OPTIMIZING ANTIBIOTIC THERAPY

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Antibiotic Resistance

Are We Winning The Battle But Losing The War?

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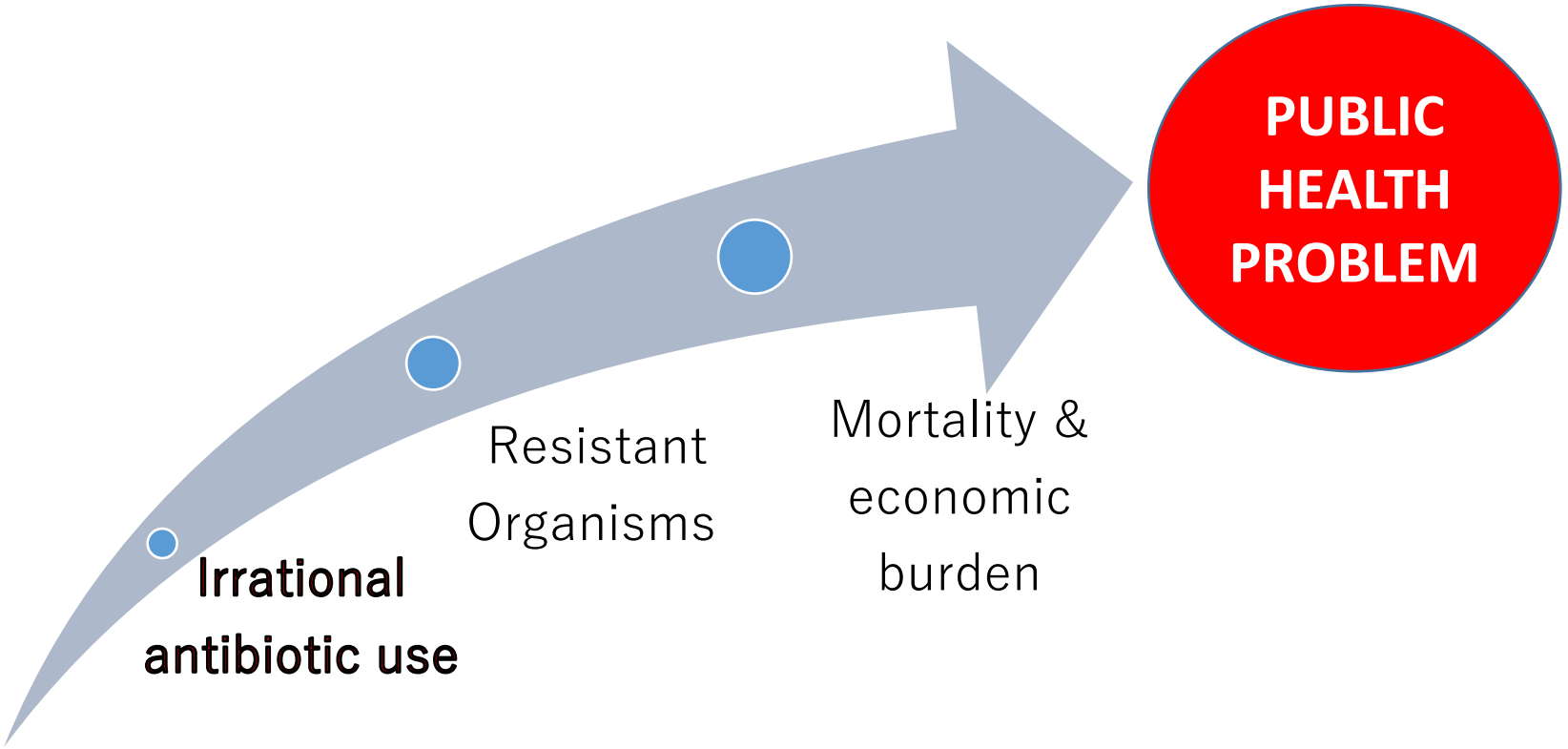
PUBLIC HEALTH PROBLEM
Irrational antibiotic use
Resistant Organisms
Mortality & economic burden

- Involves the use of antibiotics that achieve **maximum therapeutic effect** with **minimum selective pressure for resistance**
- Balance of **potency and efficacy** with **low induction of antimicrobial resistance**

Polk. Clin Infect Dis 1999;29:264-274

Why is there a need for Optimal Antibiotic Therapy?

