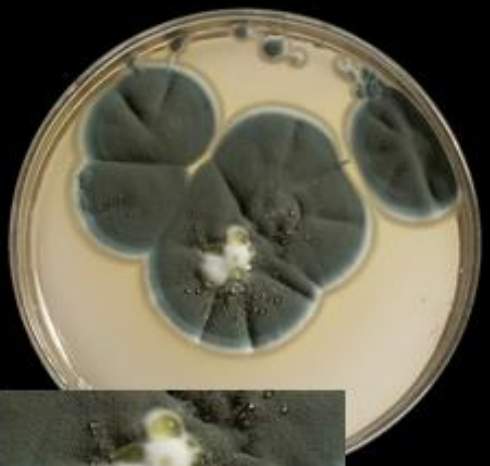
MARCELLO VIEIRA

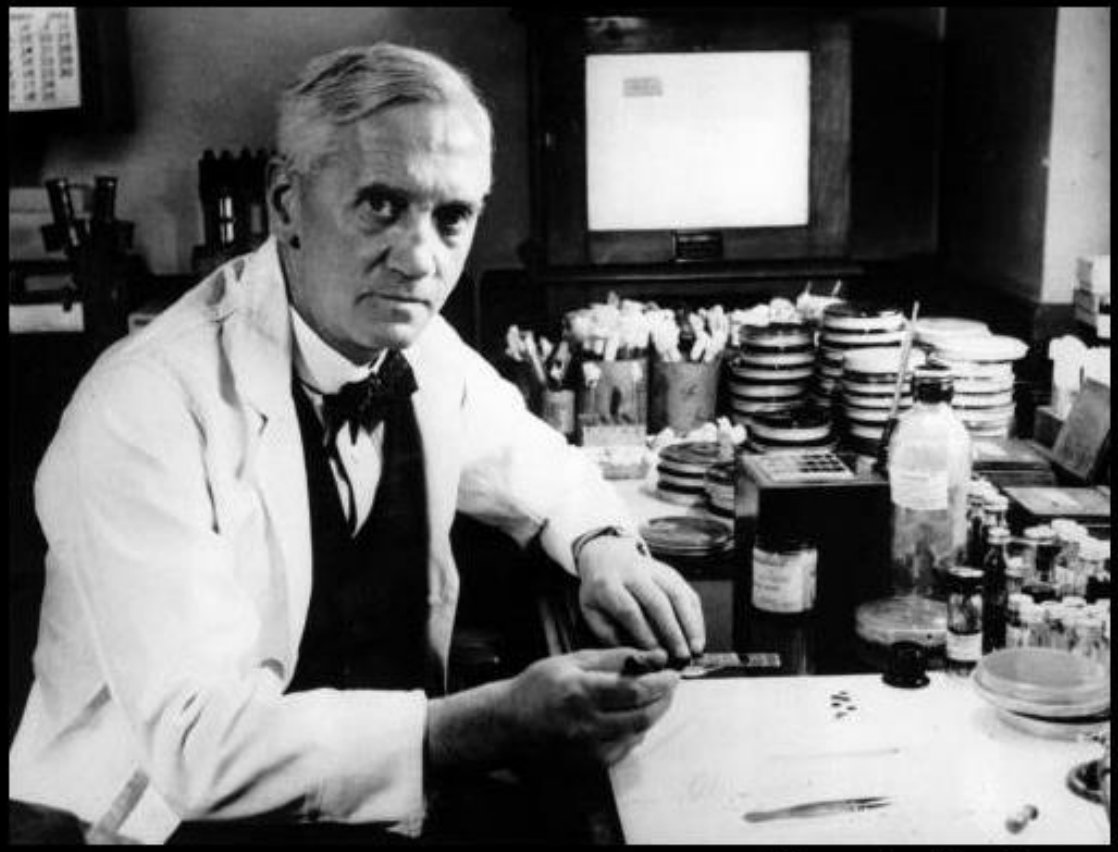
- INFECTOLOGISTA PELA UFRJ
- INTENSIVISTA PELA AMIB
- MÉDICO INTENSIVISTA E INFECTOLOGISTA HRSJ-HMG
- MÉDICO INTENSIVISTA DO HUGF
- MÉDICO INTENSIVISTA E INFECTOLOGISTA DA CSSS

ANTIBIOTICOTERAPIA NA UTI.

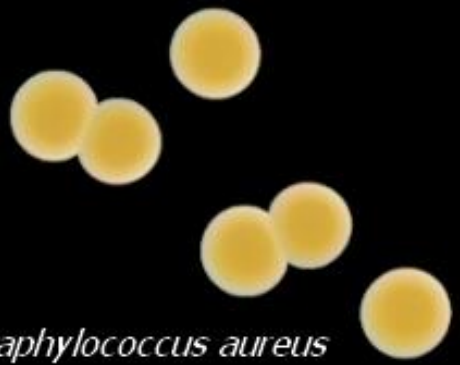
EXISTE LUZ NO FIM DO TÚNEL?



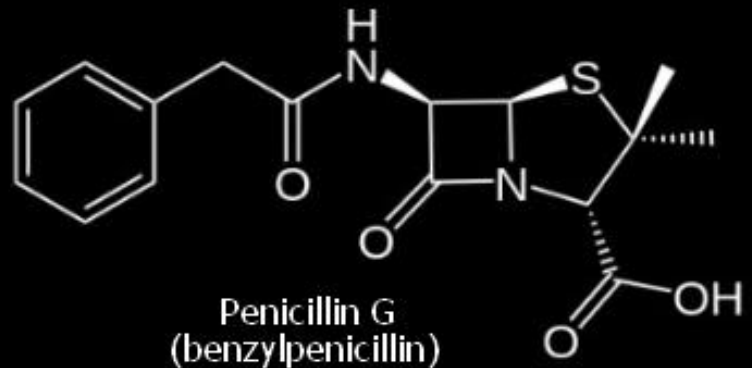
Penicillium chrysogenum
(P.notatum)



Alexander Fleming



Staphylococcus aureus

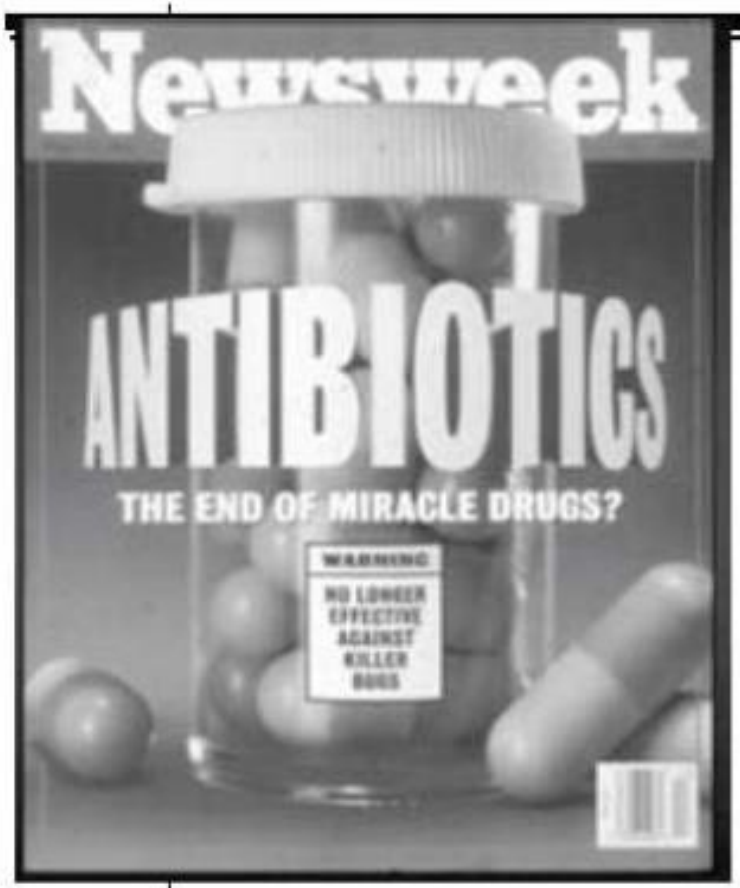


Penicillin G
(benzylpenicillin)

ANTIBIOTICOTERAPIA NA UTI.
EXISTE LUZ NO FIM DO TÚNEL?

- Resistência antimicrobiana detectada em DNA bacteriano congelado no Ártico por mais de 30.000 anos
- Resistência antimicrobiana detectada em DNA bacteriano encontrado em caverna profunda e isolado da superfície por mais de 4 milhões de anos.
- A partir dos anos 40 iniciou-se a pressão seletiva dos antibióticos.
- Alexander Fleming na sua apresentação no Premio Nobel estava preocupado com as consequências do uso dos antimicrobianos.
- Apenas 3 anos após discurso um Hospital de Londres reportou taxa 38% de S. aureus resistente a Penicilina.
- A partir daí a cada antibiótico lançado emergia uma bactéria resistente

CID 2013:56 (1 May) • HEALTHCARE EPIDEMIOLOGY



The more you use it, the faster you lose it!

