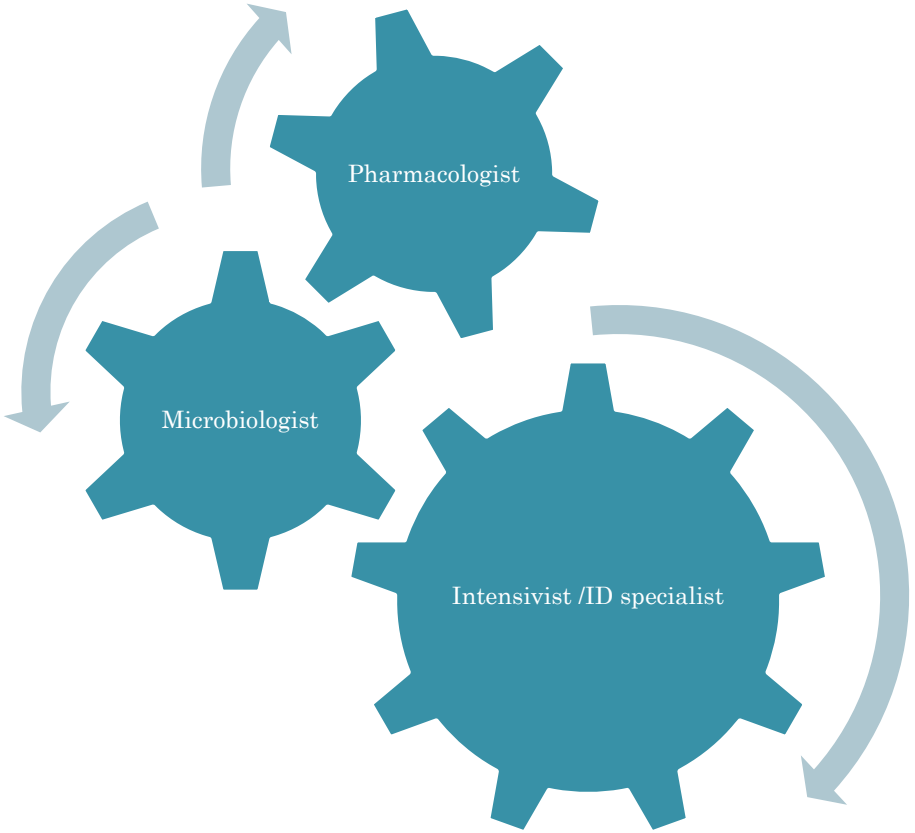
Antimicrobial Therapy in ICU

Dr Dipesh Maskey
Senior Resident
Dept of Pulmonary and Critical Care Medicine
PGIMER
11/2/11

Success of Antimicrobial therapy



PHYSICIAN AND ANTIMICROBIALS

Lets try few shots of antibiotics!!!

> 70% antibiotics prescribed during ICU stay

JAMA 2009;302(21):2323-9

20-40% of those prescribed are either unnecessary or inappropriate

EMERGENCE OF RESISTANCE

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

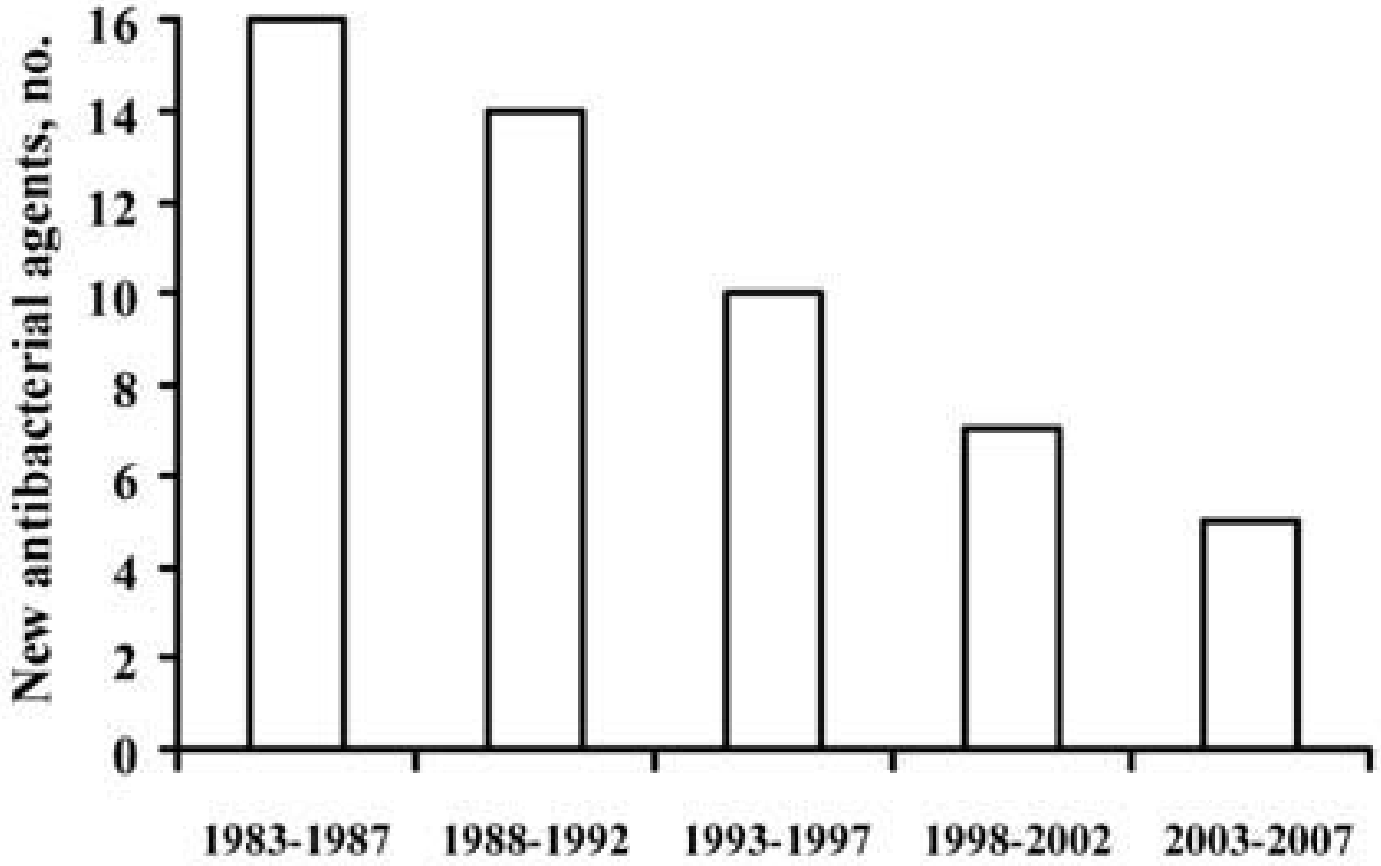
Helen W. Boucher,[1] George H. Talbot,[2] John S. Bradley,[3,4] John E. Edwards, Jr,[5,6,7] David Gilbert,[8] Louis B. Rice,[9,10] Michael Scheld,[11] Brad Spellberg,[5,6,7] and John Bartlett[12]

[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

The Infectious Diseases Society of America (IDSA) continues to view with concern the lean pipeline for novel therapeutics to treat drug-resistant infections, especially those caused by gram-negative pathogens. Infections now occur that are resistant to all current antibacterial options. Although the IDSA is encouraged by the prospect of success for some agents currently in preclinical development, there is an urgent, immediate need for new agents with activity against these panresistant organisms. There is no evidence that this need will be met in the foreseeable future. Furthermore, we remain concerned that the infrastructure for discovering and developing new antibacterials continues to stagnate, thereby risking the future pipeline of antibacterial drugs. The IDSA proposed solutions in its 2004 policy report, "Bad Bugs, No Drugs: As Antibiotic R&D Stagnates, a Public Health Crisis Brews," and recently issued a "Call to Action" to provide an update on the scope of the problem and the proposed solutions. A primary objective of these periodic reports is to encourage a community and legislative response to establish greater financial parity between the antimicrobial development and the development of other drugs. Although recent actions of the Food and Drug Administration and the 110th US Congress present a glimmer of hope, significant uncertainly remains. Now, more than ever, it is essential to create a robust and sustainable antibacterial research and development infrastructure—one that can respond to current antibacterial resistance now and anticipate evolving resistance. This challenge requires that industry, academia, the National Institutes of Health, the Food and Drug Administration, the Centers for Disease Control and Prevention, the US Department of Defense, and the new Biomedical Advanced Research and Development Authority at the Department of Health and Human Services work productively together. This report provides an update on potentially effective antibacterial drugs in the late-stage development pipeline, in the hope of encouraging such collaborative action.

CID 2009; 48:1–12

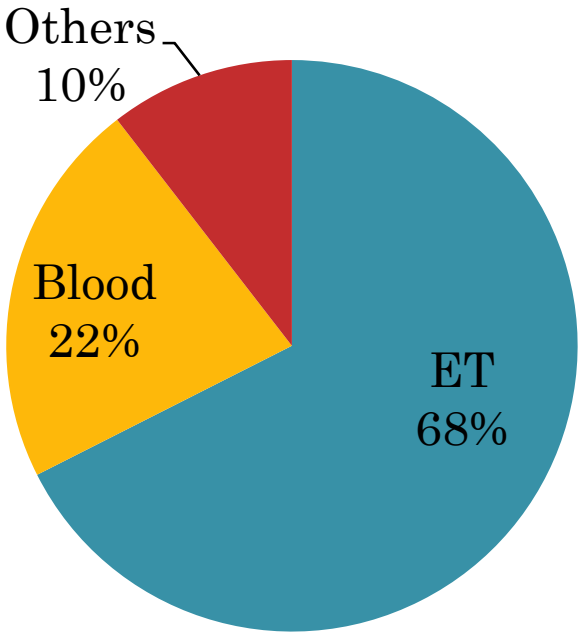
IDSA Report on Development Pipeline

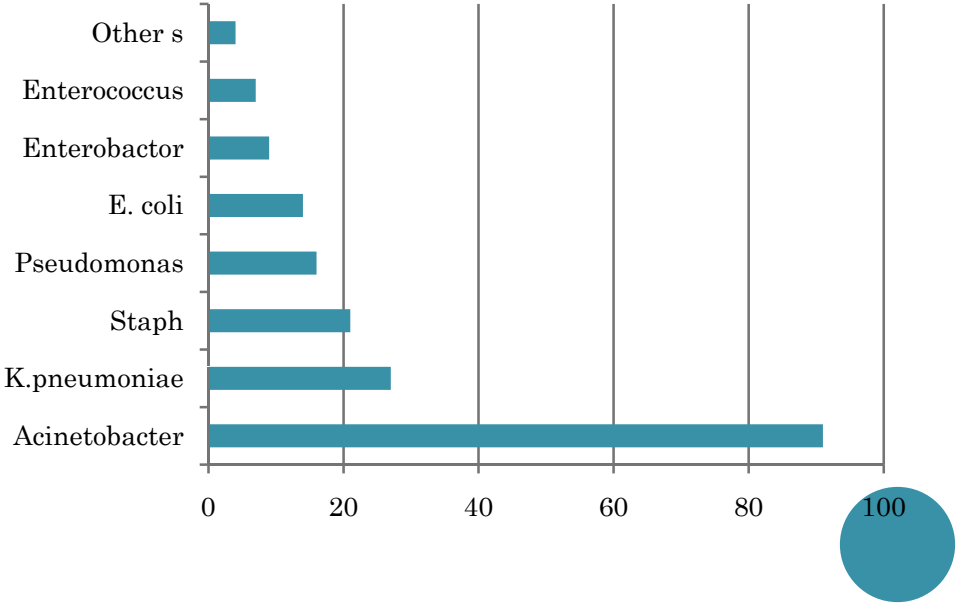


CID 2009; 48:1–12

RICU SCENARIO

- 4 months (7/10/10 – 9/2/11)
- 90 admissions/18 deaths/ 20% mortality
- 191 positive cultures





