött hatóanyag koncentrációja meghaladja a **ceftriaxon** adott célfajokra meghatározott minimális gátló koncentrációját (MIC) (vagyis %T > MIC).

A többi béta-laktám antibakteriális szerhez hasonlóan, az **imipenem** esetében is az az időtartam mutatja a legszorosabb össze-függést a hatásossággal, amely alatt a koncentráció meghaladja a minimális gátló koncentrációt (MIC) (T>MIC).

Más béta-laktám antibakteriális szerekhez hasonlóan az az idő korrelál legjobban a hatásossággal, ameddig a **meropenem** koncentrációja meghaladja a MIC-értéket (T>MIC).

A **piperacillin** hatásosságát meghatározó fő farmakodinámiás tényezőnek a minimális inhibitor koncentráció felett eltelt időt (T>MIC) tartják.

A béta-laktámok gyógyszerszint monitorozása melletti érvek

1. Az ITO-n kezelt betegekben mérhető béta-laktám völgykoncentrációk hatalmas egyéni eltéréseket mutatnak → TDM nélkül a gyógyszerexpozíció nem becsülhető, és nem mérhető
2. Az antibiotikum kezelések racionalizálása várhatóan csökkenti a szepszissel összefüggő mortalitást
3. A kialakulóban lévő globális MDR-krízis elleni fellépés
   - A multidrug-rezisztens nozokomiális kórokozó törzsek aránya dinamikusan nő
   - Az intenzív terápiás osztályokon a széles spektrumú béta-laktámokkal szemben rezisztens törzsek előfordulási aránya kb. 30%
   - Új antibiotikumok: kevés és költséges
4. A racionális antibiotikum kezelés azonnal alkalmazható, minimális erőforrás-igényű eszköz az MDR-krízis kialakulásának lassítására

A béta-laktámok gyógyszerszint monitorozásának céljai

- **Hatékonyság** biztosítása: „Setting the floor”
  - klinikai hatékonyság biztosítása
  - mikrobiológiai hatékonyság biztosítása
    - eradikáció
    - rezisztens törzs kifejlődésének megakadályozása

- **Toxicitás** elkerülése: „Setting the ceiling”
  - neurotoxicitás
  - nefrotoxicitás
  - trombocitopénia
  - csontvelő szupresszió

Barreto EF et al. *Crit Care Explor* **2021**;*11*:e0446.