Antibiótico X Resistência

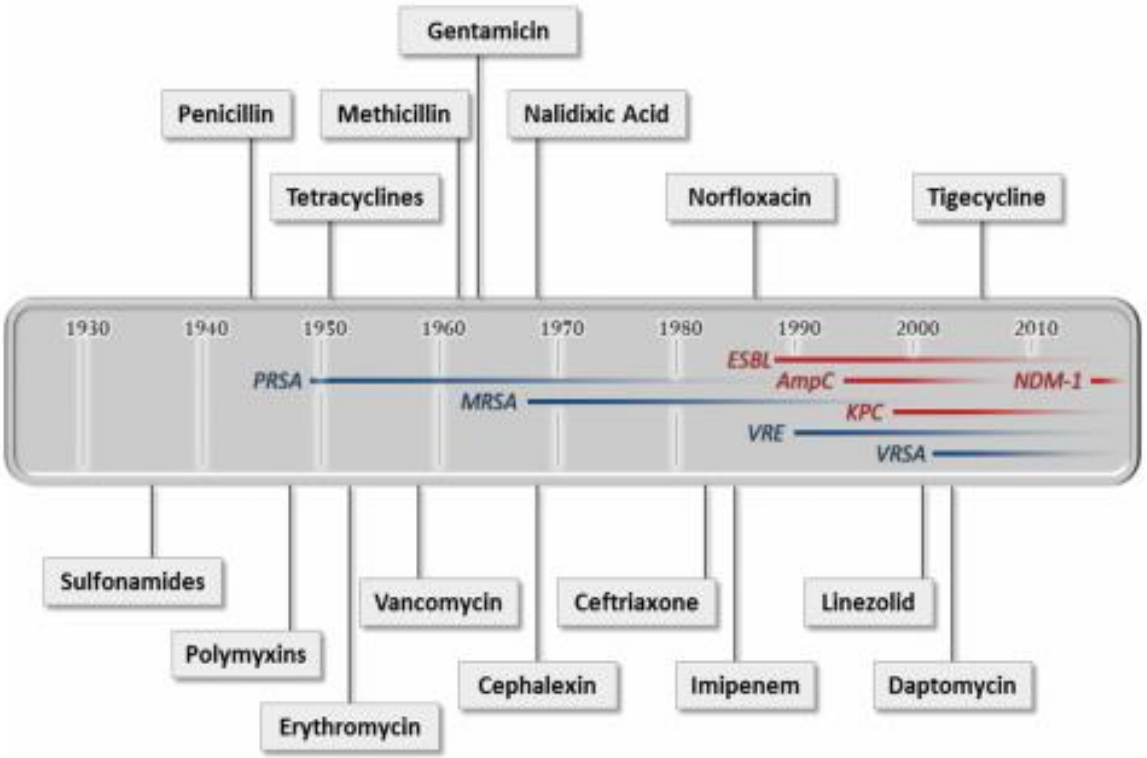


Figure 1. Antibiotic timeline. This timeline indicates the approximate dates that the major antibiotic classes or important antibiotics of each class were introduced into clinical use. The dates that resistant organisms were identified are shown in the centre of the timeline. Abbreviations: AmpC, AmpC–producing Enterobacteriaceae; ESBL, extended-spectrum β-lactamase–producing Enterobacteriaceae; KPC, *Klebsiella pneumoniae* carbapenemase–producing Enterobacteriaceae; MRSA, methicillin-resistant *Staphylococcus aureus*; NDM-1, New Delhi metallo-β-lactamase-1–producing Enterobacteriaceae; PRSA, penicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*; VRSA, vancomycin-resistant *Staphylococcus aureus*.

CID 2013:56 (1 May) • HEALTHCARE EPIDEMIOLOGY

MRSA

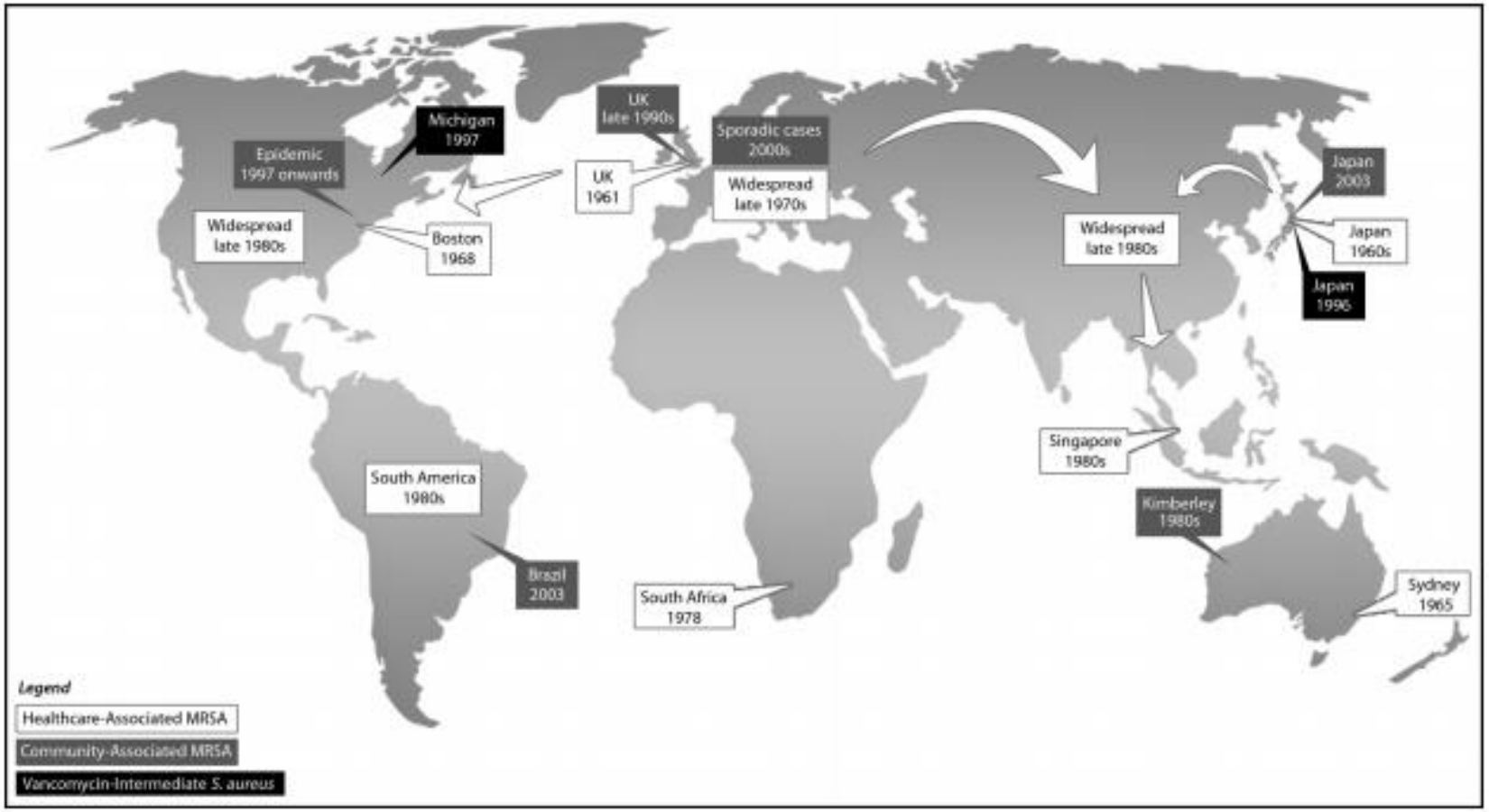


Figure 2. Global dissemination of methicillin-resistant *Staphylococcus aureus* (MRSA). This map indicates the countries in each continent providing the earliest reports of healthcare-associated MRSA, community-associated MRSA, and vancomycin-intermediate *Staphylococcus aureus*. The white arrows indicate the early movements of healthcare-associated MRSA around the world. Poor surveillance is highlighted by the lack of data for some regions. Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; UK, United Kingdom.

EMERGING INFECTIONS INVITED ARTICLE

James M. Hughes and Mary E. Wilson, Section Editors

The Globalization of Healthcare: Implications of Medical Tourism for the Infectious Disease Clinician

Lin H. Chen[1,2] and Mary E. Wilson[3]

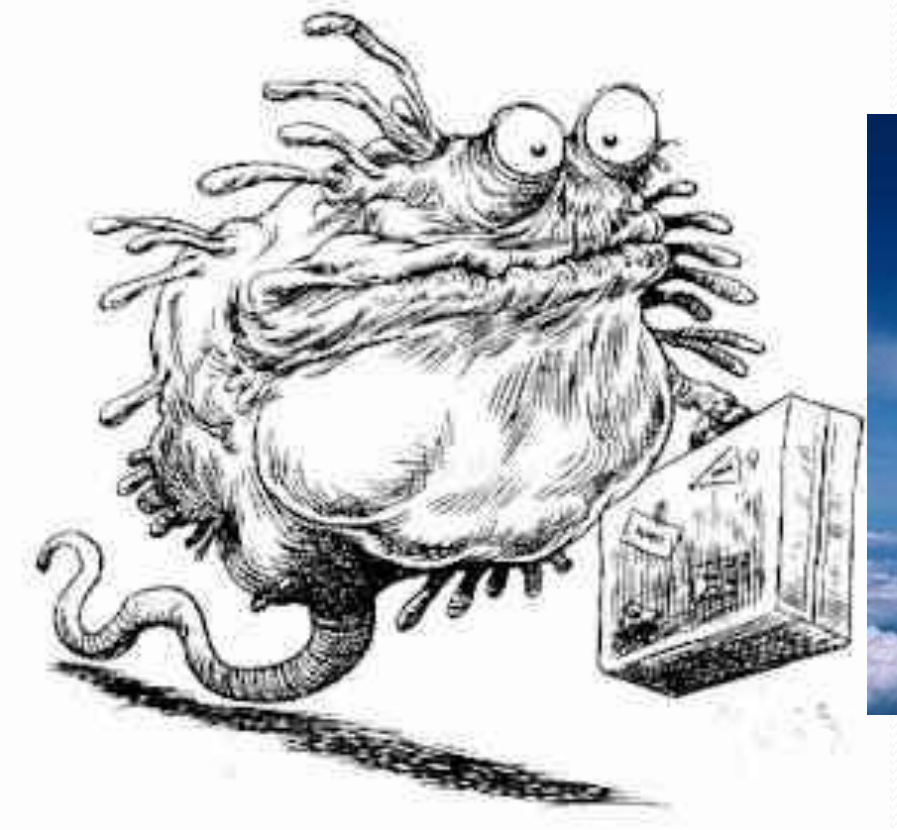
[1]Travel Medicine Center, Mount Auburn Hospital, Cambridge; [2]Harvard Medical School, and [3]Department of Global Health and Population, Harvard School of Public Health, Boston, Massachusetts

Travel abroad for healthcare has increased rapidly; interventions include organ transplant; cardiac surgery; reproductive care; and joint, cosmetic, and dental procedures. Individuals who receive medical care abroad are a vulnerable, sentinel population, who sample the local environment and can carry home unusual and resistant infections, documented in many reports. Medical tourists are at risk for hospital-associated and procedure-related infections as well as for locally endemic infections. Patients may not volunteer details about care abroad, so clinicians must inquire about medical procedures abroad as well as recent travel. Special infection control measures may be warranted. Healthcare abroad is associated with diverse financial, legal, ethical, and health-related issues. We focus on problems the infectious disease clinician may encounter and provide a framework for evaluating returned medical tourists with suspected infections. A better system is needed to ensure broad access to high-quality health services, continuity of care, and surveillance for complications.