Sensitivity of isolates in RICU

- 91 cases of Acinetobactor
  - 19 MDR
  - 1 pan-resistant
- 23 isolated staphylococci
  - 15 MRSA
- 9 isolated Enterococci
  - 4 VRE
- 27 isolated Kliebsiella
  - 16 ESBL

- Severe sepsis and septic shock has mortality of 28.6% per year[1]
- Early and appropriate antimicrobial therapy reduce mortality[2]

[1]Crit Care Med 2001;29(7):1303-10
[2] Crit Care Med 2006;34(6):1589-96

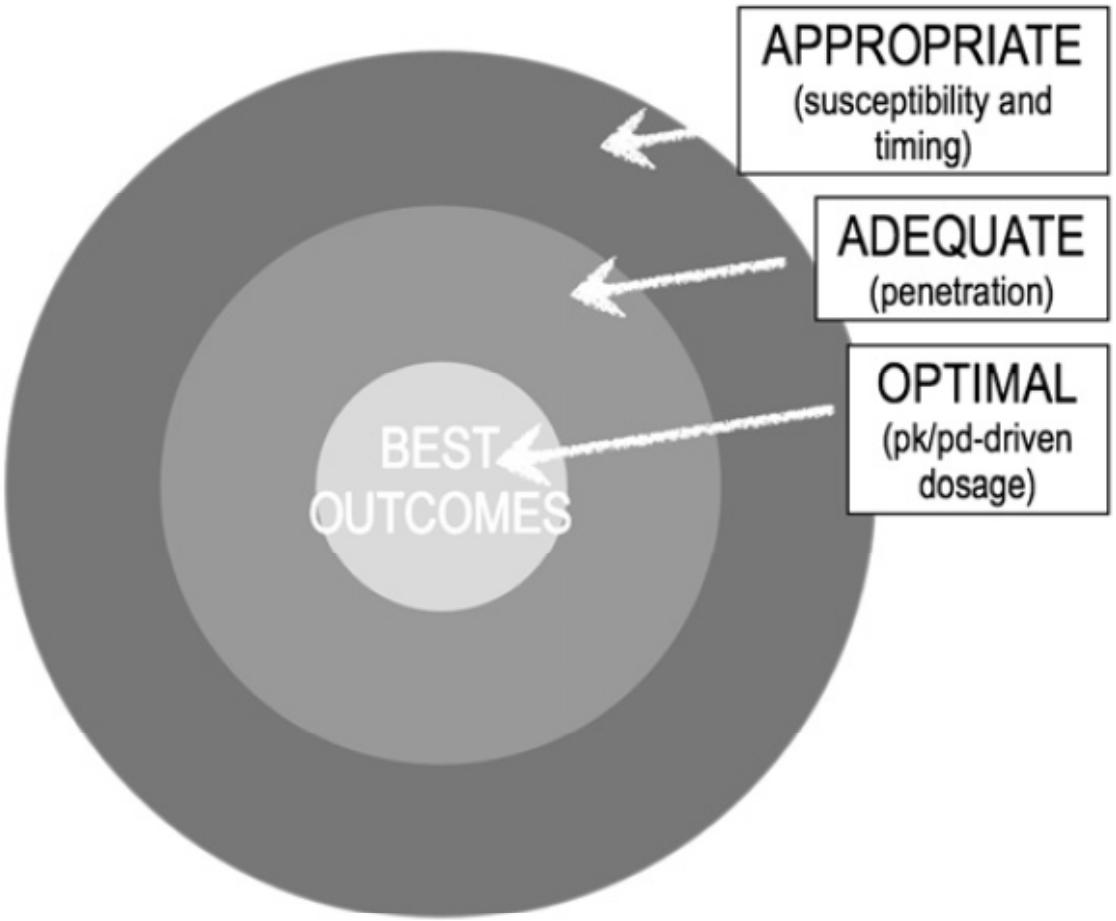
Appropriateness is critical…

Speed is life!!!

INAPPROPRIATE ANTIBIOTIC THERAPY

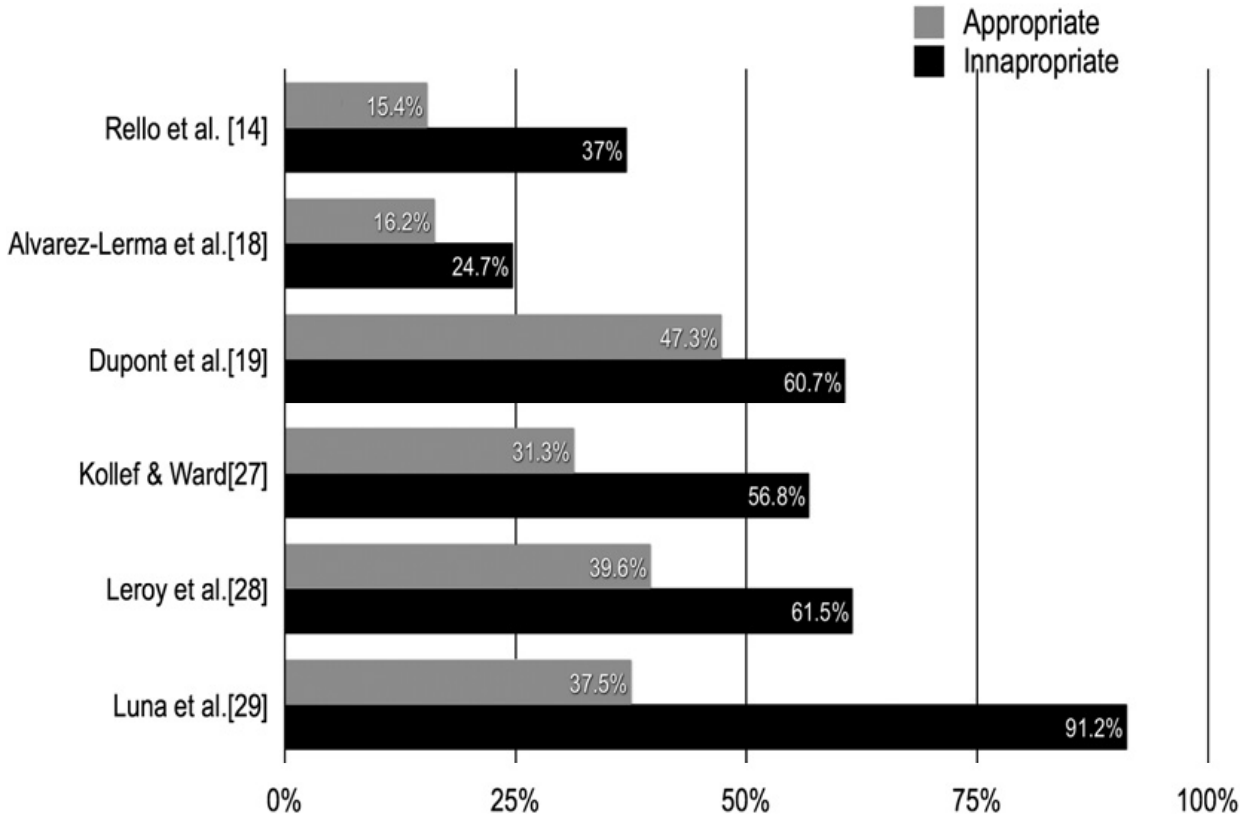
- Inappropriate antibiotic therapy can be defined as one or more of the following:
  - *ineffective* empiric treatment of bacterial infection at the time of its identification
  - the *wrong* choice, dose or duration of therapy
  - use of an antibiotic to which the pathogen is resistant
- Inappropriate empiric antibiotic therapy can lead to increases in:
  - Mortality & morbidity
  - Length of hospital stay
  - Cost burden
  - Resistance selection