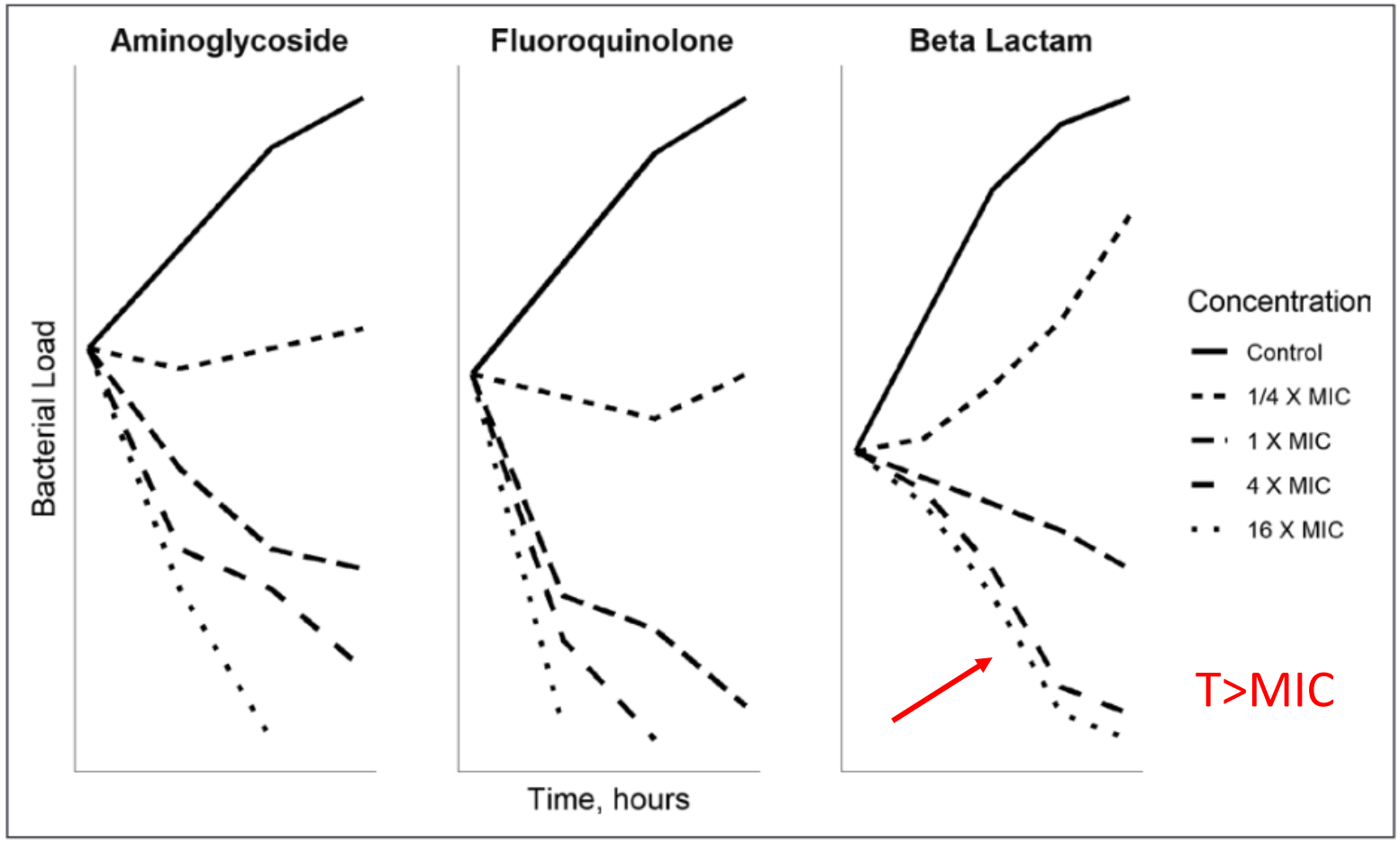


Figure 2. Example time-kill curves for *Pseudomonas aeruginosa* with three antibiotics of different classes at varying concentrations. For beta-lactams, exposure of the bacteria to a concentration 1× the minimum inhibitory concentration (MIC) of the organism is bactericidal. Drug concentrations greater than 4× the MIC of the organism elicit no additional increase in bacterial killing. For aminoglycosides and fluoroquinolones increases in drug exposure increases bacterial kill (23).

Megnevezés	Moltömeg (g)	Megoszlási térfogat (l)	Fehérjéhez kötött frakció	Felezési idő (h)	Elimináció útja	Metabolizmus
ampicillin	349.4	15	15-20%	1	vese, máj	máj
cefazolin	454.5	11 l/1.73 m^2	70-86%	1.5	vese	nincs
cefepim	480.6	18	<20%	2	vese, máj	kismértékű
ceftazidime	546.6	15-20	10%	2	vese	nincs
ceftriaxone	554.6	7-12	95% (telíthető)	8	vese, máj	bélflóra
imipenem	299.3	0.23-0.31 l/ttkg	20%	1	vese	vese (dehidropeptidáz-I)
meropenem	383.5	0.25 l/ttkg	<5%	1	vese, máj	kismértékű
piperacillin	516.5	15.4	30%	0.84	vese, máj	kismértékű (van aktív metabolit)
sulbactam	233.2	23.5	40%	1	vese	nincs
tazobactam	300.3	14.7	30%	0.82	vese, kismértékében máj	kismértékű

A betegek béta-laktám expozíció szempontjából fontos jellemzői

- Veseműködés
- Testsúly
- Keringés, kapillárisfalak állapota
- Szérum fehérjeszint (cefazolin, ceftriaxon)
- Folyadékterhelés
- Máj- és epeműködés (ampicillin, cefepim, ceftriaxon)

REVIEW Open Access

Optimization of the treatment with beta-lactam antibiotics in critically ill patients—guidelines from the French Society of Pharmacology and Therapeutics (Société Française de Pharmacologie et Thérapeutique—SFPT) and the French Society of Anaesthesia and Intensive Care Medicine (Société Française d'Anesthésie et Réanimation—SFAR)

Romain Guilhaumou[1], Sihem Benaboud[2], Youssef Bennis[3], Claire Dahyot-Fizelier[4], Eric Dailly[5], Peggy Gandia[6], Sylvain Goutelle[7], Sandrine Lefeuvre[8], Nicolas Mongardon[9], Claire Roger[10], Julien Scala-Bertola[11], Florian Lemaitre[12] and Marc Garnier[13*]

Crit Care Med 2019;**23**:104

R1.1. We suggest considering systematically and daily the many sources of pharmacokinetic variability when prescribing beta-lactam antibiotics to critical care patients. (*Optional recommendation, strong agreement*)

- Volume of distribution: polytrauma vs sepsis, obesity
- Protein binding increases in the obese (fatty acids, α1-glycoprotein)
- Elevated renal clearance (obesity)

R2.1. We suggest considering the percentage of the dosing interval during which the free plasma concentration of beta-lactams is above a multiple ("k") of the minimum inhibitory concentration (MIC) of the causative bacteria (%fT > k× MIC) as the therapeutic target for treatment with beta-lactam antibiotics. (*Optional recommendation, strong agreement*)

R3.1. Pending the result of therapeutic drug monitoring (TDM), we suggest that a higher daily dose of beta-lactam antibiotics than that administered in patients outside the ICU should be administered at the onset of treatment, especially in the most critically ill patients and in those with preserved renal function. (*Optional recommendation, strong agreement*)

- Increased volume of distribution and clearance results in lower systemic concentrations
- In sepsis, tissue hypoperfusion leads to extended formation of equilibrium

R4.1. We suggest performing therapeutic drug monitoring in ICU patients with expected beta-lactam PK variability and/or in patients with clinical signs potentially related to beta-lactams toxicity.