Keywords. medical tourism; cross-border healthcare; multidrug-resistant organisms; transplant tourism; healthcare globalization.

Clinical Infectious Diseases 2013;57(12):1752–9

Turismo na Saúde



CID 2013:56 (1 May) • HEALTHCARE EPIDEMIOLOGY

ERC X TURISMO DA SAÚDE

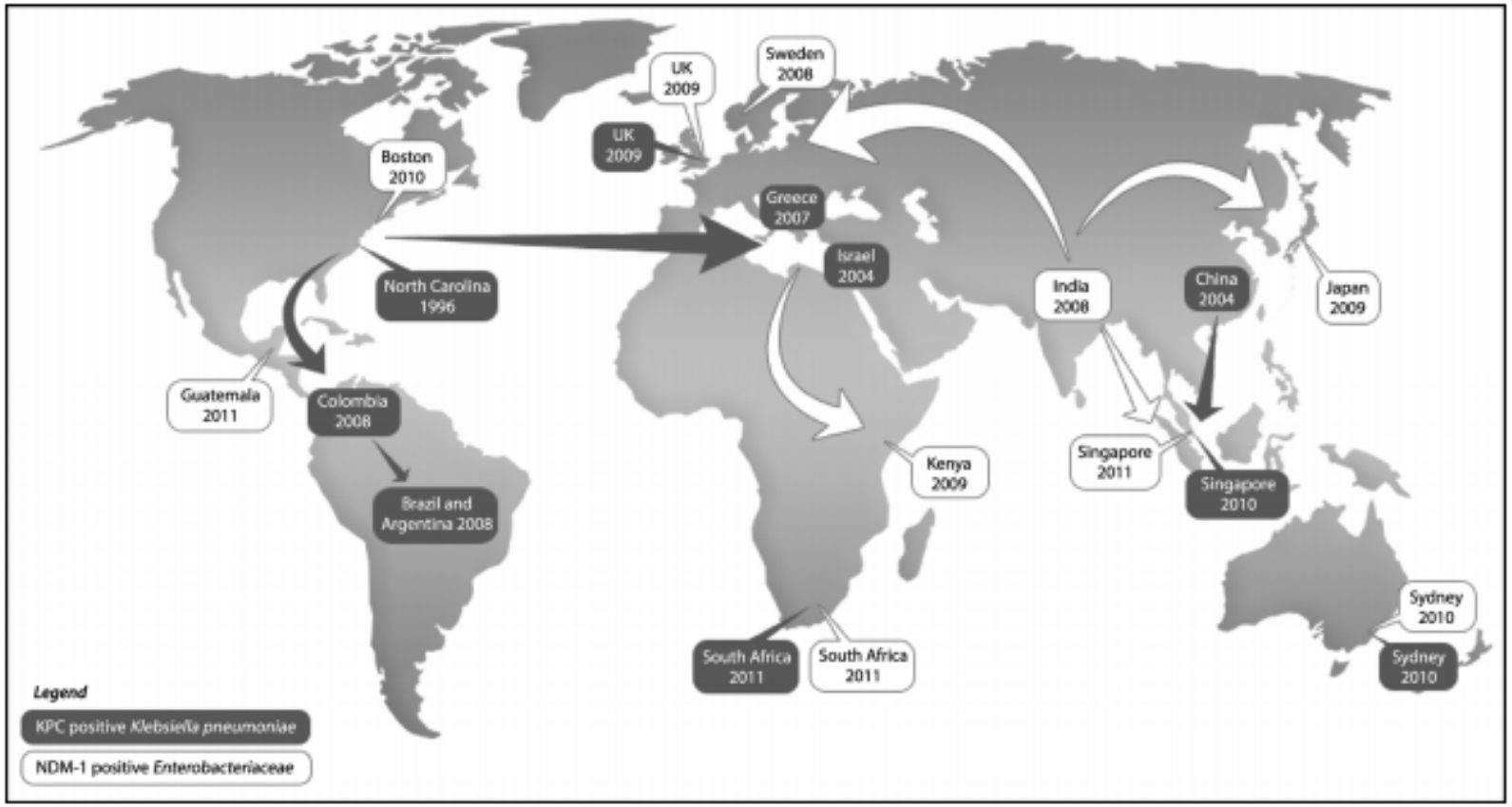


Figure 4. Global dissemination of *Klebsiella pneumoniae* carbapenemase–producing *K.* pneumoniae and New Delhi metallo-β-lactamase-1–producing Enterobacteriaceae. The earliest reported cases in each continent are shown. Arrows indicate the significant international movements of these organisms. Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase; NDM-1, New Delhi metallo-β-lactamase–1; UK, United Kingdom.

CID 2013:56 (1 May) • HEALTHCARE EPIDEMIOLOGY

IDSA REPORT

Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America

Helen W. Boucher,[1] George H. Talbot,[2] John S. Bradley,[3,4] John E. Edwards, Jr,[5,6,7] David Gilbert,[8] Louis B. Rice,[9,10] Michael Scheld,[11] Brad Spellberg,[5,6,7] and John Bartlett[12]

[1]Division of Geographic Medicine and Infectious Diseases, Tufts University and Tufts Medical Center, Boston, Massachusetts; [2]Talbot Advisors, Wayne, Pennsylvania; [3]Division of Infectious Diseases, Rady Children's Hospital San Diego, and [4]University of California at San Diego, San Diego, [5]Division of Infectious Diseases, Harbor–University of California at Los Angeles (UCLA) Medical Center, and [6]Los Angeles Biomedical Research Institute, Torrance, and [7]The David Geffen School of Medicine at UCLA, Los Angeles, California; [8]Division of Infectious Diseases, Providence Portland Medical Center and Oregon Health Sciences University, Portland; [9]Medical Service, Louis Stokes Cleveland Veterans Administration Medical Center, and [10]Department of Medicine, Case Western Reserve University School of Medicine, Cleveland, Ohio; [11]Department of Medicine, University of Virginia School of Medicine, Charlottesville; and [12]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland

Clinical Infectious Diseases 2009; 48:1–12

Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America

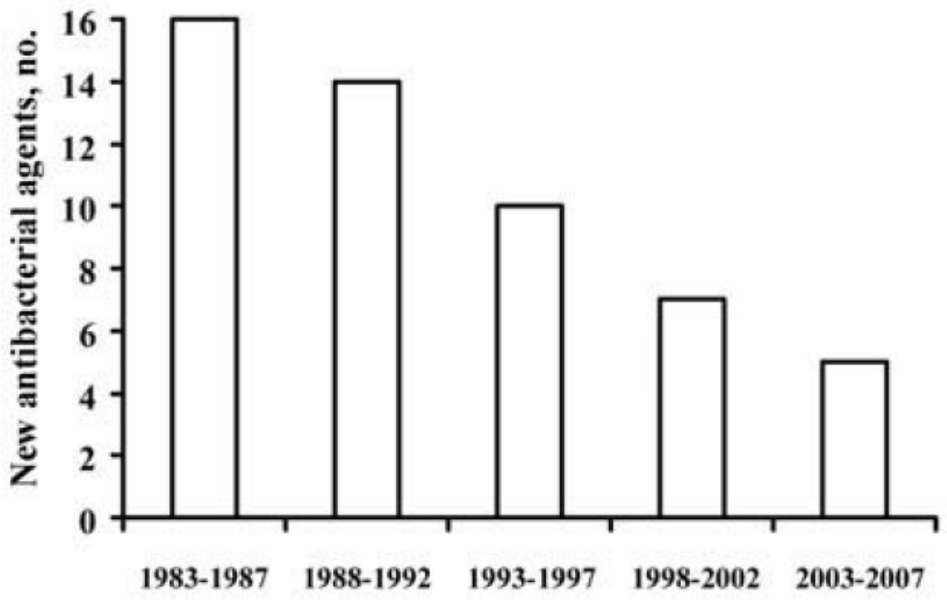
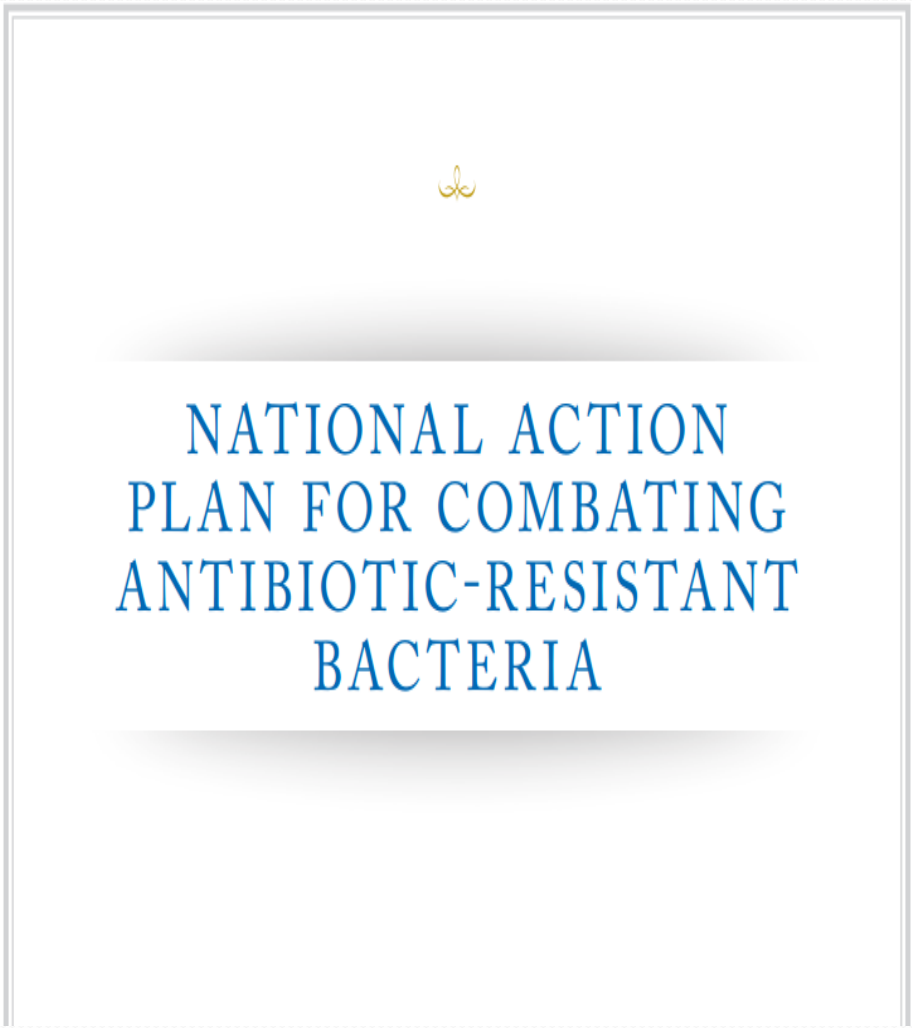