Components of Appropriate antibiotic therapy



Crit Care Clin 2011;27: 35–51

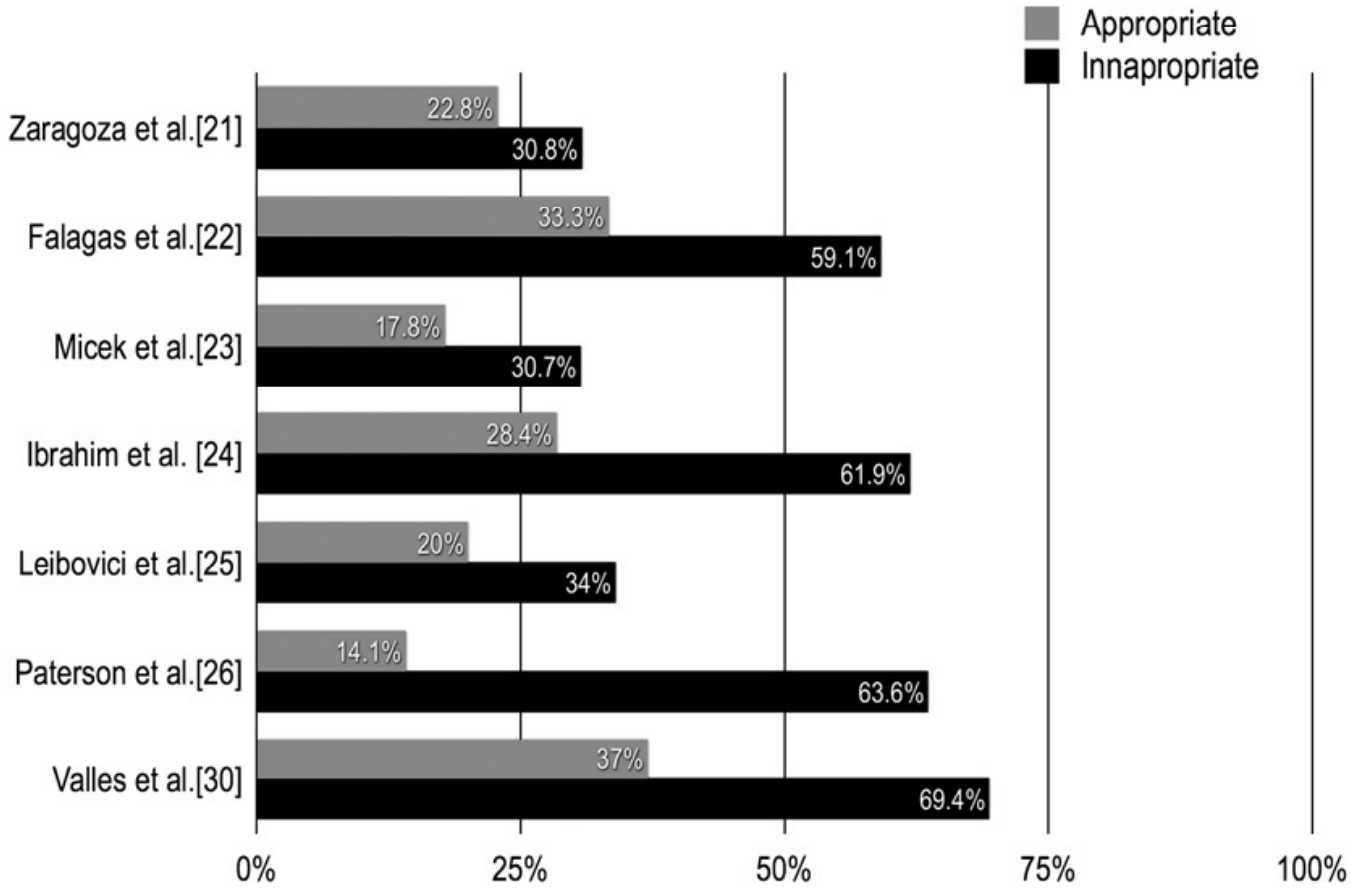
Appropriate vs Inappropriate therapy



The mortality in appropriate versus inappropriate empirical antibiotic treatment of VAP

Crit Care Clin 2011;27: 35–51

Appropriate vs Inappropriate therapy



The mortality in appropriate versus inappropriate empirical antibiotic treatment of bloodstream infections

Crit Care Clin 2011;27: 35–51

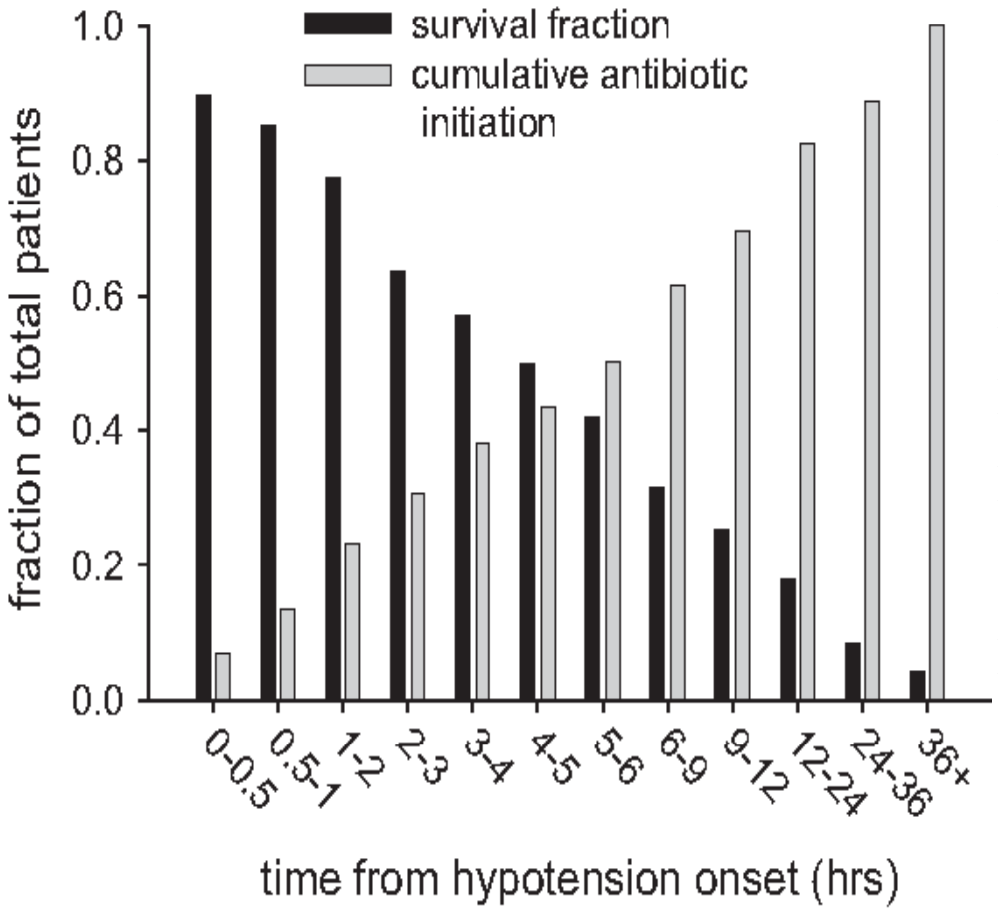
Causes of Inappropriate antibiotic therapy

- Prior antibiotic exposure
- Prolonged length of stay in hospital and previous hospitalization
- Presence of invasive devices
- Local susceptibilities
- Admission category and underlying diseases
- Colonization pressure by resistant pathogens

This thing all things devours:
Birds, beasts, trees, flowers;
Gnaws iron, bites steel
Grinds hard stones to meal;
Slays king, ruins town,
And beats High Mountain down.

- Acute illness – time is critical
- Golden hour
  - Trauma
- Door to needle time
  - Myocardial infarction
  - Stroke
- Sepsis
  - *Speed is life*

CUMULATIVE INITIATION OF EFFECTIVE ANTIMICROBIAL THERAPY AND SURVIVAL IN SEPTIC SHOCK



- Retrospective, multicentric
- Cohort study
- 2,154 septic shock patients
- Median time was 6 hours
- For every hour delay > first 6 h, projected mortality ↑ by 7.6%/h
- only 50% received within 6 h

Crit Care Med 2006;34:1589–96

SURVIVING SEPSIS GUIDELINES

- Rapid initiation (< 1 hour) of antimicrobial therapy for sepsis and septic shock

Crit Care Med 2004;32:858-73

Causes of delay of effective antimicrobial therapy

- Failure to recognize infection in a timely way
- Failure to recognize that hypotension represents septic shock
- Effect of inappropriate antimicrobial initiation
- Failure to appreciate risk of resistant organisms
- Wait for blood cultures from intravenous technicians before giving antibiotic
- Requirement for 2 nurses to check for potential drug sensitivity before dosing of antimicrobials
- Transfer from ER before ordered antibiotics given
- Failure to use stat orders
- Failure to recognize that administration of inappropriate antimicrobials is equivalent to absent antimicrobial therapy when responding to clinical failure (ie, should not delay appropriate antimicrobials because inappropriate drugs recently given)
- No specified order with multiple drug regimens so that key drug (usually most expensive and hardest to access) may be given last
- Administrative/logistic delays (nursing/pharmacy/ward clerk)

Potential approaches to minimize delays in initiation of empiric antimicrobial therapy

- The presence of hypotension in a patient with known or suspected infection should be considered to be septic shock in the absence of a definitive alternate explanation
- No transfer from ER before ordered antibiotics given
- All initial orders for any intravenous antibiotic automatically stat
- Syndrome-based, algorithm-driven guidelines similar to meningitis and neutropenic sepsis with designated broad-spectrum antimicrobial regimen at each center
- Antimicrobial order to include sequence and time limit (eg, within 30 minutes of order)
- First intravenous dose of most broad-spectrum agents (ie, b-lactam/carbapenems) push by physician
- Health care worker and support staff education; a team approach

DICTUM OF ANTIMICROBIAL THERAPY IN SEPTIC SHOCK

HIT HARD, HIT EARLY

Pharmacokinetics and Pharmacodynamics:

Critically ill with severe sepsis and septic shock

INTERRELATIONSHIP BETWEEN PHARMACOKINETICS AND PHARMACODYNAMICS

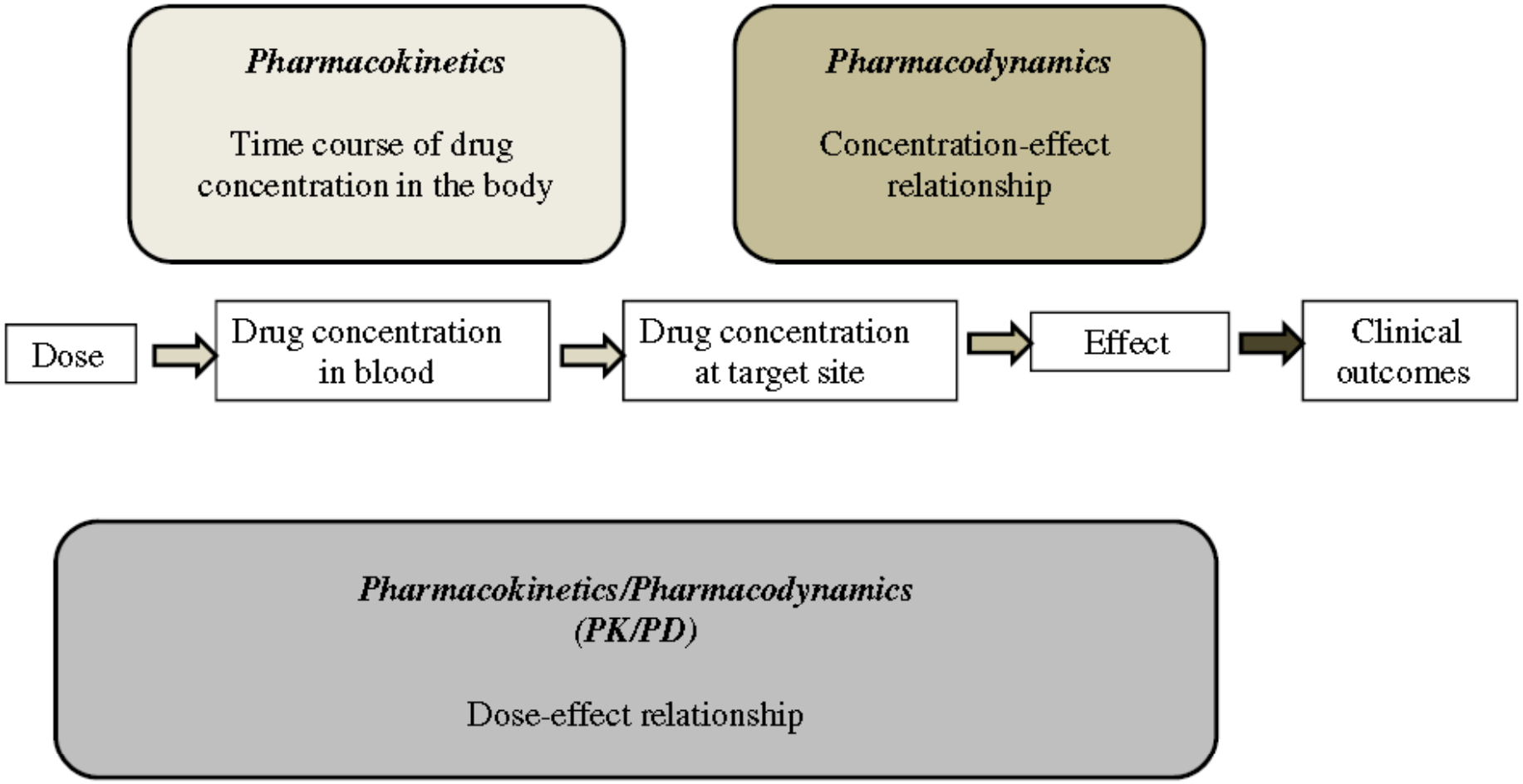


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Table 1
Relevant PK parameters for drug dosing

PK Parameter	Definition	Description
Clearance (CL)	The volume of blood cleared of drug per unit time	CL measures the irreversible elimination of a drug from the body by excretion and/or metabolism
Volume of distribution (V_d)	Apparent volume of fluid that contains the total drug dose administered at the same concentration as in the plasma	V_d is the parameter that relates the total amount of drug in the body to the plasma concentration
Half-life ($t_{1/2}$)	Time required for the plasma drug concentration to decrease by half	Half-life is dependent on CL and V_d; half-life is increased with a decrease in CL or an increase in V_d
C_{max}	Peak drug concentration during a dosing interval	
C_{min}	Minimum drug concentration during a dosing interval	
AUC_{0-24}	Area under the concentration-time curve from 0 to 24 h	

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PK IN SEPTIC SHOCK: CHANGES IN DISTRIBUTION

Volume of distribution	• Increased capillary leak → third spacing • Increase Vd for hydrophilic drugs with lower plasma and tissue concentration
Tissue perfusion,penetration & target site distribution	• Impaired due to capillary leakage, tissue edema and microvascular failure • Higher plasma concentration required to achieve target concentrations needed in tissues
Protein binding & hypoalbuminemia	• Albumin binds acidic drugs (ceftriaxone, ertapenem, teicoplanin, flucloxacillin) • Acute phase reactant – reduced due to decreased synthesis and leakage to extracellular space • Increase unbound fraction of drug

PK IN SEPTIC SHOCK: CHANGES IN CL

Increased CO	• Sepsis – hyperdynamic state → high CO & ↑ RBF → increased clearance • Hydrophilic and unbound drugs rapidly cleared
End organ dysfunction & clearnace	• Renal/ hepatic dysfunction – impair metabolism and clearance with increased accumulation → increased toxicity
RRT/ECMO/Plasma exchange	• Decrease in drug concentration by increased Vd (ECMO) or removal

Table 3
PK characteristics of antimicrobials based on classification according to hydrophilicity and lipophilicity in general ward patients (General PK) compared with altered PK observed in critically ill patients

	General PK		Altered PK in Critically Ill
Hydrophilic antibiotics	Low	V_d	↑ V_d
	Predominantly renal	CL	↑ or ↓ depending on renal function
	Poor intracellular penetration	Distribution	↓ Interstitial penetration
	Examples: Beta-lactams, carbapenems, aminoglycosides, glycopeptides, linezolid		
Lipophilic antibiotics	High	V_d	Unchanged
	Predominantly hepatic	CL	↑ or ↓ depending on hepatic function
	Good intracellular penetration	Distribution	Unchanged interstitial penetration
	Examples: fluoroquinolones, macrolides, tigecycline, lincosamides		

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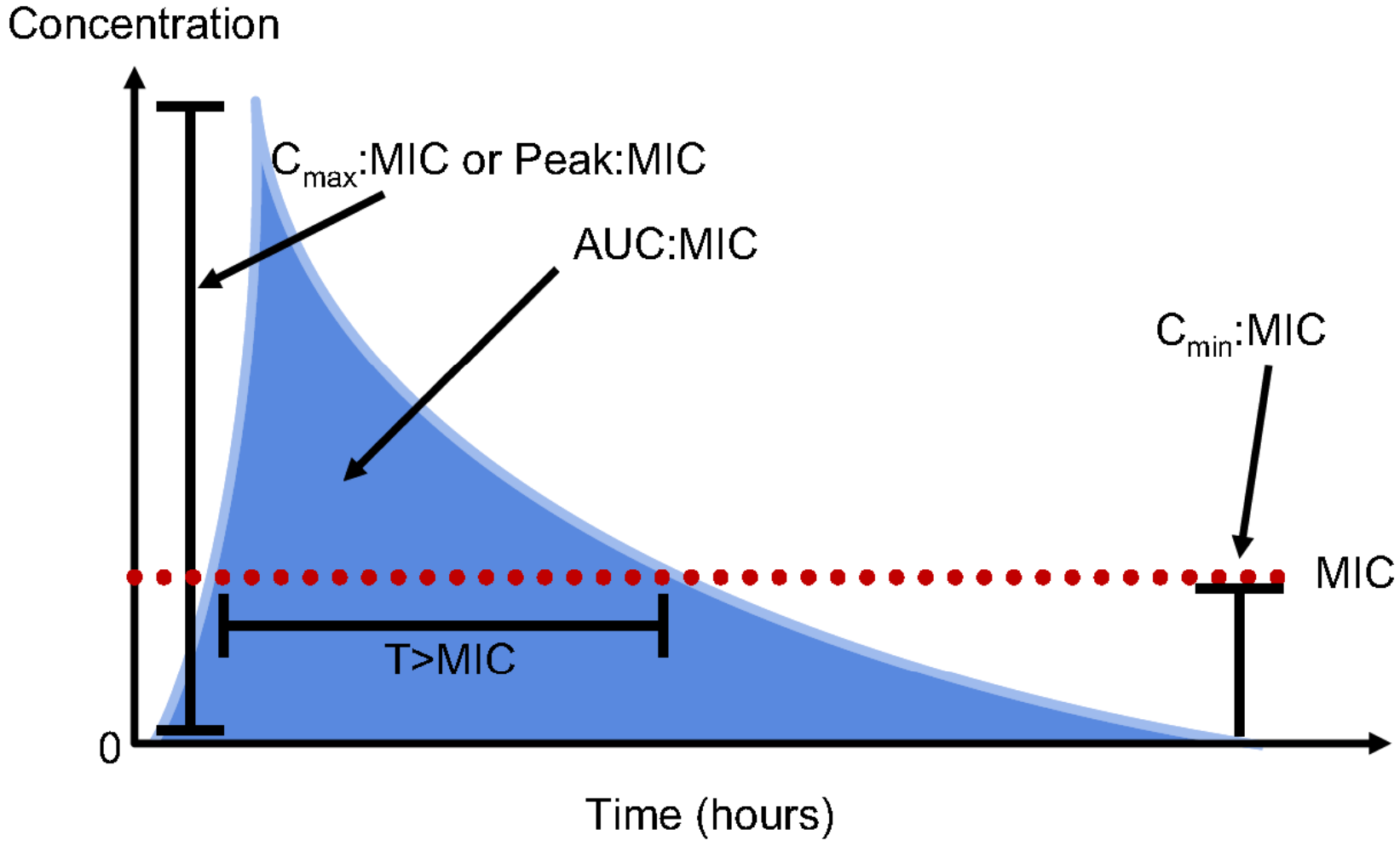
PHARMACODYNAMICS: FROM BENCH TO BEDSIDE

- Minimum Inhibitory Concentration
  - Pharmacodynamic parameter most often used to describe relationship between antimicrobial drug and physiologic activity
  - Defined as lowest or minimum antimicrobial concentration that inhibits visible microbial growth in artificial media after fixed incubation time
  - Quantitative measure of drug activity and allows calibration of drug exposure to its potency
  - Static measure – don't reflect physiologic conditions
  - Doesnot measure rate at which bacteria is killed
  - Can't determine exposure-kill response of particular antibiotic-pathogen pairing
  - Doesnot account for postantibiotic effect

Antimicrobial Pharmacodynamics



Crit Care Clin 27 (2011) 1–18

Table 2
PK/PD indices of significance for antimicrobials

Antibiotic Classification	PK/PD Index	Definition of PK/PD Index	Examples of Antibiotics
Time-dependent	T>MIC	Percentage time for which the concentration of a drug remains more than the minimum inhibitory concentration (MIC) during a dosing interval	Beta-lactams Carbapenems Lincosamides
Concentration-dependent	C_{max}/MIC	Ratio of the peak drug concentration to the MIC of the pathogen	Aminoglycosides
Concentration-dependent with time dependence	AUC_{0-24}/MIC	Ratio of the area under the concentration-time curve (AUC) during a 24-h period to the MIC of the pathogen	Fluoroquinolones Glycopeptides Tigecycline