R2.2. We suggest targeting a free plasma beta-lactam concentration between four and eight times the MIC of the causative bacteria for 100% of the dosing interval (fT ≥ 4–8 x MIC = 100%) to maximize bacteriological and clinical response in critical care patients.

R4.2. We suggest performing therapeutic drug monitoring (TDM) of beta-lactam antibiotics in critical care patients undergoing renal replacement therapy.

R4.5. In case of central nervous system infection, we suggest performing beta-lactam TDM, if possible, on blood and cerebrospinal fluid samples collected concomitantly.

R4.4. We suggest performing beta-lactam TDM 24 to 48 h after the onset of treatment; after any change in dosage; and in the event of a significant change in the patient's clinical condition.

R1.3.1. We suggest measuring albumin (or at least plasma proteins) at least once at the onset of treatment with beta-lactam antibiotics in order to guide the prescription.

R1.3.2. We suggest measuring albumin (or at least plasma proteins) when performing beta-lactam TDM in order to help in interpreting the result.

Guilhaumou R et al. *Crit Care Med* 2019;**23**:104

CONFERENCE REPORT AND EXPERT PANEL

Antimicrobial therapeutic drug monitoring in critically ill adult patients: a Position Paper#

Mohd H. Abdul-Aziz[1], Jan-Willem C. Alffenaar[2,3,4], Matteo Bassetti[5], Hendrik Bracht[6], George Dimopoulos[7], Deborah Marriott[8], Michael N. Neely[9,10], Jose-Artur Paiva[11,12], Federico Pea[13], Fredrik Sjovall[14], Jean F. Timsit[15,16], Andrew A. Udy[17,18], Sebastian G. Wicha[19], Markus Zeitlinger[20], Jan J. De Waele[21], Jason A. Roberts[1,22,23,24]* on behalf of the Infection Section of European Society of Intensive Care Medicine (ESICM), Pharmacokinetic/pharmacodynamic and Critically Ill Patient Study Groups of European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Group of International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) and Infections in the ICU and Sepsis Working Group of International Society of Antimicrobial Chemotherapy (ISAC)

Intensive Care Med 2020;**46**:1127-1153

Take-home message:

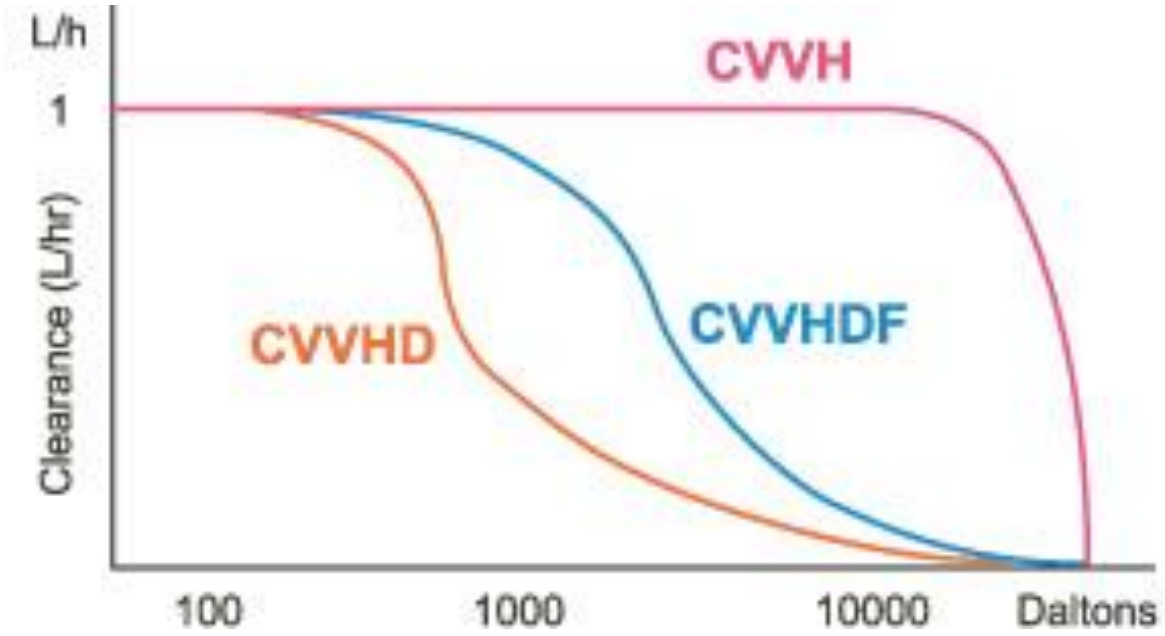
The Panel Members recommend routine TDM to be performed for aminoglycosides, beta-lactam antibiotics, linezolid, teicoplanin, vancomycin and voriconazole in critically ill patients.