Figure 1. New antibacterial agents approved in the United States, 1983–2007, per 5-year period [2, 3].

Clinical Infectious Diseases 2009; 48:1–12

Barack Obama. O cara!



Goals of the *National Action Plan*

The *National Action Plan*—informed by the guiding principles in Table 2—is organized around five goals for collaborative action by the U.S. Government, in partnership with foreign governments, individuals, and organizations aiming to strengthen healthcare, public health, veterinary medicine, agriculture, food safety, and research and manufacturing. Aggressive action will move the nation towards major reductions in the incidence of urgent and serious drug-resistant threats (Table 3), including carbapenem-resistant *Enterobacteriaceae* (CRE), methicillin-resistant *Staphylococcus aureus* (MRSA), and *Clostridium difficile*.

- Misuse and over-use of antibiotics in healthcare and food production continue to hasten the development of bacterial drug resistance, leading to loss of efficacy of existing antibiotics.
- Detecting and controlling antibiotic-resistance requires the adoption of a "One-Health" approach to disease surveillance that recognizes that resistance can arise in humans, animals, and the environment.
- Implementation of evidence-based infection control practices can prevent the spread of resistant pathogens.
- Interventions are necessary to accelerate private sector investment in the development of therapeutics to treat bacterial infections because current private sector interest in antibiotic development is limited.
- Researchers can use innovations and new technologies—including whole genome sequencing, metagenomics, and bioinformatic approaches—to develop next-generation tools to strengthen human and animal health, including:
  - Point-of-need diagnostic tests to distinguish rapidly between bacterial and viral infections as well as identify bacterial drug susceptibilities;
  - New antibiotics and other therapies that provide much needed treatment options for those infected with resistant bacterial strains; and
  - Antibiotic resistance is a global health problem that requires international attention and collaboration, because bacteria do not recognize borders.

Bad Bugs, No Drugs: Are We Part of the Problem, or Leaders in Developing Solutions?

- 21% das admissõs nas UTIs são por infecção.
- 10% das admissões por não infecção desenvolverão infecção nas 24h após a admissão
- Nos pacientes com internação > 7 dias cerca de 70% estarão infectados
- A qualquer período de tempo cerca de 51% dos pacientes nas UTIs estão infectados e cerca de 71% estão em uso de antibióticos
- MRSA, ERC (KPC, NDM), VRE, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Clostridium difficile,* entre outros.

Vincent JL, Rello J, Marshall J, et al: International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009;302(21):2323–2329

Bad Bugs, No Drugs: Are We Part of the Problem, or Leaders in Developing Solutions?

3 áreas importantes de atuação

1- Prevenção de infecções => Bundles, higienização das mãos (cada paciente na UTI é tocado em média 178 vezes/dia, adesão à pratica 30-40%), medidas de precauções de contato para germes MDR.

2- Antibiotic stewardship (gestão de uso de antibióticos): não usar desnecessariamente, reduzir tempo de uso, adequar terapêutica conforme identificação do agente, **adequando PK/PD dos antimicrobianos nos pacientes críticos.**

3- Políticas Públicas => IDSA, OMS e Governo Americano

Brooke Decker, MD
University of Pittsburgh
Henry Masur, MDNIH-Clinical Center
Critical Care Medicine June 2015 • Volume 43 • Number 6

DALI: Defining Antibiotic Levels in Intensive Care Unit Patients: Are Current β-Lactam Antibiotic Doses Sufficient for Critically Ill Patients?

Background. Morbidity and mortality for critically ill patients with infections remains a global healthcare problem. We aimed to determine whether β-lactam antibiotic dosing in critically ill patients achieves concentrations associated with maximal activity and whether antibiotic concentrations affect patient outcome.

Methods. This was a prospective, multinational pharmacokinetic point-prevalence study including 8 β-lactam antibiotics. Two blood samples were taken from each patient during a single dosing interval. The primary pharmacokinetic/pharmacodynamic targets were free antibiotic concentrations above the minimum inhibitory concentration (MIC) of the pathogen at both 50% (50% $f\,T_{>MIC}$) and 100% (100% $f\,T_{>MIC}$) of the dosing interval. We used skewed logistic regression to describe the effect of antibiotic exposure on patient outcome.

Results. We included 384 patients (361 evaluable patients) across 68 hospitals. The median age was 61 (interquartile range [IQR], 48–73) years, the median Acute Physiology and Chronic Health Evaluation II score was 18 (IQR, 14–24), and 65% of patients were male. Of the 248 patients treated for infection, 16% did not achieve 50% $f\,T_{>MIC}$ and these patients were 32% less likely to have a positive clinical outcome (odds ratio [OR], 0.68; $P = .009$). Positive clinical outcome was associated with increasing 50% $f\,T_{>MIC}$ and 100% $f\,T_{>MIC}$ ratios (OR, 1.02 and 1.56, respectively; $P < .03$), with significant interaction with sickness severity status.

Conclusions. Infected critically ill patients may have adverse outcomes as a result of inadeqaute antibiotic exposure; a paradigm change to more personalized antibiotic dosing may be necessary to improve outcomes for these most seriously ill patients.

Keywords. continuous infusion; extended infusion; adverse events; pharmacokinetics; pharmacodynamics.

Clinical Infectious Diseases 2014;58(8):1072–83

PK/PD	ceftriaxona	Cefepime	Pipetazo	meropenem
Dose 24 h	2,0 g	6,0 g	12,0 g	3,0
50% $_{F}T$ > MIC	97%	78,6%	80,6%	95%
50%$_{F}T$ > $_{4\,x}$MIC	93,9%	50%	48,9%	68,8%
100%$_{F}T$ > MIC	93,9%	78%	67,0%	69,7%
100%$_{F}T$ >$_{4\,x}$ MIC	87,9%	71,4%	30,3%	41,6%

Clinical Infectious Diseases 2014;58(8):1072–83


Ok.....
Mas por onde começar??

Usem o antimicrobiano por via oral, intravenosa mas nunca por via das dúvidas!!!!

PK/PD

- Farmacocinética (PK)

É o estudo do resultado de uma dose de um fármaco na sua concentração plasmática e tecidual

- Farmacodinâmica (PD)

É o estudo da relação entre concentração do fármaco e seu efeito farmacológico

Características físico-químicas

- Drogas hidrofílicas -> se relaciona com volume extravascular, com penetração em região com alta concentração de água. Clearance geralmente renal.

B-lactâmicos, aminoglicosídeos, glicopeptídeos (Vancomicina e teicoplamina) e lipopetídeos.

- Drogas lipofílicas=> se dissolvem através das membranas celulares dos lipídeos e com alta concentração intra-celular. Clearence geralmente hepático.