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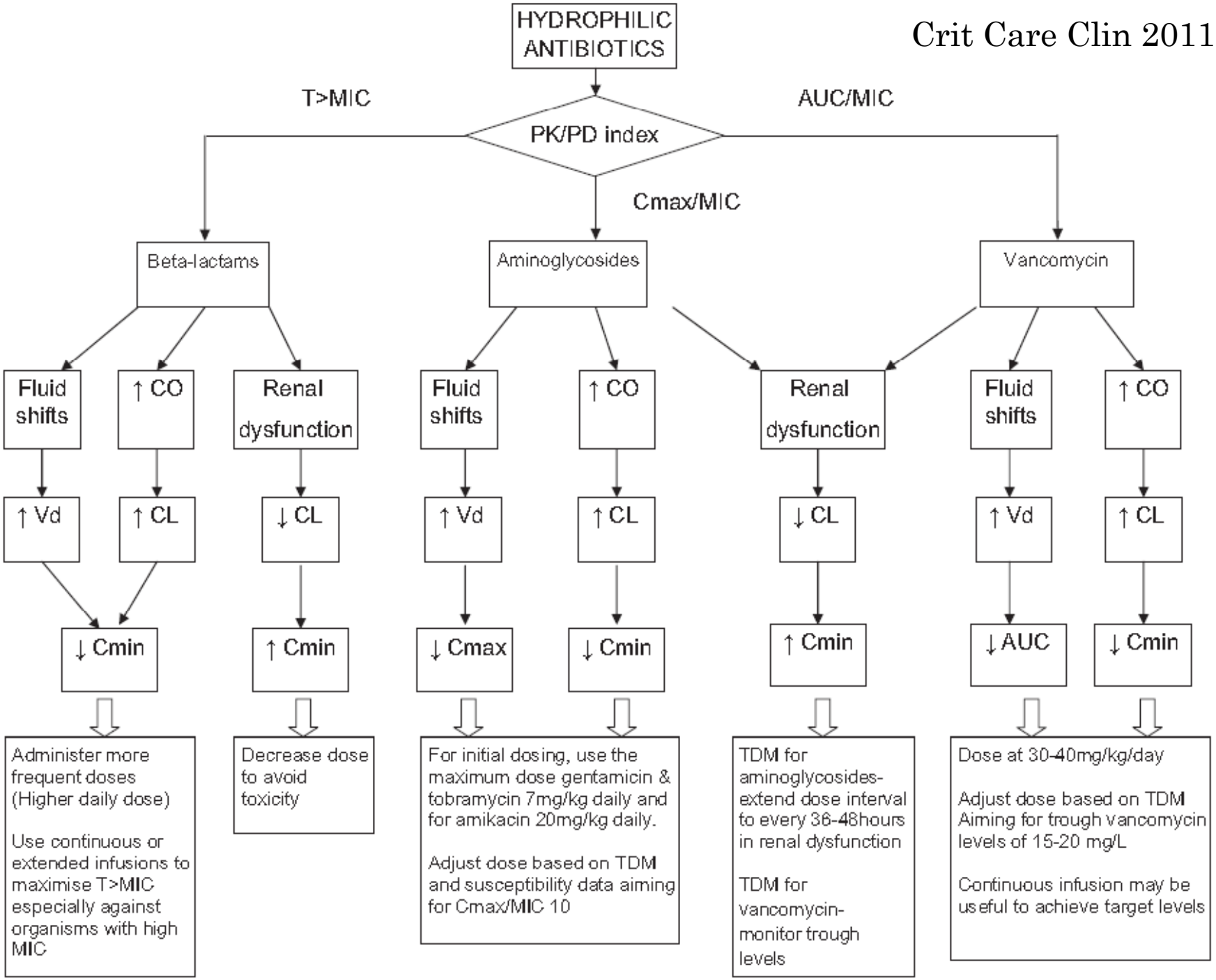

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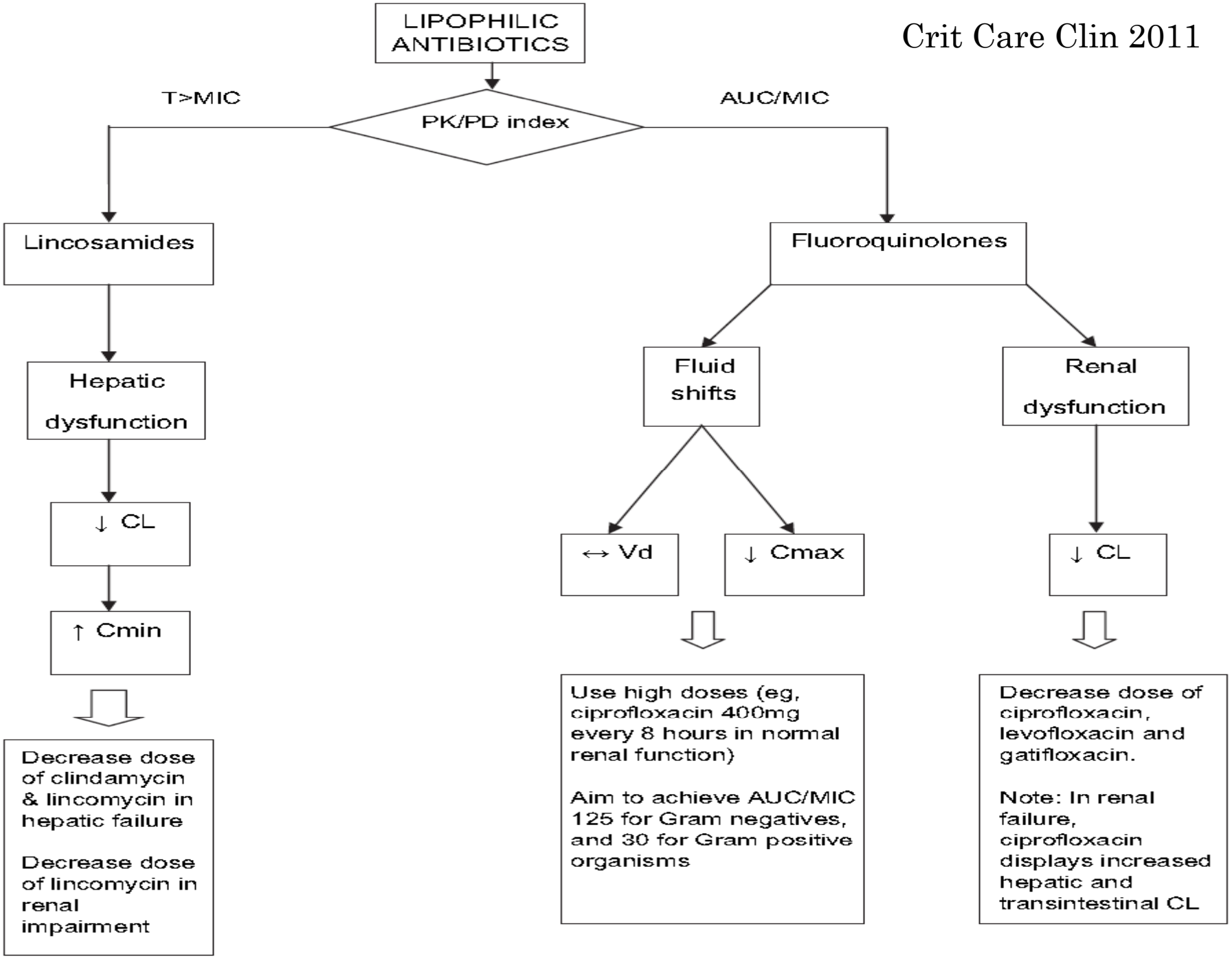


OPTIMAL DOSING STRATEGIES

- With respect to the dosing regimen, there are 3 ways to alter the shape of the concentration time profile:
  - changes to dose,
  - dosing interval, and
  - Infusion time

MONTE CARLO SIMULATION

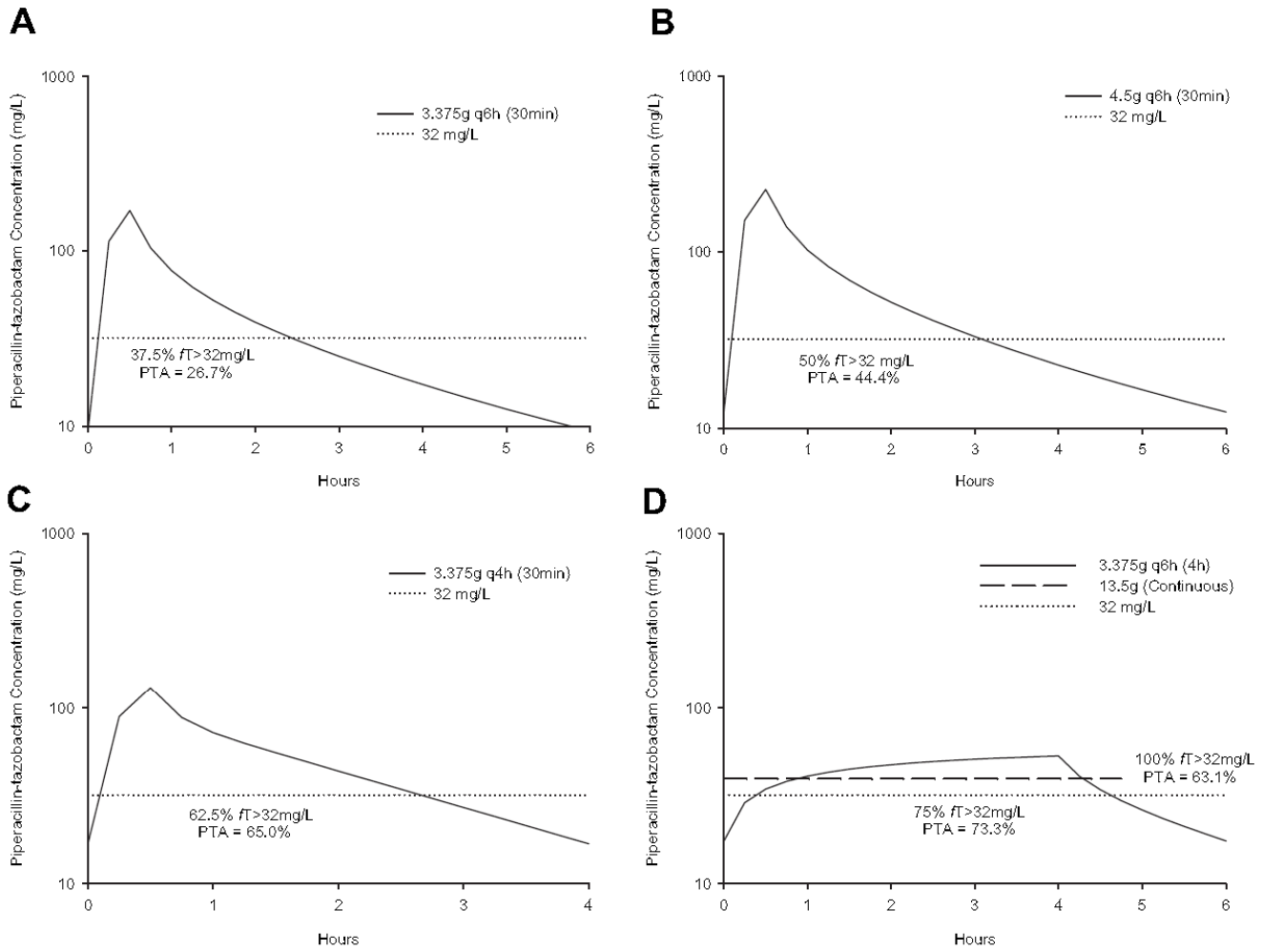
- Mathematical modeling technique
- Simulates dispersion of concentration-time exposure values that would be seen in large population after administration of specific drug dose or regimen
- Probability of achieving PD target at each MIC value for given range can be ascertained
- Used to design drug dosing and interval