- Critically ill patients often demonstrate extreme variability in antimicrobial PK, which can be partly explained by patient covariates (e.g. body weight and renal function). Unexplained PK variability can be observed across patients (i.e. inter-individual variability) and also, within a patient (i.e. intra-individual PK variability). TDM-based dosing adjustment is clinically useful for an antimicrobial if the unexplained inter-individual PK variability exceeds the intra-individual variability. Otherwise, solely applying covariate-based dosing strategies would be sufficient, as is the case with Product Information and nomogram-based dosing.
- The Panel recommends that TDM be routinely performed when **beta-lactam** antibiotics are used in critically ill patients.
- The PK/PD index associated with optimal beta-lactam activity is the **% fT>MIC (40–70%).** Critically ill patients data suggest that patients may benefit from longer (e.g. 100% fT>MIC) [41–43] and higher (e.g. **2–5 × MIC**) [42–44] beta-lactam exposures than those previously described. Although the beta-lactams generally have a wide therapeutic index, high exposures have been associated with neurotoxicity. Although myelosuppression is well-known toxicity for the beta-lactams [45], no toxicity thresholds have been well established to date.
- An initial loading dose (LD) followed by prolonged beta-lactam infusion (continuous or extended infusion) **maximises PK/PD target attainment** and is likely to improve clinical outcomes in critically ill patients [46].

Table 2 Target trough total (Cmin) or free (*f*Cmin) plasma concentration following intermittent administration and target total (Css) or free (*f*Css) steady-state plasma concentration following continuous administration for the main beta-lactam antibiotics

	Free fraction (%)	Recommended target concentrations[#]		MIC threshold[£] [130]	Ref.
		Documented infection	Non-documented infection		
Amoxicillin	≈ 80%	*f*Cmin or *f*Css ≥ 4× MIC Cmin or Css < 80 mg/L	Cmin 40–80[*] mg/L[§] Css 40–80 mg/L	8 mg/L (ECOFF *E. coli*)	[131]
Cefazolin	≈ 15–20%	*f*Cmin or *f*Css ≥ 4× MIC Cmin or Css < 80 mg/L	Cmin 40–80 mg/L[§] Css 40–80 mg/L	2 mg/L (ECOFF *S. aureus*)	[132]
Cefepime	80%	*f*Cmin or *f*Css ≥ 4× MIC Cmin < 20 mg/L Css < 35 mg/L	Cmin 5–20 mg/L Css 5–35 mg/L	1 mg/L (*Enterobacteriaceae*)[§§]	[21, 72, 73]
Cefotaxime	≈ 60–80%	*f*Cmin or *f*Css ≥ 4× MIC Cmin or Css < 60 mg/L	Cmin 25–60 mg/L Css 25–60 mg/L	4 mg/L (ECOFF *S. aureus*)	[133]
Ceftazidime	≈ 90%	*f*Cmin or *f*Css ≥ 4× MIC Cmin or Css < 80 mg/L	Cmin 35–80 mg/L[§] Css 35–80 mg/L	8 mg/L (ECOFF *P. aeruginosa*)	[77]
Ceftriaxone	≈ 10%	*f*Cmin ≥ 4× MIC Cmin < 100 mg/L	Cmin 20–100 mg/L	0.5 mg/L (ECOFF *E. cloacae*)	[129]
Cloxacillin	≈ 10%	*f*Cmin or *f*Css ≥ 4× MIC Cmin ou Css < 50 mg/L	Cmin 20–50 mg/L[§] Css 20–50 mg/L	0.5 mg/L (ECOFF *S. aureus*)	[131]
Ertapenem	≈ 10%	*f*Cmin ou *f*Css ≥ 4× MIC Cmin < 10 mg/L	Cmin 5–10 mg/L	0.125 mg/L (*H. influenzae*)[§§§]	[117, 134]
Imipenem	≈ 80%	*f*Cmin ≥ 4× MIC Cmin < 5 mg/L	Cmin 2.5–5 mg/L	0.5 mg/L (ECOFF *E. coli*)	[135]
Meropenem	≈ 100%	*f*Cmin ou *f*Css ≥ 4× MIC Cmin ou Css < 16 mg/L	Cmin 8–16 mg/L[§] Css 8–16 mg/L	2 mg/L (ECOFF *P. aeruginosa*)	[136]
Piperacillin	≈ 80%	*f*Cmin ou *f*Css ≥ 4× MIC Css < 160 mg/L	Css 80–160 mg/L	16 mg/L (ECOFF *P. aeruginosa*)	[75]

A folyamatos vesepótló kezelések típusai



Mechanizmusok:
konvekció, diffúzió, adszorpció

Mindhárom mechanizmus szerepet játszik a béta-laktám clearance alakulásában!

Összefüggés a CRRT intenzitása és a becsült *f*T>4xMIC értékek között (cefepime, ceftazidime, meropenem, piperacillin/tazobactam)

Beumier M et al. *Crit Care* **2014**;*18*:R105.