Fluoroquinolonas, macrolideos, lincosaminas, tetraciclinas,

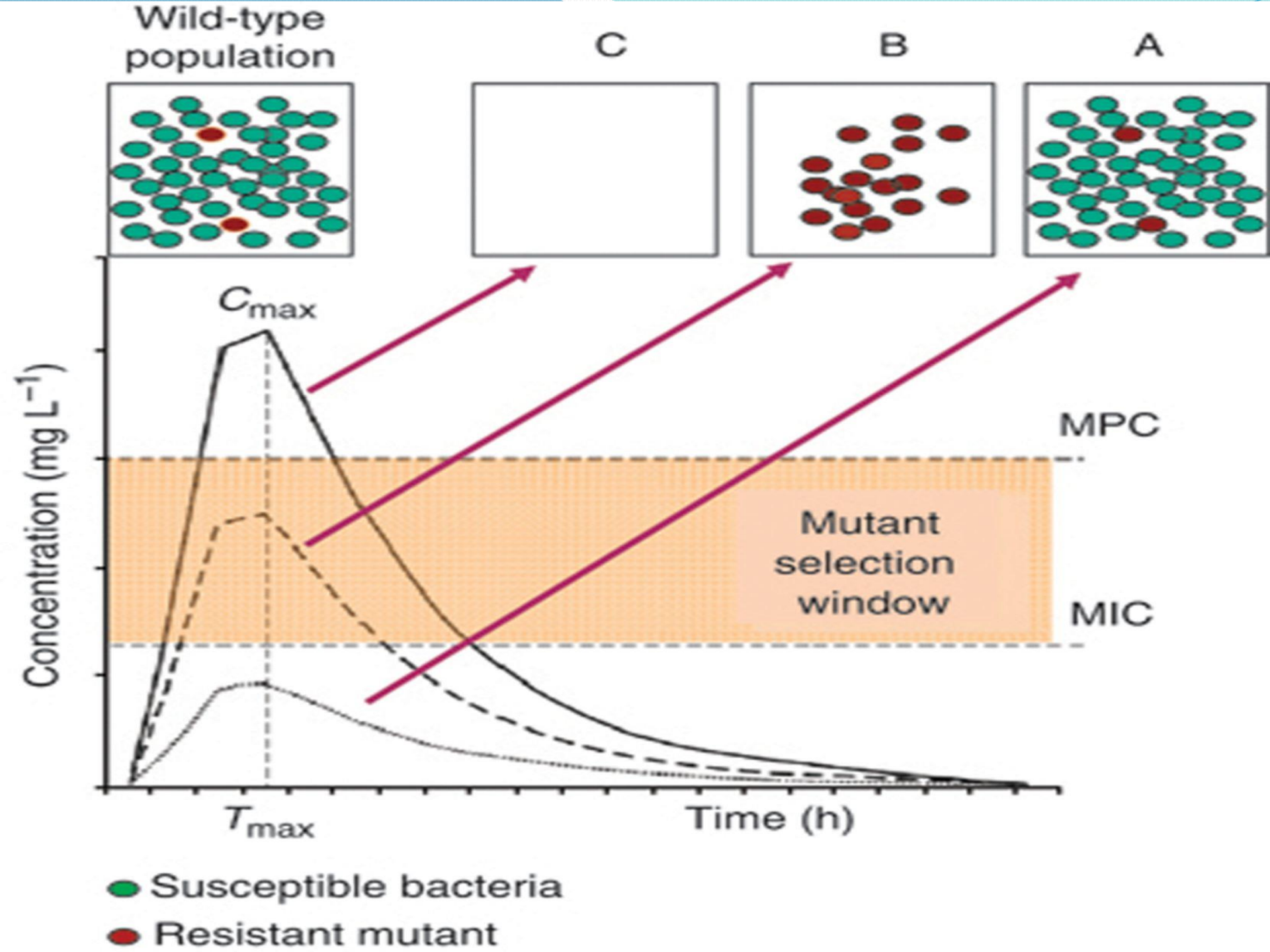
Vincent et alCritical Care (2016) 20:133

Farmacocinética

- $C_{máx}$: pico de concentração após uma dose
- $T_{máx}$: tempo após administração até atingir $C_{máx}$
- **Volume de distribuição (Vd):** volume aparente de fluido que contém a dose total administrada na mesma concentração plasmática
- **Clearance (CL):** quantifica a eliminação irreversível do fármaco por metabolismo/excreção.
- **Meia-vida de eliminação ($t_{1/2}$):** tempo da conc. Plasmática para cair a metade (relacionado com o CL e VD)
- **Ligação proteica**: ligação do fármaco às ptns plasmáticas (albumina e $\alpha_1$glicoproteína
- **AUC $_{0\text{-}24h}$** área total sob a curva concentração-tempo ao longo de 24 h

PK/PD

- **$F_{T>CIM}$: tempo entre intervalo de doses que a concentração de droga livre excede a CIM**
- **$C_{máx}$/CIM: razão entre a concentração de pico e a concentração inibitória mínima**
- **AUC_{0-24}/CIM: razão entre a área total sob a curva concentração-tempo ao longo de 24 h e a CIM**
- **Antibióticos tempo-dependente: cuja atividade depende do tempo em que as concentrações plasmáticas são mantidas acima da CIM ($F_{T>CIM}$)**
- **Antibióticos concentração-dependente: atividade se correlaciona com a magnitude do pico de concentração obtido ($C_{máx}$/CIM)**
- **Concentração no sítio de infecção**
- **Supressão de resistência**


Wild-type population
C
B
A
C_{max}
MPC
Mutant selection window
MIC
Concentration (mg L^{-1})
T_{max}
Time (h)
Susceptible bacteria
Resistant mutant

PK/PD nos pacientes críticos

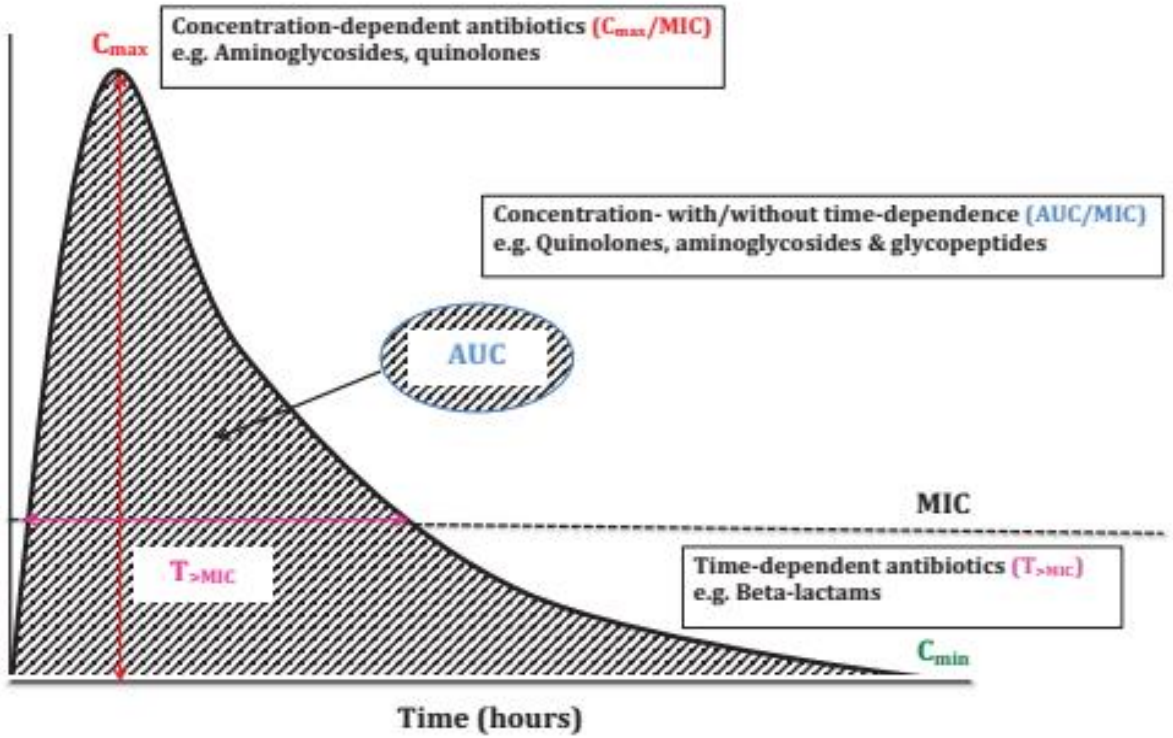


Fig. 1 The graphical illustration of fundamental pharmacokinetic and pharmacodynamic parameters of antibiotics on a hypothetical concentration–time curve. AUC, area under the concentration–time curve; C_{max}, maximum drug concentration; C_{min}, minimum drug concentration; MIC, minimum inhibitory concentration; $T_{>MIC}$, duration of time that drug concentration remains above MIC.

Seminars in Respiratory and Critical Care Medicine
Vol. 36 No. 1/2015

Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions

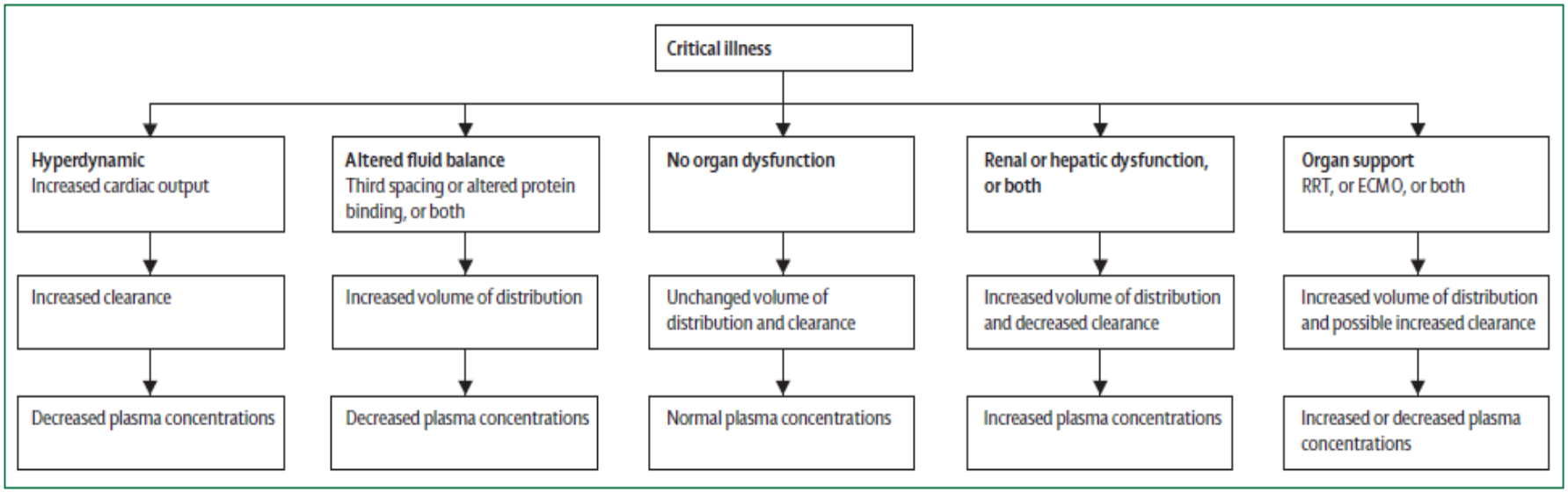


Figure: **The range of altered pathophysiology in patients with critical illness, and its effects on drug concentrations**
RRT=renal replacement therapy. ECMO=extracorporeal membrane oxygenation.