BETA-LACTUMS

- Penicillins and cephalosporins
- Hydrophilic
- Slow concentration-independent continuous kill characteristic and time for which free antimicrobial concentration is maintained above MIC
- fT>MIC is PK/PD index → efficacy[1]
- For penicillin and cephalosporins the time above MIC required for efficacy is 40-50% of dosing interval

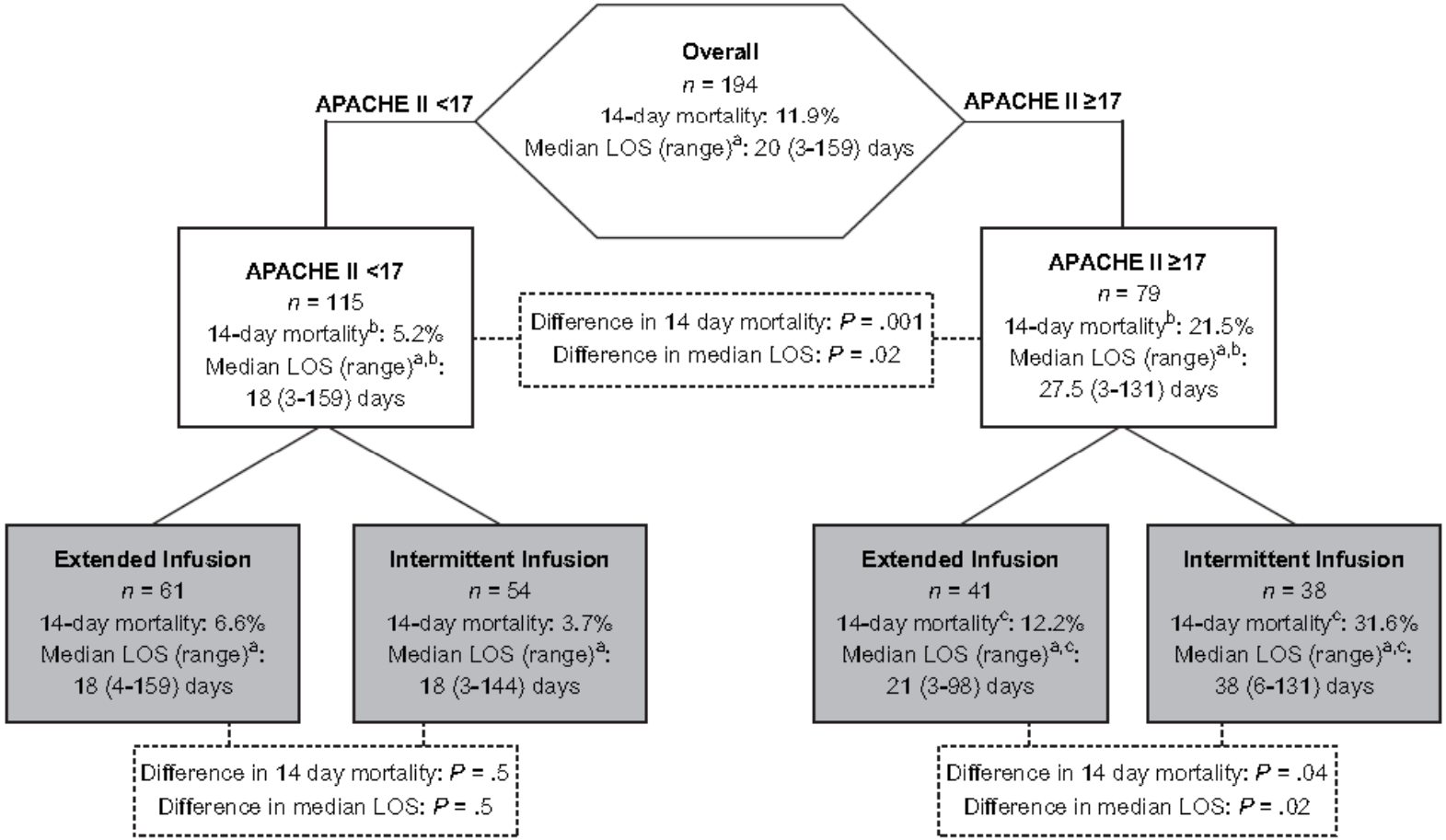
[1] CID 1998;26(1):1-10

Pharmacodynamic profiling of piperacillin in the presence of tazobactam in patients through the use of population pharmacokinetic models and Monte Carlo simulation



Antimicrob Agents Chemother 2004;48:4718–24

Piperacillin-tazobactam for Pseudomonas aeruginosa infection: clinical implications of an extended-infusion dosing strategy.



Clin Infect Dis 2007;44(3):357–63

QUINOLONES

- Concentration dependent bacterial killing
- Induce moderate persistent or post-antibiotic effect (PAE)
- Driver for efficacy is AUC/MIC ratio
- $AUC_{0\text{-}24}$/MIC 100-125 for efficacy
- Maximizing dose or administering entire daily dose as single dose can optimize efficacy
- Underdosage and injudicious use over last 2 decades – increase resistance
- Efficacy in ICU is limited to combination therapy

Application of fluoroquinolone pharmacodynamics

Table 3
f-AUC-24/MIC ratios

	MIC (mg/L)				
	2.0	1.0	0.5	0.25	0.125
Ciprofloxacin 400 mg every 8 h					
Total AUC = 33	—	—	—	—	—
f-AUC = 22	11	22	44	88	177
Levofloxacin 750 mg every 24 h					
Total AUC = 72	—	—	—	—	—
f-AUC = 50	25	50	100	200	400
Moxifloxacin 400 mg every 24 h					
Total AUC = 48	—	—	—	—	—
f-AUC = 24	12	24	48	96	192

J Antimicrob Chemother 2000;46:669–83.

AMINOGLYCOSIDES

- Quintessential concentration-dependent killing agents
- Cmax/MIC of atleast 10 → clinical efficacy
- Show PAE
- High trough concetration – increased nephrotoxicity as well as prolonged exposure
- Critically ill patients display increased Vd and lead to decreased Cmax
- High dose of 7mg/kg for gentamicin & tobramycin and 20 mg/kg for amikacin is recommended

VANCOMYCIN

- AUC/MIC ratio is best predictor of response
- Need to give in prolonged infusion
- Microbiologic success is optimized when AUC/MIC ratio is ≥ 400 and MIC of 0.5mg/L
- With increasing MIC to 1-2 mg/L the target attainments falls to 70% & 22%
- Higher doses of 3-4 g/d is required
- Trough level 15-20mg/L

ANTIBIOTIC DE-ESCALATION

- Mechanism whereby the provision of effective initial antibiotic treatment is achieved while avoiding unnecessary antibiotic use that would promote the development of resistance

- Two key features:-
  - Intent to narrow spectrum of antimicrobial coverage depending on clinical response, culture results, and susceptibilities of pathogens
  - Commitment to stop antimicrobial treatment if no infection is established

Crit Care Med 2011;27:149-162

Benefits of de-escalation

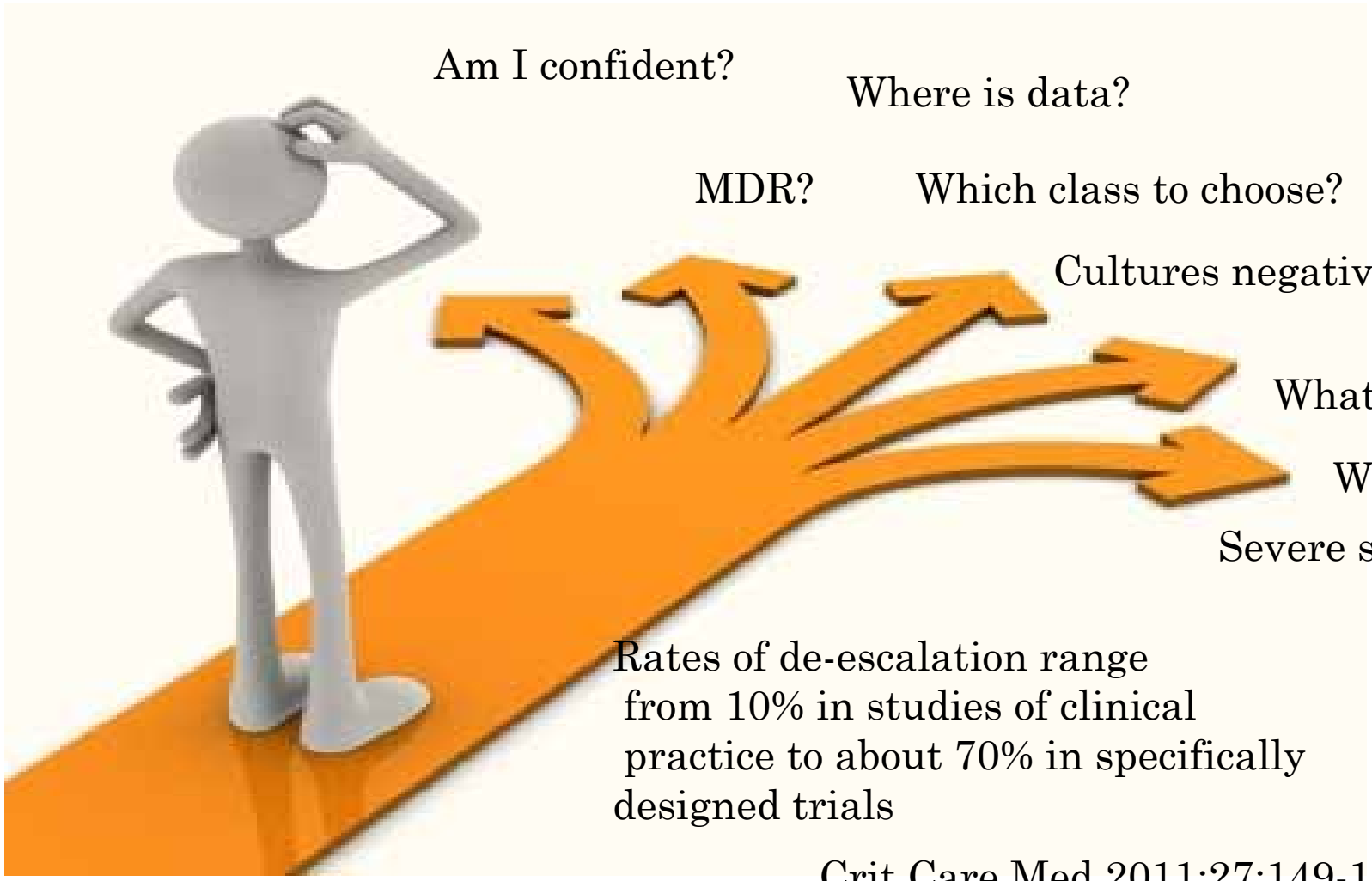
- Treatment Outcome remains unaltered
- Reduce antimicrobial resistance
- Decrease antibiotic related adverse events (C. difficile infection, superinfection with resistant bacteria and candida organism)
- Cost benefit