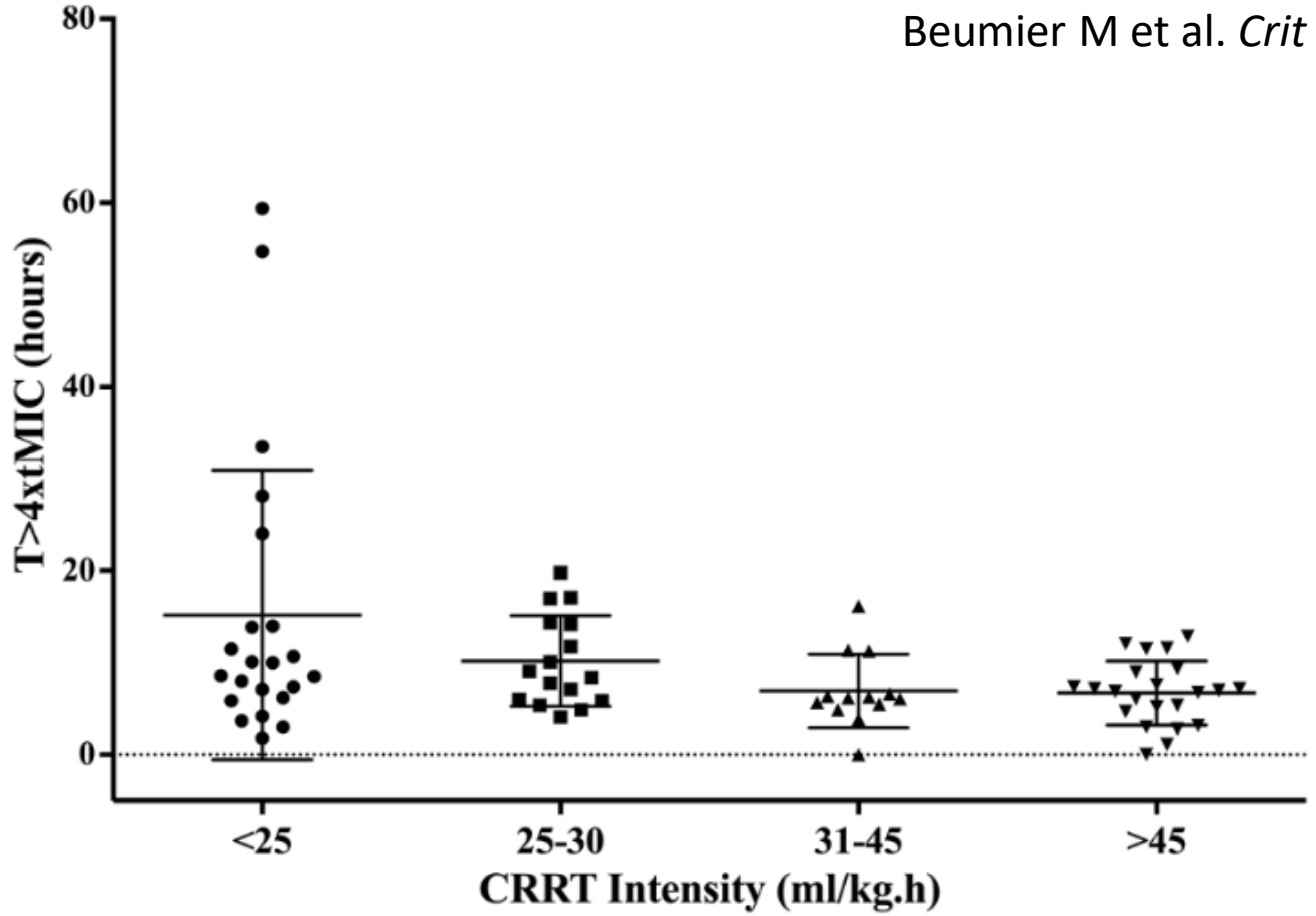
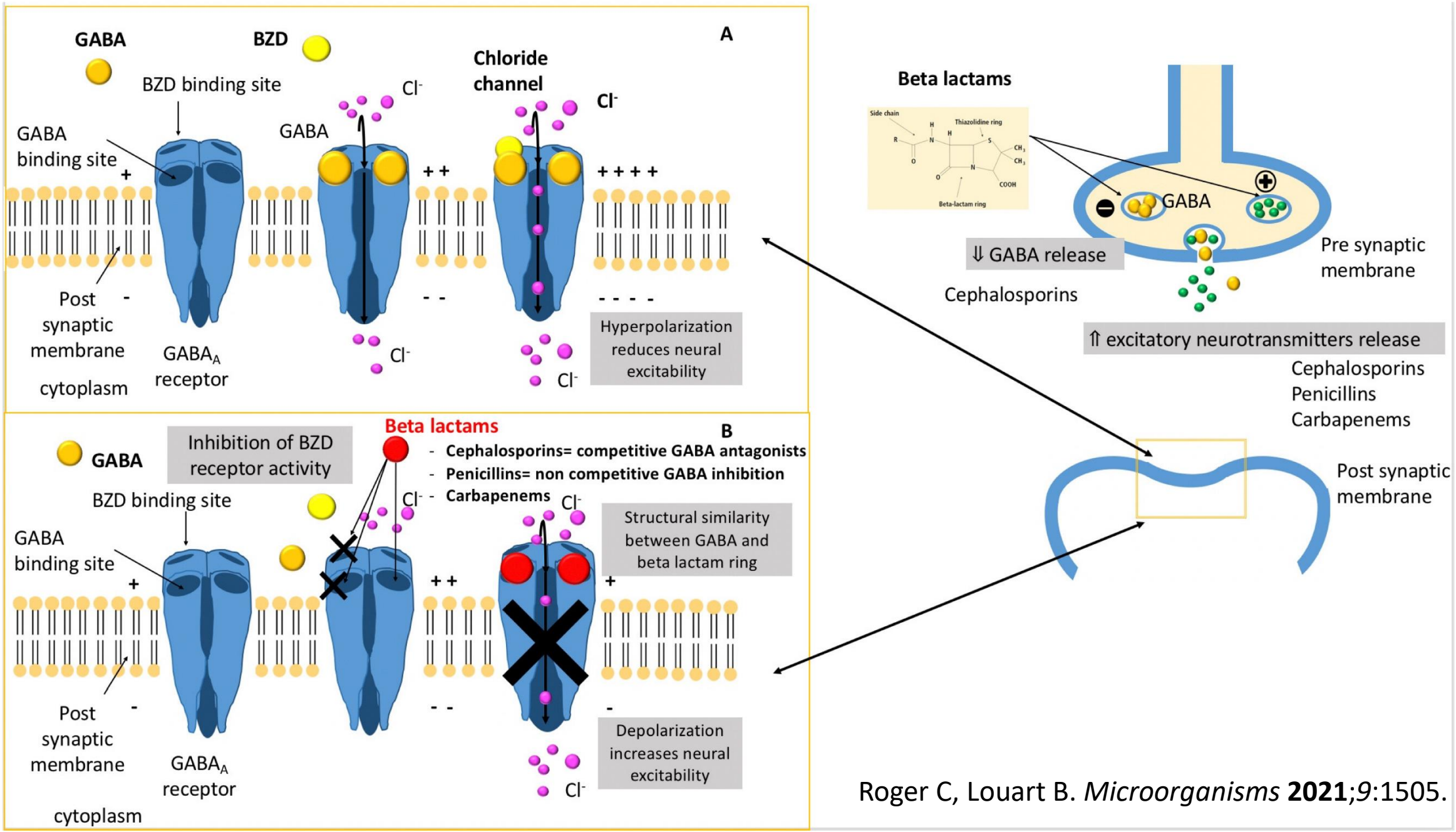