Lancet Infect Dis 2014;14: 498–509

Como Otimizar infusão de β-Lactâmicos

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Review

Prolonging β-lactam infusion: A review of the rationale and evidence, and guidance for implementation

Continuous Infusion of Beta-Lactam Antibiotics in Severe Sepsis: A Multicenter Double-Blind, Randomized Controlled Trial

Clinical Outcomes With Extended or Continuous Versus Short-term Intravenous Infusion of Carbapenems and Piperacillin/Tazobactam: A Systematic Review and Meta-analysis

International Journal of Antimicrobial Agents 43 (2014) 105– 113
Clinical Infectious Diseases 2013;56(2):236–44
Clinical Infectious Diseases 2013;56(2):272–82

Infusão prolongada/continua de β-Lactâmicos

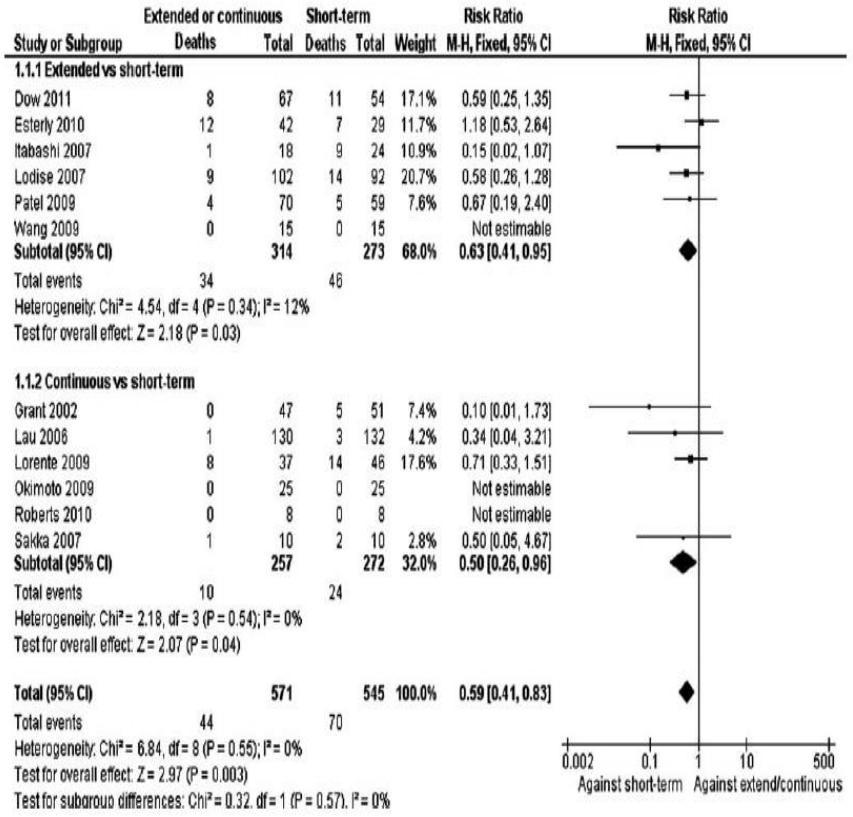


Figure 2. Forest plot depicting the risk ratios of mortality of patients receiving extended or continuous versus short-term infusion of carbapenems and piperacillin/tazobactam, stratified by continuous and extended infusion. Vertical line, "no difference" point between the 2 regimens; squares, risk ratios; diamonds, pooled risk ratios; horizontal lines, 95% confidence interval. Abbreviation: CI, confidence interval.

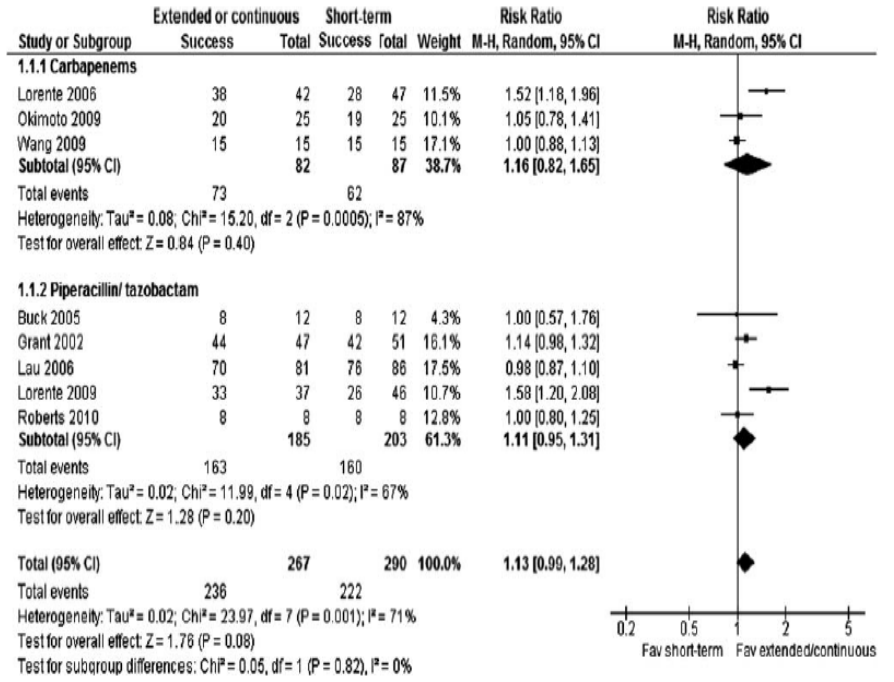
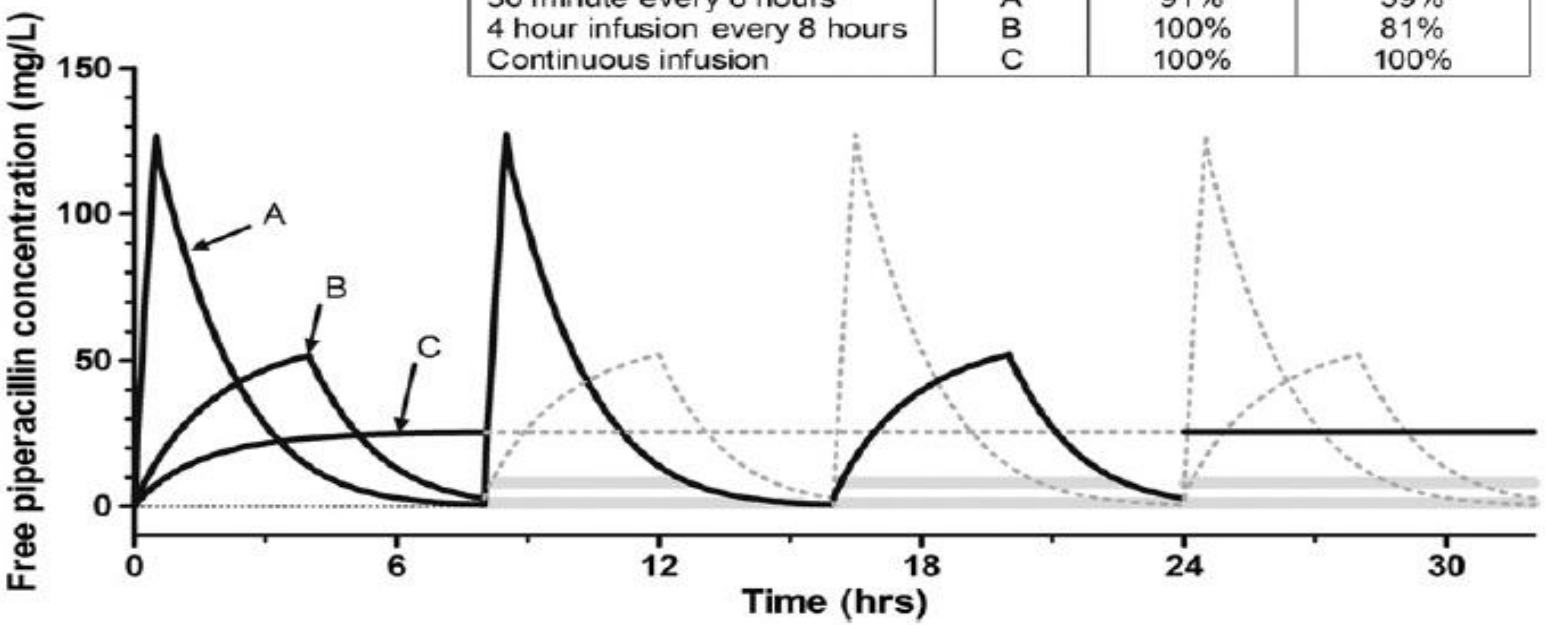


Figure 4. Forest plot depicting the risk ratios of clinical cure of patients receiving extended or continuous versus short-term infusion of carbapenems and piperacillin/tazobactam, stratified by continuous and extended infusion. Vertical line, "no difference" point between the 2 regimens; squares, risk ratios; diamonds, pooled risk ratios; horizontal lines, 95% confidence interval. Abbreviation: CI, confidence interval.

Clinical Infectious Diseases 2013;56(2):272–82

Bolus X infusão prolongada/contínua de β-Lactâmicos

	Graph label	Free drug Time>MIC	
		1mg/L	8mg/L
30 minute every 8 hours	A	91%	59%
4 hour infusion every 8 hours	B	100%	81%
Continuous infusion	C	100%	100%



How severe is antibiotic pharmacokinetic variability in critically illpatients and what can be done about it? Diagnostic Microbiology and Infectious Disease 79 (2014) 441–447

Piperacillin concentration in relation to therapeutic range in critically ill patients – a prospective observational study

Johannes Zander[1], Gundula Döbbeler[2], Dorothea Nagel[1], Barbara Maier[1], Christina Scharf[2], Mikayil Huseyn-Zada[1], Jette Jung[3], Lorenz Frey[2], Michael Vogeser[1] and Michael Zoller[2*]

Abstract

Background: Piperacillin levels after standard dosing have been shown frequently to be subtherapeutic, especially when renal clearance was augmented. Here, we aimed to determine if piperacillin was in its therapeutic range in a typically heterogeneous intensive care unit patient group, and also to describe target attainment dependent on daily dosage, creatinine clearance, and renal replacement therapy (RRT).