Evidence from clinical de-escalation studies

- Lack of well controlled RCTs to decide appropriate time to de-escalate, standard criterias to decide, and stopping of antimicrobials
- Most studies did not show worse treatment outcome or decrease antimicrobial resistance
- Lower mortality rates, shorter LOS and lower hospital costsin de-escalation groups than conventional group

Crit Care Med 2011;27:149-162

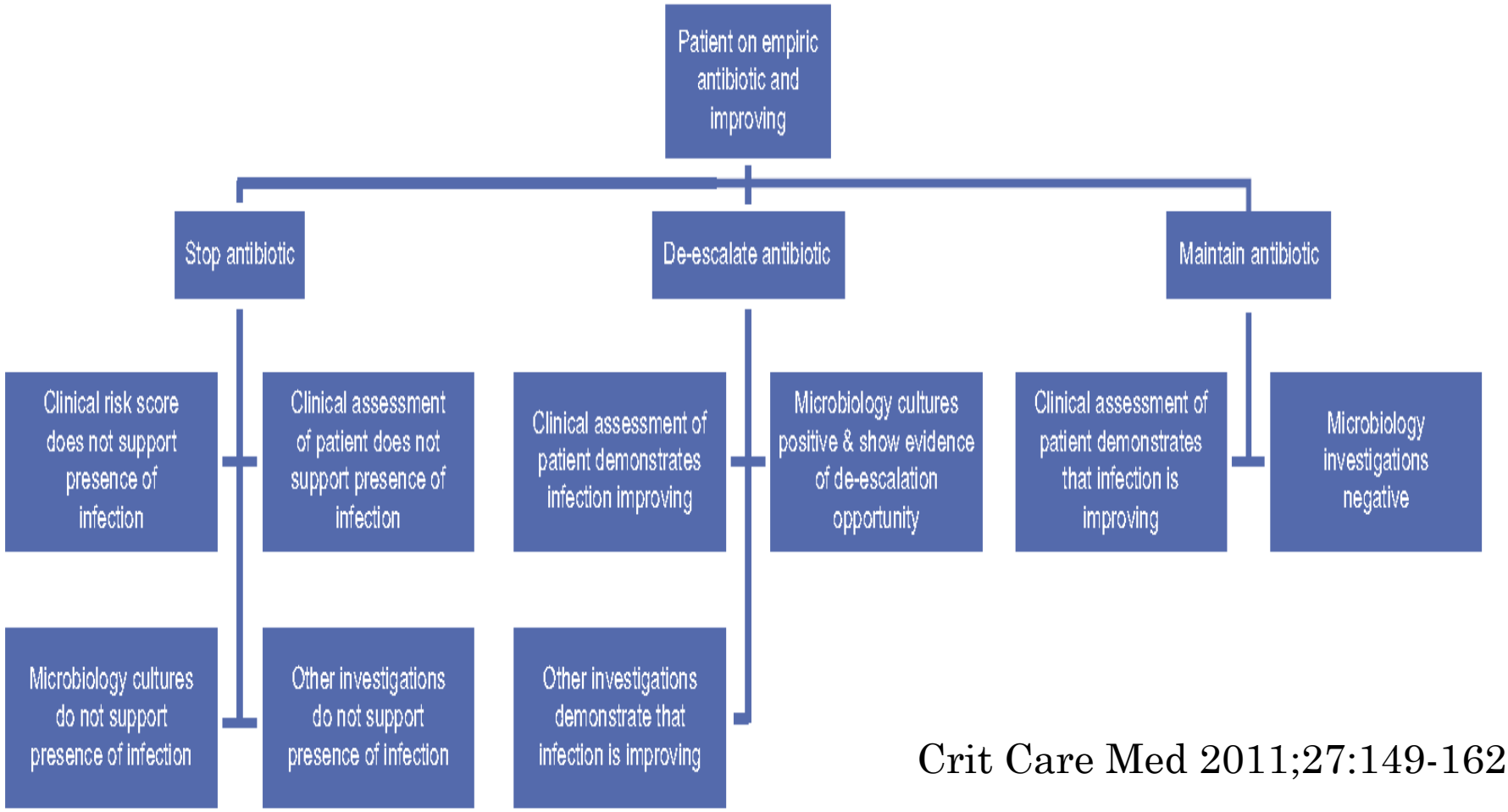
ANTIBIOTIC DE-ESCALATION



Rates of de-escalation range from 10% in studies of clinical practice to about 70% in specifically designed trials

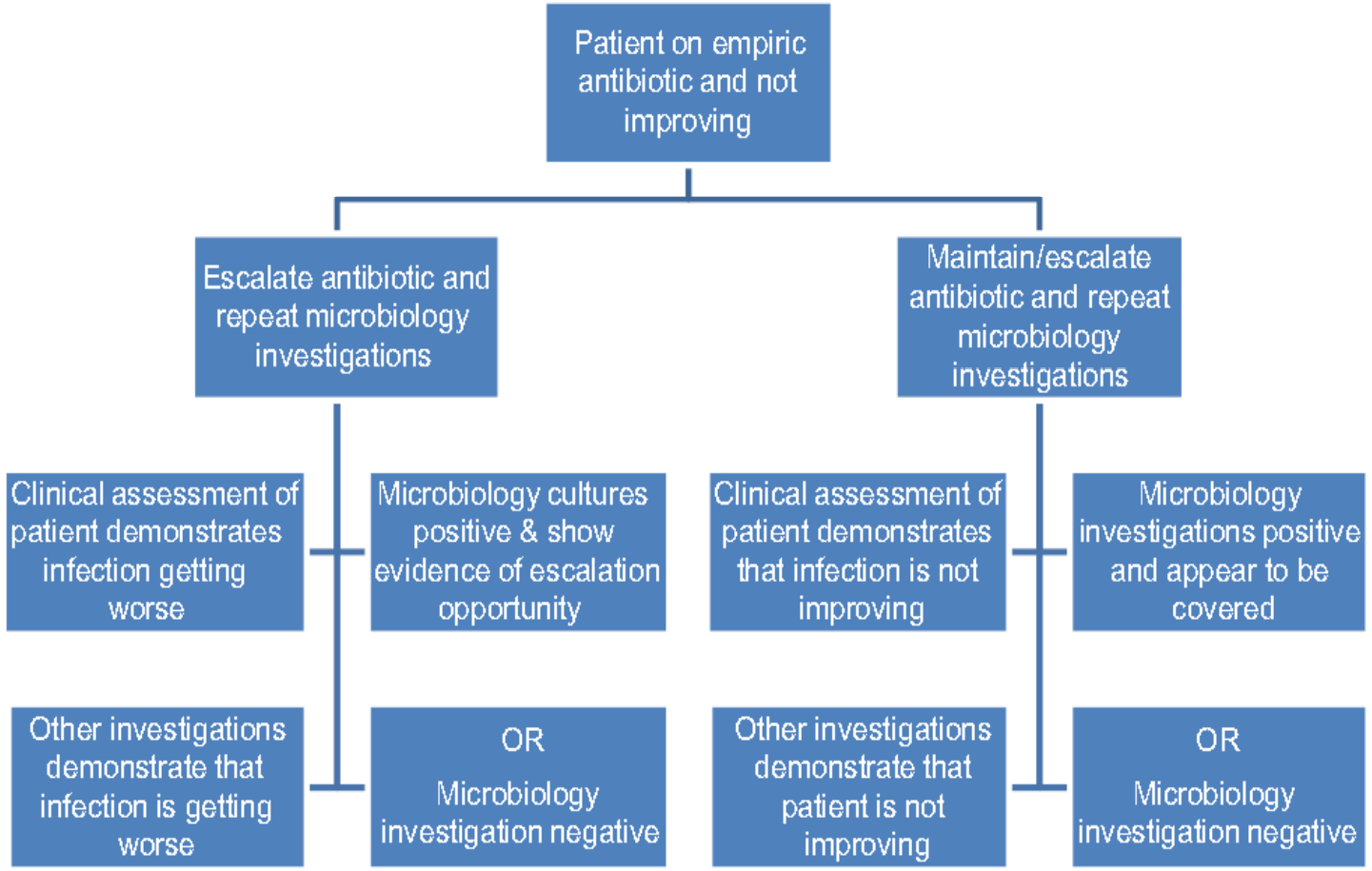
Crit Care Med 2011;27:149-162

Algorithm for de-escalation decision-making at day 3 in an improving patient



Crit Care Med 2011;27:149-162

Algorithm for de-escalation decision-making at day 3 in a patient not improving on the empiric antibiotic therapy



Crit Care Med 2011;27:149-162

KEY PRINCIPLES OF THE NEW TREATMENT PARADIGM

- Get effective antibiotic selection right first time
- Base antimicrobial selection, both empiric and targeted, on knowledge of local susceptibility patterns
- Use broad-spectrum antibiotics early – SPEED IS LIFE
- Optimize the antibiotic dose and route of administration – APPROPRIATE IS CRITICAL
- Administer antibiotics for the shortest possible duration
- Adjust or stop antibiotic therapy as early as possible to best target the pathogen(s) and remove pressure for resistance development (ie, de-escalation)

Fungal Sepsis

- Invasive fungal infection and fungal sepsis in ICU are increasing
- Invasive candidemia is fourth most common health care associated infection in US[1]
- Incidence of blood stream candidiasis has rose by 200% from 1979 to 2000.[2]
- Mortality attributable to candidemia range from 10% to 49%[3]

[1]CID 2004;39(3):309-17
[2] NEJM 2003;348(16):1546-54
[3] CID 2005;41(9):1232-9

INVASIVE CANDIDIASIS(IC)

- Of 17 Candida species reported to cause IC in humans, 5 species(C albicans, C glabrata, C parapsilosis, C tropicalis, and C krusei) represent > 90%.
- C albicans has historically been the predominant pathogen in IC with rates of 80% or higher in the 1980s.
- Presently, C albicans accounts for less than 50% of all BSIs caused by the Candida genus.
- Predominant non-albicans species in US is C glabrata, with an estimated frequency of 20%-25%.
- In other countries - dramatic increases in C parapsilosis and C tropicalis.
- As C glabrata often exhibits reduced susceptibility to triazoles and C parapsilosis has reduced susceptibility to echinocandins, knowledge of the local epidemiology is imperative for selection of appropriate empirical therapy.