Figure 5 The time (T) above four times the target (t) minimal inhibitory concentration (MIC) (T > × of *Pseudomonas aeruginosa* was lower in patients with higher continuous renal replacement therapy (CRRT) intensity (<25 mL/kg.h = 9.3 (ranges = 1.8 to 59.4) h; 25 to 30 mL/kg.h = 8.7 (4.1 to 19.8) h; 31 to 45 mL/kg.h = 6.2 (0 to 16.2) h; >45 mL/kg.h = 6.9 (0 to 12.9) h; *P* = 0.01).

Béta-laktámok mellékhatásai



Roger C, Louart B. *Microorganisms* **2021**;*9*:1505.

Table 1 Convulsing activity of beta-lactams compared to penicillin G, from [67, 69, 70]

Beta-lactam	Relative pro-convulsive activity (reference: penicillin G = 100)
Cefazolin	294
Cefepime	160
Penicillin G	*100*
Imipenem	71
Aztreonam	42
Ampicillin	21
Ceftazidime	17
Meropenem	16
Ceftriaxone	12
Piperacillin	11
Cefotaxime	8,8
Cefoxitine	1,8

Table 4 Cefepime-induced neurotoxicity – a clinical picture

Risk factors	Signs and symptoms	EEG characteristics	Treatments
- Renal dysfunction - Critical illness - Altered BBB - Older age - Drug overdose	- Altered mental status - Reduced consciousness - Confusion - Myoclonus - Aphasia - Agitation - Seizures	- Abnormalities - Tri-phasic waves - Multi-focal sharp waves - Non-convulsive SE - Generalized slowing - Myoclonic SE	- Cefepime discontinuation - Cefepime-free interval w/dose reduction - Hemodialysis - Benzodiazepine[a]

EEG electroencephalography, *BBB* blood–brain barrier, *SE* status epilepticus
[a]For EEG abnormalities/seizure activity associated with toxicity

Table 2 Cefepime characteristics

Characteristic	Value
Cefepime dosing	
Median dose over 24 hours (IQR), g	3.5 (2–5.9)
Median frequency of dosing (IQR), hours	12 (12–24)
Appropriately dosed for renal function, *n* (%)	
No	65 (48%)
Yes	35 (26%)
Unable to assess	35 (26%)
Indication, *n* (%)	
Febrile neutropenia	11 (8%)
Pneumonia	37 (27%)
Other[a]	31 (23%)
Not reported	56 (41%)
Drug concentrations, mg/L	
Median serum, n = 21 (range)	45 (15–284)
Median trough, n = 13 (range)	38 (15–224)
Median CSF, n = 4 (range)	13 (6–18)
Median for appropriately dosed patients, n = 7 (range)	60 (22–74)
Median for inappropriately dosed patients, n = 10 (range)	39 (15–284)
Trough for appropriately dosed patients, n = 6 (range)	54 L (37–65)
Median onset of neurotoxic effects (IQR), days	4 (2–6)