Methods: Sixty patients with severe infections were included in this monocentric prospective observational study. Patients received 4.5 g of piperacillin-tazobactam two to three times daily by intermittent infusion depending on renal function according to clinical guidelines. Over 4 days, multiple serum samples (median per patient, 29; in total, 1627) were obtained to determine total piperacillin concentrations using ultra-high-performance liquid chromatography/tandem mass spectrometry.

Results: A high heterogeneity of patient characteristics was observed (e.g., on day 1: creatinine clearance 2–233 mL/min and ten patients on RRT). Piperacillin trough levels showed inter-individual variation from 123 to >1785-fold on different study days. Each day, approximately 50 % and 60 % of the patients had piperacillin levels below the target ranges 1 and 2, respectively [defined for the calculated unbound piperacillin fraction according to the literature as 100 % time above MIC (100 %fT > MIC) (target range 1) and ≥ 50 %fT > 4 × MIC (target range 2); MIC = 16 mg/L]. Whereas only the minority of patients who received piperacillin-tazobactam three times daily (TID) reached target 1 (38 % on day 1), most patients who received piperacillin-tazobactam only twice daily (BID) because of severely impaired renal function reached this target (100 % on day 1). Patients with RRT had significant higher percentages of fT > MIC. Zero percent, 55 % and 100 % of patients without RRT who received antibiotics TID reached target 1 when creatinine clearance was > 65 mL/min, 30–65 mL/min and < 30 mL/min, respectively. In patients with causative strains only sensitive to piperacillin-tazobactam of all antibiotics given to the patient, piperacillin levels negatively correlated with CRP concentrations of day 4 ($p < 0.05$).

Conclusions: A dosage of 4.5 g piperacillin-tazobactam TID seems to be frequently insufficient in critically ill patients, and also in patients where renal function is mildly to moderately impaired. For these patients, prescription of 4.5 g piperacillin-tazobactam four times daily could be considered.

Trial registration: Clinicaltrials.gov NCT01793012. Registered 24 January 2013.

Keywords: Target range, Intensive care unit, Creatinine clearance, Variability, Dosage, Antibiotics, Renal replacement therapy, C-reactive protein

Enterobacterias ESBL

Enterobactérias produtoras de Carbapenemases

Fatores de Risco para ESBL e ERC

FR ESBL comunitária	FR ESBL hospitalar	FR ERC hospitalar
> 70 anos	Prevalencia local (surto)	Prevalencia local (surto)
DM	Hospitalização prolongada	> 70 anos
Internação Hosp. Prévia	Procedimentos invasivos (VM)	DM
Transferência de Unidade de saúde	Colonização prévia	Internação na UTI
Cateter urinário	Uso prévio de cefalosporinas	Procedimentos invasivos (CVC, endoscopia, VM)
Uso de aminopenicilinas	Uso prévio de fluoroquinolonas	Uso prévio de cefalosporinas
Uso de fluoroquinolonas	Uso prévio de carbapenêmicos	Uso previo de fluoroquinolonas
Uso de cefalosporinas		Uso prévio de carbapenêmicos
Viagem recente a áreas endêmicas		

Curr Opin Infect Dis 2016, 29:000–000

Classificação das Carbapenemases

Table 3. Classification of most frequent carbapenemases

Type of carbapenemase	Molecular class	Substrates of hydrolysis	Species distribution in *Enterobacteriaceae*	Geographical epicenters
KPC	A	All β-lactams	*K. pneumoniae*, *Escherichia coli*, *Enterobacter* spp. Diverse *Enterobacteriaceae*	The United States, Greece, Italy, Israel, China
VIM (MBLs)	B	All β-lactams except aztreonam	*K. pneumoniae*	Greece, Italy
NDM (MBLs)	B	All β-lactams except aztreonam	*K. pneumoniae* and *E. coli* predominantly Diverse *Enterobacteriaceae*	Indian subcontinent, Balkans, the Middle East
OXA-48	D	Penicillins and carbapenems	*K. pneumoniae* predominantly Diverse *Enterobacteriaceae*	North Africa, the Middle East, Spain

KPC, *Klebsiella pneumoniae* carbapenemase; MBLs, metallo-β-lactamases; NDM, New Delhi metallo-β-lactamase; OXA-48, oxacillinase-48; VIM, Verona integron-encoded metallo-β-lactamase.

Curr Opin Infect Dis 2016, 29:000–000

Carbapenem Therapy Is Associated With Improved Survival Compared With Piperacillin-Tazobactam for Patients With Extended-Spectrum β-Lactamase Bacteremia

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β-lactam and β-lactamase inhibitor combinations in the treatment of extended-spectrum β-lactamase producing Enterobacteriaceae: time for a reappraisal in the era of few antibiotic options?

Patrick N A Harris, Paul A Tambyah, David L Paterson

The spread of extended-spectrum β-lactamase (ESBL) genes in Enterobacteriaceae such as *Escherichia coli* or *Klebsiella* spp is a major challenge to modern medical practice. Carbapenems are the treatment of choice for serious infections caused by ESBL producers; however, carbapenem resistance has increased globally. ESBL producers might be susceptible to β-lactam-β-lactamase inhibitor (BLBLI) combination antibiotics such piperacillin–tazobactam or amoxicillin–clavulanate. These drugs are frequently avoided in serious infections caused by ESBL producers because of the inoculum effect in-vitro (especially for piperacillin–tazobactam), animal data suggesting inferior efficacy when compared with carbapenems, concerns about pharmacokinetic–pharmacodynamic drug target attainment with standard doses, and poor outcomes shown in some observational studies. Prospective cohort data and a meta-analysis suggest that BLBLIs are non-inferior to carbapenems in the treatment of bloodstream infections caused by ESBL producers. We examine why BLBLIs are perceived as inferior in the treatment of infection with ESBL producers, and discuss data that suggest these concerns might not be strongly supported by clinical evidence.

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The management of multidrug-resistant *Enterobacteriaceae*

Matteo Bassetti, Maddalena Peghin, and Davide Pecori

Purpose of review

Multidrug-resistant (MDR) *Enterobacteriaceae* are often related to the production of extended-spectrum β-lactamases (ESBLs) and carbapenemases. ESBL and carbapenemase-producing *Enterobacteriaceae* (CRE), in particular, represent an increasing global threat. Recommendations for the therapeutic management of MDR-related infections, however, are mainly derived from retrospective and nonrandomized prospective studies. The aim of this review is to discuss the challenges in the treatment of patients with infections because of MDR *Enterobacteriaceae* and provide an expert opinion while awaiting for more definitive data.

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Insights into Newer Antimicrobial Agents Against Gram-negative Bacteria

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ABSTRACT: Currently, drug resistance, especially against cephalosporins and carbapenems, among gram-negative bacteria is an important challenge, which is further enhanced by the limited availability of drugs against these bugs. There are certain antibiotics (colistin, fosfomycin, temocillin, and rifampicin) that have been revived from the past to tackle the menace of superbugs, including members of *Enterobacteriaceae*, *Acinetobacter* species, and *Pseudomonas* species. Very few newer antibiotics have been added to the pool of existing drugs. There are still many antibiotics that are passing through various phases of clinical trials. The initiative of Infectious Disease Society of America to develop 10 novel antibiotics against gram-negative bacilli by 2020 is a step to fill the gap of limited availability of drugs. This review aims to provide insights into the current and newer drugs in pipeline for the treatment of gram-negative bacteria and also discusses the major challenging issues for their management.

KEYWORDS: novel antibiotics, gram-negative bacteria, challenges in management, drug resistance, carbapenem resistance

Tratamento Enterobactérias ESBL
MIC PIPETAZO ≤ 16/4 mg/l

antibiótico	PNM	BSI	IAI	UTI
PIPETAZO	4,5 g 6/6 h Inf. Cont/prolongada)	4,5 g 6/6 h Inf. Cont/prolongada)	4,5 g 6/6 h Inf. Cont/prolongada)	4,5 g 6/6 h Inf. Cont/prolongada)
Carbapenêmicos infusão cont/prolongada*	Meropenem 1-2 g 8/8 h/IMP 0,5 g 6/6 h ou IMP 1 g 8/8 h	Meropenem 1-2 g 8/8 h/IMP 0,5 g 6/6 h ou IMP 1 g 8/8 h	Meropenem 1-2 g 8/8 h/IMP 0,5 g 6/6 h ou IMP 1 g 8/8 h	Meropenem 1-2 g 8/8 h/IMP 0,5 g 6/6 h ou IMP 1 g 8/8 h
Tigeciclina	não	não	100 mg de ataque -> 50 mg 12/12 h	não
Carbapenêmicos + Amicacina	* + amicacina 15-20 mg/kg 1 x dia	* + amicacina 15-20 mg/kg 1 x dia	* + amicacina 15-20 mg/kg 1 x dia	* + amicacina 15-20 mg/kg 1 x dia

Tratamento das Enterobactérias Produtoras de carbapenemases (ERC)

MAJOR ARTICLE

Population Pharmacokinetics of Intravenous Polymyxin B in Critically Ill Patients: Implications for Selection of Dosage Regimens

Ana M. Sandri,[1,a] Cornelia B. Landersdorfer,[2,3,a] Jovan Jacob,[4] Márcio M. Boniatti,[5] Micheline G. Dalarosa,[6] Diego R. Falci,[6] Tainá F. Behle,[7] Rosaura C. Bordinhão,[6] Jiping Wang,[4] Alan Forrest,[3] Roger L. Nation,[4] Jian Li,[4,b] and Alexandre P. Zavascki[7,b]

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Clinical Infectious Diseases 2013;57(4):524–31

Tratamento das Enterobactérias Produtoras de carbapenemases (ERC)

Infect Dis Ther (2015) 4:391–415
DOI 10.1007/s40121-015-0093-7

REVIEW

Optimizing Polymyxin Combinations Against Resistant Gram-Negative Bacteria

Phillip J. Bergen · Zackery P. Bulman · Cornelia B. Landersdorfer · Nicholas Smith · Justin R. Lenhard · Jürgen B. Bulitta · Roger L. Nation · Jian Li · Brian T. Tsuji

Tratamento das Enterobactérias Produtoras de carbapenemases (ERC)

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Short communication

Impact of various conditions on the efficacy of dual carbapenem therapy against KPC-producing *Klebsiella pneumoniae*

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Tratamento das Enterobactérias Produtoras de carbapenemases (ERC)

CURRENT OPINION

The management of multidrug-resistant *Enterobacteriaceae*

Matteo Bassetti, Maddalena Peghin, and Davide Pecori

Purpose of review
Multidrug-resistant (MDR) *Enterobacteriaceae* are often related to the production of extended-spectrum β-lactamases (ESBLs) and carbapenemases. ESBL and carbapenemase-producing *Enterobacteriaceae* (CRE), in particular, represent an increasing global threat. Recommendations for the therapeutic management of MDR-related infections, however, are mainly derived from retrospective and nonrandomized prospective studies. The aim of this review is to discuss the challenges in the treatment of patients with infections because of MDR *Enterobacteriaceae* and provide an expert opinion while awaiting for more definitive data.