- Increasing number of cases of antibiotic failure
- Need to maximize the efficacy of existing antibiotics
- Need to preserve their potency and reduce the problems of antimicrobial resistance

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Evolution of *Staphylococcus aureus*

Discovery of *S. aureus*

Commercial use of Penicillin

Isolation of **MRSA**

Use of **Vancomycin**

Isolation of **VRSA**

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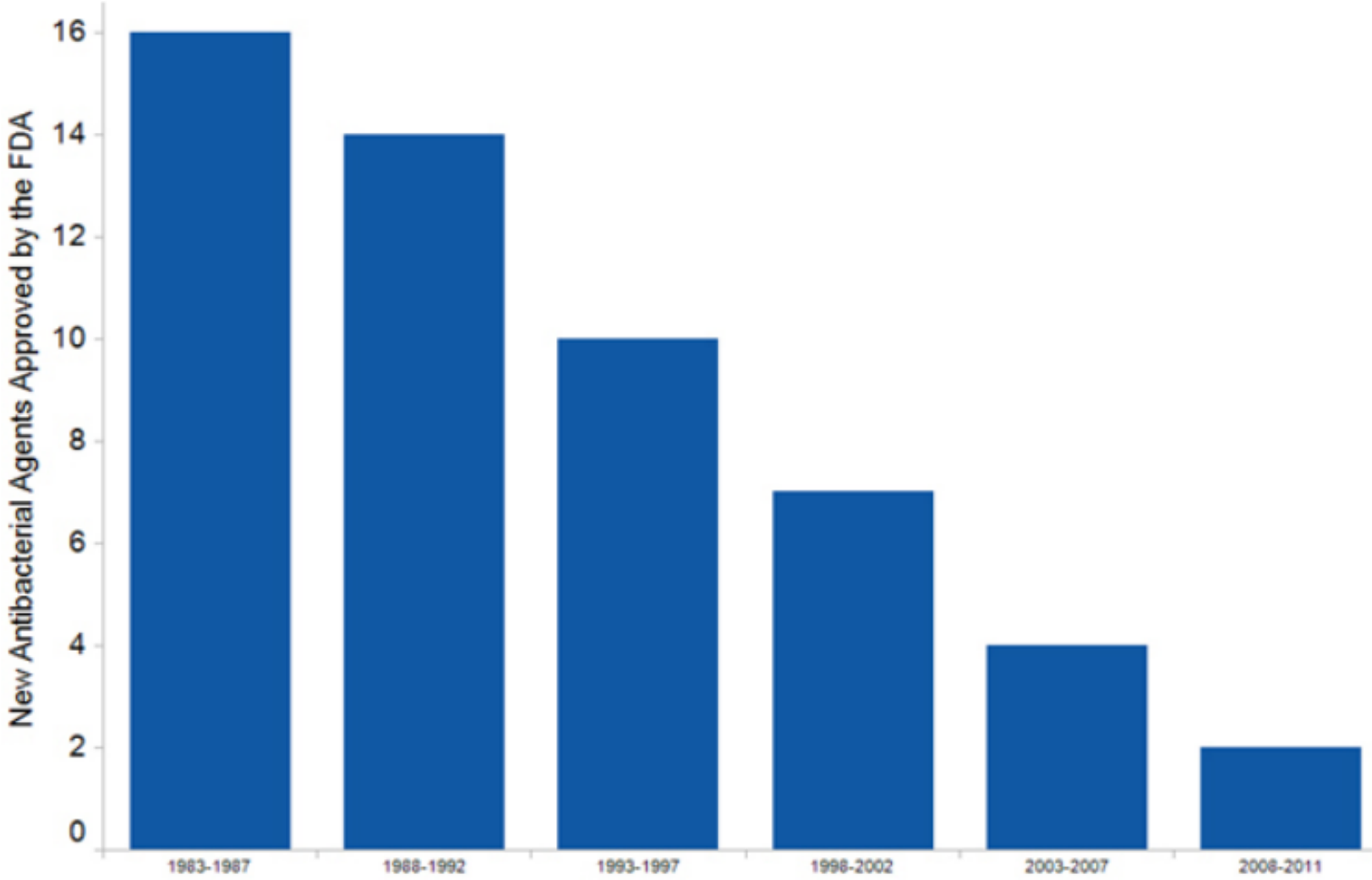
Decline in the Approval of New Antibiotics



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Drivers of Resistance

Patient

- Neonate
- Advanced age
- Extended LOS
- Immunocompromised

Bug

- Intrinsic Resistance Mechanisms
- Acquired Resistance Mechanisms

Drug

- Prolonged Therapy
- Under-dosage
- PK/PD
- Routine Combination Therapy

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E *Enterococcus faecium*

S *Staphylococcus aureus*

K *Klebsiella pneumoniae*

A *Acinetobacter baumanii*

P *Pseudomonas aeruginosa*

E *Enterobacter* spp.