CNS central nervous system
[a]No patients were treated for meningitis/CNS infections

- Median CSF/serum cefepime concentration ratio: 21% (6-45%)
- CNS infection was not among the indications
- Interventions:
  - Cefepime discontinuation (81%)
  - Administration of anticonvulsive (36%)
  - Hemodialysis (8%)
  - Cefepime dose reduction (4%)

Table 3 Patient outcomes

Outcome	Value
Discharge outcome, *n* (%)	
Survived	117 (87%)
Died	18 (13%)
Received dialysis, *n* (%)	11 (8%)
Antiepileptic drug administered, *n* (%)	48 (36%)
Symptom resolution, *n* (%)	
Complete resolution of symptoms	68 (50%)
Symptom improvement	53 (39%)
No improvement	11 (8%)
Unreported/indeterminate	3 (2%)
Median time to clinical improvement, days	
All patients, n = 67 (IQR)	2 (1–3)
Emergent dialysis employed, n = 3[a] (range)	1 (1–3)
Antiepileptic drug used, n = 26 (IQR)	2 (1–3)

[a]Only 3 of 11 patients who received emergent dialysis had reported times to improvement

Payne LE et al. *Crit Care* **2017**;*21*:276.

Table 2. Suggested beta-lactam toxicity thresholds and main clinical manifestations of neurotoxicity according to the beta-lactam agent considered.

Beta-Lactam	Toxicity Threshold	Clinical Signs
Flucloxacillin [6]	Cmin > 125.1 mg/L	Seizures Confusion Myoclonia
Amoxicillin [46]	Css < 8 × MIC	Psychotic symptoms
Ceftazidime [46]	Css < 8 × MIC	Encephalopathy Confusion, disturbed vigilance
Cefepime [45]	Cmin > 20 mg/L	Encephalopathy Confusion, disturbed vigilance
Piperacillin tazobactam [6,20,33]	Css > 157.2 mg/L (pip taz CI) Cmin > 64 (pip taz)–361(pip alone) mg/L	Seizures Hallucinations
Imipenem [46]	Css < 8 × MIC	Seizures Confusion Myoclonia
Meropenem [6]	Cmin > 64 mg/L	Seizures

Roger C, Louart B. *Microorganisms* **2021**;*9*:1505.

Béta-laktámok nefrotoxicitása

- Idioszinkrázia miatt kialakuló akut intersticiális nephritis
- A kezelés után néhány nappal jelentkezik
- A betegek jelentős arányát érinti, de nehéz diagnosztizálni
- A legfontosabb teendő a gyógyszer elhagyása

Nast C. *Adv Chronic Kidney Dis* **2017**;*24*:72-79.

Béta-laktámok által okozott trombocitopénia

- Trombocitopénia és kritikus állapot:
  - Előfordulási gyakoriság kb. 50%
  - Mortalitás fontos tényezője (>30% mértékű TC szám csökkenés → 2x mortalitás)
- Trombocitopénia és gyógyszerek:
  - Többnyire immunmediált, ritkábban csontvelő szuppresszió által okozott trombocitopénia
  - Kezelés megkezdése után több (akár 14) nappal jelentkezik
  - Immunmediált formánál a vérlemezke membrán fehérjék ellen képződnek antitestek
  - Béta-laktám kezelés az egyik legfontosabb ok

Beaulieu C et al. *J Thromb Thrombolysis* **2019**;*48*:167-170.
Boyce K et al. *J Clin Pharm Ther* **2016**;*41*:730-32.
Strauss R et al. *Crit Care Med* **2002**;*30*:1765-1771.

Gatti M et al. *Crit Care* **2022**;*26*:178.