Curr Opin Infect Dis 2016, 29:000–000

Tratamento das Enterobactérias Produtoras de carbapenemases (ERC)

Insights into Newer Antimicrobial Agents Against Gram-negative Bacteria

Neelam Taneja and Harsimran Kaur

Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

ABSTRACT: Currently, drug resistance, especially against cephalosporins and carbapenems, among gram-negative bacteria is an important challenge, which is further enhanced by the limited availability of drugs against these bugs. There are certain antibiotics (colistin, fosfomycin, temocillin, and rifampicin) that have been revived from the past to tackle the menace of superbugs, including members of *Enterobacteriaceae*, *Acinetobacter* species, and *Pseudomonas* species. Very few newer antibiotics have been added to the pool of existing drugs. There are still many antibiotics that are passing through various phases of clinical trials. The initiative of Infectious Disease Society of America to develop 10 novel antibiotics against gram-negative bacilli by 2020 is a step to fill the gap of limited availability of drugs. This review aims to provide insights into the current and newer drugs in pipeline for the treatment of gram-negative bacteria and also discusses the major challenging issues for their management.

KEYWORDS: novel antibiotics, gram-negative bacteria, challenges in management, drug resistance, carbapenem resistance

Microbiology Insights 2016:9

Tratamento das Enterobactérias Produtoras de carbapenemases (ERC)

CURRENT OPINION

Options for treating carbapenem-resistant Enterobacteriaceae

Petros I. Rafailidis[a,b] *and Matthew E. Falagas*[a,c,d]

Purpose of review
To address the therapeutic management of carbapenem-resistant Enterobacteriaceae on the basis of literature of the last 12 months.

Recent findings
Retrospective and prospective (nonrandomized noncontrolled) studies provide data regarding the management of infections due to carbapenem-resistant Enterobacteriaceae. The combination of a carbapenem with colistin or high-dose tigecycline or aminoglycoside or even triple carbapenem-containing combinations if the minimum inhibitory concentration (MIC) range of carbapenem (meropenem and imipenem) resistance is 8 mg/l or less seems to have an advantage over monotherapy with either colistin or tigecycline or fosfomycin. For Enterobacteriaceae with MIC for carbapenems over 8 mg/l, combination regimens involve colistin, tigecycline usually administered in a double dose than that suggested by its manufacturer, fosfomycin and aminoglycosides in various combinations.

Summary
Suggestions based on the limited literature cannot be made safely. Combination regimens involving carbapenems for Enterobacteriaceae with MICs 8 mg/l or less for carbapenems (in dual combination with colistin or high-dose tigecycline or aminoglycoside or even triple combinations) seem to confer some therapeutic advantage over monotherapy. For Enterobacteriaceae with higher than the above-mentioned MICs, a combination of two or even three antibiotics among colistin, high-dose tigecycline, aminoglycoside and fosfomycin seems to confer decreased mortality.

Keywords
aminoglycoside, carbapenem-resistant Enterobacteriaceae, colistin, fosfomycin, meropenem, tigecycline

Curr Opin Infect Dis 2014, 27:479–483

Tratamento das Enterobactérias Produtoras de carbapenemases (ERC) MIC ≤ 8 mg/l

BSI	PNM	IAI	UTI
Meropenem 2 g 8/8 h+ Polimixina b 2,5 ataque; 1,25 mg 12/12 h± Tigeciclina 100 mg 12/12 h	**Meropenem 2 g 8/8 h+ Polimixina b 2,5 ataque; 1,25 mg 12/12 h± Tigeciclina 100 mg 12/12 h * Atb inalado**	**Meropenem 2 g 8/8 h+ Polimixina b 2,5 ataque; 1,25 mg 12/12 h+ Tigeciclina 100 mg 12/12 h**	**Meropenem 2 g 8/8 h+ Polimixina b 2,5 ataque; 1,25 mg 12/12 h+**
Ceftazidima + avibactam 2,5 g 8/8 h inf 2-3 h	**Ceftazidima + avibactam 2,5 g 8/8 h inf 2-3 h**	**Ceftazidima + avibactam 2,5 g 8/8 h inf 2-3 h + Metronidazol 500 mg 8/8 h**	**Ceftazidima + avibactam 2,5 g 8/8 h inf 2-3 h**

Tratamento das Enterobactérias Produtoras de carbapenemases (ERC) MIC > 8 mg/l

BSI	PNM	IAI	UTI
Polimixina b 2,5 mg ataque, 1,25 mg 12/12 h + tigeciclina 100 mg 12/12 h + gentamicina 7 mg/kg dia	Polimixina b 2,5 mg ataque, 1,25 mg 12/12 h + tigeciclina 100 mg 12/12 h + gentamicina 7 mg/kg dia+* atb inalatório	Polimixina b 2,5 mg ataque, 1,25 mg 12/12 h + tigeciclina 100 mg 12/12 h + gentamicina 7 mg/kg dia	Polimixina b 2,5 mg ataque, 1,25 mg 12/12 h + tigeciclina 100 mg 12/12 h + gentamicina 7 mg/kg dia
Ceftazidima +avibactam, 2,5 g 8/8 h em 2-3 horas	Ceftazidima +avibactam, 2,5 g 8/8 h em 2-3 horas	Ceftazidima +avibactam, 2,5 g 8/8 h em 2-3 horas + Meropenem	Ceftazidima +avibactam, 2,5 g 8/8 h em 2-3 horas

Antibioticoterapia Inalatória

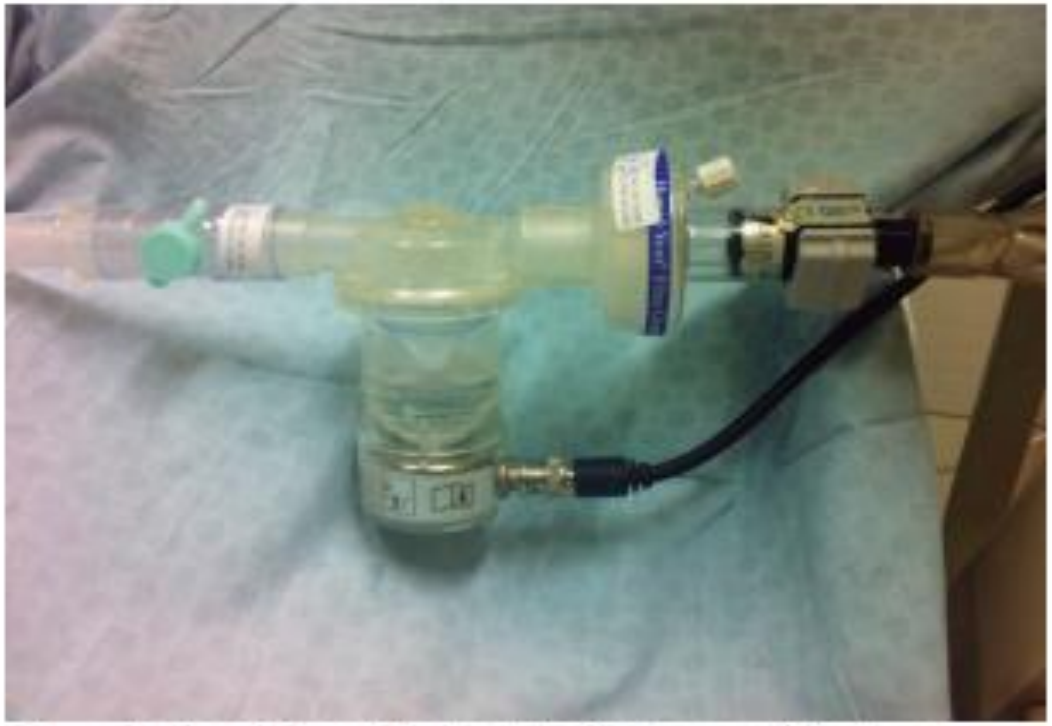

Figura 2. Dispositivo nebulizador ultrassónico em posição de uso próximo a componente do circuito ligada na traqueostomia de paciente sob VM.

Antibioticoterapia Inalatória

- Partículas grandes > 5 µm ficam aderidos no circuito
- Partículas muito pequenas < 0,5 µm são expelidas na expiração
- Partícula ideal entre 1 e 3 µm (geradores aerossol USG)
- VM: pelo menos 500 ml de VC, FR reduzida, I:E invertida (2-3:1), paciente não pode interferir na VM (muito sedado ou BNM), filtro na fase expiratória e após NBZ.
- Doses: poli b: 2,5 mg/Kg dividido 4 x [] máx 10 mg/ml 1mg=10.000UI, tobramicina 300 mg 12/12 h; amicacina 150 mg 12/12 h

Sim!
Existe Luz no Fim do Túnel!

Basta utilizarmos melhor o arsenal terapêutico que dispomos e medidas de prevenção.

Obrigado!

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