Clin Microbiol Rev 2007;20(10):133-63

TIME TO THERAPY

- Studies on patients with IC have shown excessive rates of inappropriate initial therapy and even higher mortality than infections caused by bacterial pathogens in the ICU setting
- 33% reduction in mortality on appropriate antifungal therapy[1]
- Blot and colleagues reported 78% mortality in patients with IC when therapy was delayed >48 hours from onset of candidemia; in contrast the mortality was 44% in those who had adequate initial therapy[2]

[1] Chest 2000;118(1):146-55
[2] Am J Med 2002;113(6):480-5

Time to Initiation of Fluconazole Therapy Impacts Mortality in Patients with Candidemia: A Multi-Institutional Study

Kevin W. Garey,[1] Milind Rege,[1] Manjunath P. Pai,[2] Dana E. Mingo,[3] Katie J. Suda,[4] Robin S. Turpin,[5] and David T. Bearden[6]

[1]Department of Clinical Science and Administration, University of Houston College of Pharmacy, Houston, Texas; [2]University of New Mexico College of Pharmacy, Albuquerque; [3]Baptist Memorial Health Care and [4]Department of Pharmacy, University of Tennessee Health Science Center, Memphis; [5]Merck, West Point, Pennsylvania; and [6]Oregon State University College of Pharmacy, Portland

Background. Inadequate antimicrobial treatment is an independent determinant of hospital mortality, and fungal bloodstream infections are among the types of infection with the highest rates of inappropriate initial treatment. Because of significant potential for reducing high mortality rates, we sought to assess the impact of delayed treatment across multiple study sites. The goals our analyses were to establish the frequency and duration of delayed antifungal treatment and to evaluate the relationship between treatment delay and mortality.

Methods. We conducted a retrospective cohort study of patients with candidemia from 4 medical centers who were prescribed fluconazole. Time to initiation of fluconazole therapy was calculated by subtracting the date on which fluconazole therapy was initiated from the culture date of the first blood sample positive for yeast.

Results. A total of 230 patients (51% male; mean age ± standard deviation, 56 ± 17 years) were identified; 192 of these had not been given prior treatment with fluconazole. Patients most commonly had nonsurgical hospital admission (162 patients [70%]) with a central line catheter (193 [84%]), diabetes (68 [30%]), or cancer (54 [24%]). *Candida* species causing infection included *Candida albicans* (129 patients [56%]), *Candida glabrata* (38 [16%]), *Candida parapsilosis* (25 [11%]), or *Candida tropicalis* (15 [7%]). The number of days to the initiation of antifungal treatment was 0 (92 patients [40%]), 1 (38 [17%]), 2 (33 [14%]) or ⩾3 (29 [12%]). Mortality rates were lowest for patients who began therapy on day 0 (14 patients [15%]) followed by patients who began on day 1 (9 [24%]), day 2 (12 [37%]), or day ⩾3 (12 [41%]) ($P = .0009$ for trend). Multivariate logistic regression was used to calculate independent predictors of mortality, which include increased time until fluconazole initiation (odds ratio, 1.42; $P < .05$) and Acute Physiology and Chronic Health Evaluation II score (1-point increments; odds ratio, 1.13; $P < .05$).

Conclusion. A delay in the initiation of fluconazole therapy in hospitalized patients with candidemia significantly impacted mortality. New methods to avoid delays in appropriate antifungal therapy, such as rapid diagnostic tests or identification of unique risk factors, are needed.

CID 2006;43(1):25-31

CHALLENGES IS EARLY DIAGNOSIS

- IC lacks specific and objective clinical findings
- Blood culture → Gold standard diagnostic test for IC → insensitive (50-67% case detection)
- Detection of candidemia by blood culture often takes more than 24 hours
- Serologic tests like mannan antibody/antigen detection, ß-1,3-D-glucan and nested PCR can be used to diagnose IC
- Can be positive even 2-6 days prior positive blood culture
- Sensitivity and specificity variable

Infect Dis Clin North Am 2006;20(3)485-506

EMPIRICAL AND PREEMPTIVE STRATEGIES BASED ON RISK IDENTIFICATION

Composite of risk factors		Sn	Sp
Candida colonization index (CI): Addition of no of nonblood sites that are culture positive for the same Candida species divided by the total number of sites cultured	Index > 0.5	100%	55%
Candida score: point value for 4 risk factors (multifocal colonization 1 point, TPN 1 point, surgery 1 point, and sepsis 2 points)	> 2.5	77.6%	66.2%
Clinical prediction rule: 2 major risk factors: receipt of a systemic antibiotic and presence of a CVC Minor risk factors:TPN, dialysis, surgery in the preceding week/MV,pancreatitis, and use of steroids or other immunosuppressive agents	2 major+ 2 minor	34%	90%

Infect Dis Clin North Am 2006;20(3)485-506
Crit Care Med 2011;27:123-147

Optimal Drug Choice

Class	Drugs	M/A	PK/PD	Spectrum
Polyene	Ampho B	Cidal Bind to ergosterol in cell wall	Cmax/MIC =2-4 PAFE Good tissue penetration	C.albicans (MIC90 1µg/ml) C.glabrata (4µg/ml) C. krusei (8µg/ml)
Triazoles	Fluconazole voriconazole	Inhibit cyt P450 dependent enzyme	AUC/MIC =25 PAFE Voriconazole not excreted in urine	C. krusei inherently resitant to fluconazole Glabrata variable resistance
Echinocandins	Caspofungin Micafungin anidulofungin	Inhibit ß-1,3-glucan synthase	AUC/MIC = 5-20 Low CSF,vitrous, urine distribution	C.Parapsilosis r educed susceptibility

Crit Care Med 2011;27:123-47

ANTIMICROBIAL RESISTANCE IN ICU

- Antibiotic resistance either arises as a result of innate consequences or is acquired from other sources
- Bacteria acquire resistance by:
  - Mutation : spontaneous single or multiple changes in bacterial DNA
  - Addition of new DNA: usually via plasmids, which can transfer genes from one bacterium to another
  - Transposons: short, specialised sequences of DNA that can insert into plasmids or bacterial chromosomes

MANY PATHOGENS POSSESS MULTIPLE MECHANISMS OF ANTIBACTERIAL RESISTANCE

	Modified target	Altered uptake	Drug inactivation
β-lactam	+	+	++
Glycopeptide	+		
Aminoglycoside	–	+	++
Tetracycline	–	+	
Chloramphenicol		–	+
Macrolide	++		
Sulphonamide	++	–	
Trimethoprim	++	–	
Quinolones	–	+	

MDR Nonfermenting GNB: P.aeruginosa, Acinetobactor spp & Stenotrophomonas maltohlia

- Soil, water and health care environment, including on respiratory therapy/ventilator equipment, environmental surfaces
- Colonizers of patients and HCWs
- Acinetobactor is the most common cause of nosocomial sepsis in our ICU
- High incidence of MDR -NLF GNB in Latin America, Asia, Africa, and Europe

METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA)

- Introduction of methicillin in 1959 was followed rapidly by reports of MRSA isolates
- Recognised hospital pathogen since the 1960s
- Major cause of nosocomial infections worldwide
  - contributes to 64.4% of infectious morbidity in ICUs in USA[1]
- Risk factors
  - Prior antibiotic exposure, ICU admission, surgery, exposure to MRSA colonised patient

[1] CID 2006;42:389-91

MECHANISMS & GENETICS

- Mediated by mecA gene which encodes penicillin-binding protein — PBP 2' (PBP 2a)
- Confers resistance to all β-lactams
- Gene carried on a mobile genetic element — staphylococcal cassette chromosome *mec* (SCC*mec*)
- Cross-resistance common with many other antibiotics (erythromycin and clindamycin)
- Ciprofloxacin resistance is a worldwide problem in MRSA:
  - involves ≥2 resistance mutations
  - usually involves *par*C and *gyr*A genes
  - renders organism highly resistant to ciprofloxacin, with cross-resistance to other quinolones
- Intermediate resistance to glycopeptides first reported in 1997

Trends Microbiol 2001;9:486–493
Arch Microbiol 2002;178:165–171

EMERGENCE OF MRSA IN THE COMMUNITY

- CAMRSA is more recent phenomenon – mid 1990s
- Genetic lineages distinct from HAMRSA
- Carry smaller SCCmec elements – USA400/300
- Wide array of virulent trait – Panton Valentine Leukocidin(PVL)
- SSTI, osteomyelitis, bacteremia, and pneumonia
- In a hospital-based study, >40% of MRSA infections were acquired prior to admission

Curr Opin Infect Dis 2002;15:407–413
Infect Control Hosp Epidemiol 1995;16:12–17
Infect Control Hosp Epidemiol 2003;290:2976–2984

Treatment of MRSA

	Preferred agent	Alternative
Bacteremia and endocarditis	Vancomycin (MIC <1 μg/ml) Daptomycin (MIC >1 μg/ml)	Linezolid Tigecycline
HAP/VAP	Vancomycin (trough 15-20μg/ml) Linezolid	
CAMRSA	Linezolid Clindamycin TMP-SMX	Tigecycline

Crit Care Med 2011;27:163-205