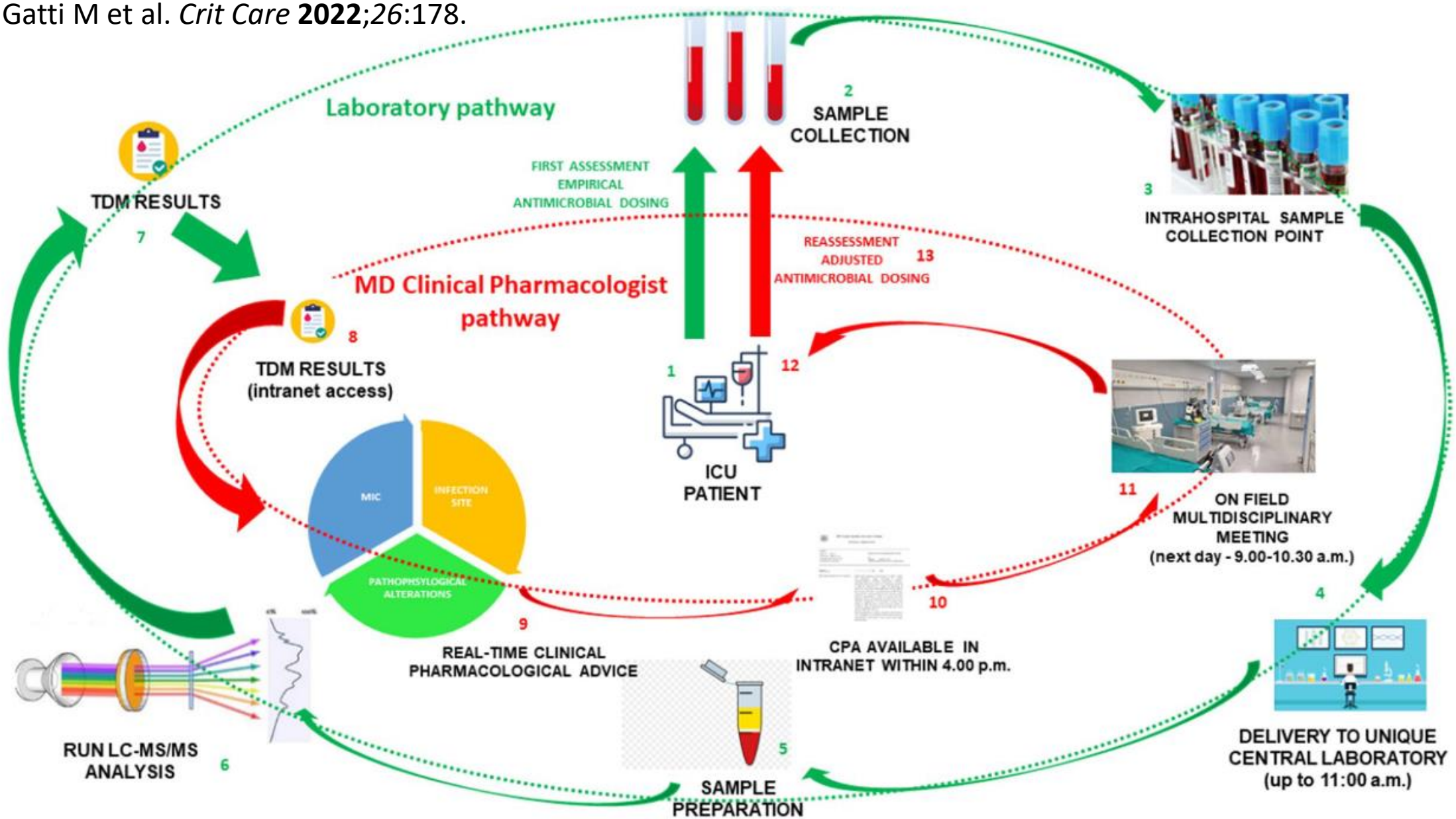


Fig. 3 Final structured plan of the organizational phase of the TDM-based ECPA program. Two complementary pathways were identified: the laboratory pathway (in green, points 1–7), the MD clinical pharmacologist pathway (in red, points 8–14)

Table 2. Available Resources in the Participating Intensive Care Units (ICUs)

Resource	No. (%) by gross national income per capita[a]		
	Low to lower middle (n = 73)	Upper middle (n = 432)	High (n = 645)
Availability of infectious diseases specialist or clinical microbiologist			
At all times	30 (41.1)	203 (47.1)	440 (68.8)
Just during the week	31 (42.5)	157 (36.4)	169 (26.4)
Never	12 (16.4)	71 (16.5)	31 (4.8)
Pharmacist (full-time or part-time) assigned to the ICU team	35 (47.9)	250 (58.0)	342 (53.5)
Antibiotics often or always available			
Piperacillin/tazobactam	59 (80.8)	383 (89.1)	633 (98.9)
Echinocandins	34 (46.6)	285 (66.3)	585 (91.5)
Tigecycline	49 (68.1)	300 (69.8)	516 (80.8)
Therapeutic monitoring often or always performed			
Vancomycin	22 (30.1)	188 (43.7)	587 (91.9)
Voriconazole	3 (4.1)	34 (7.9)	143 (22.4)
β-Lactam antibiotics	8 (11.0)	47 (11.0)	61 (9.6)
Echinocandins	3 (4.1)	25 (5.8)	51 (8.0)
Aminoglycosides	0	1 (0.2)	0

Vincent JL et al. *JAMA* **2020**;*323*:1478-1487.

Béta-laktámok alkalmazása vesepótló kezeléssel (RRT) egyidejűleg Franciaországban

- Orvosok 70%-a a CRRT-t részesítette előnyben az intermittens hemodialízissel szemben
- Orvosok 56%-a nem módosította a dózist az RRT megkezdésekor
- Leggyakrabban elnyújtott vagy folyamatos infúziót adtak
- Orvosok 62%-a ellenőriztette a gyógyszerszinteket
- Orvosok mindössze 3%-a használt MIPD szoftvert
- Célérték: megkérdezettek 53%-a 100% T>4xMIC, 16%-a T>1xMIC, 16%-a T>8xMIC értéket adott meg
- Orvosok 66%-a nem értett egyet azzal, hogy CRRT kezelés során gyakrabban jelennek meg neurotoxicitásra utaló tünetek

Matusik E et al. *BMC Nephrology* **2022**;*23*:48.

Köszönöm a figyelmet!