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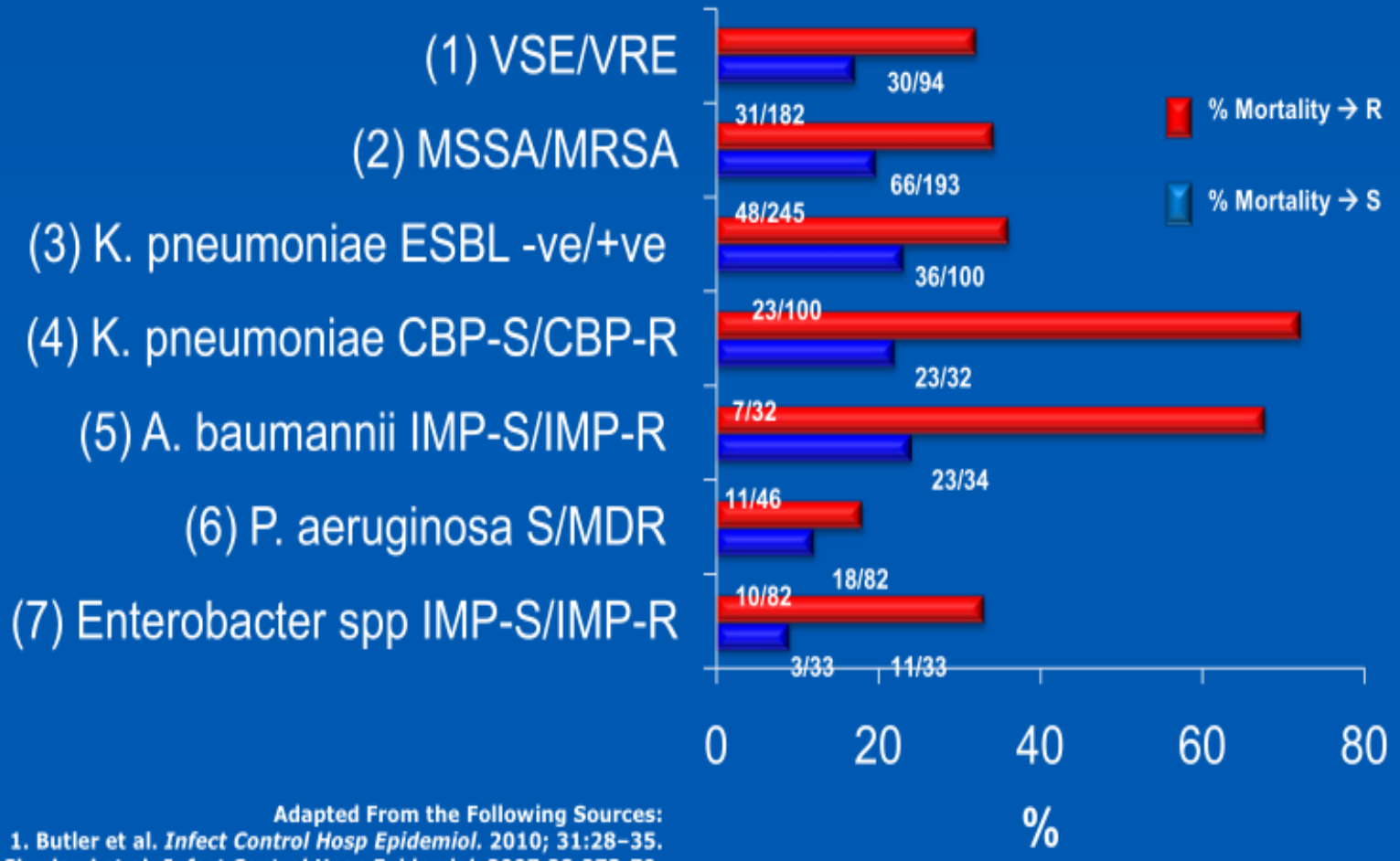
"ESKAPE" Pathogens

Poor Clinical Outcomes & Increased Mortality as Shown in Different Studies



Adapted From the Following Sources:

1. Butler et al. *Infect Control Hosp Epidemiol.* 2010; 31:28–35.
2. Shurland et al. *Infect Control Hosp Epidemiol.* 2007;28:273-79.
3. Szilágyi et al. *Acta Microbiol Immunol Hung.* 2009;56:251-62.
4. Borer A, et al. *Infect Control Hosp Epidemiol.* 2009;30:972-6.
5. Kwon K. et al. *J Antimicrob Chemother.* 2007;59:525–530.
6. Aloush V. et al. *Antimicrob Agents Chemother.* 2006;50: 43–48.
7. Marchaim D. et al. *Antimicrob Agents Chemother.* 2008; 52:1413-1418.

$P < 0.01$

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Redefining ESKAPE → ESCAPE

E *Enterococcus faecium*

S *Staphyloccus aureus*

C ***Clostridium difficile***

A *Acinetobacter baumanii*

P *Pseudomonas aeruginosa*

E **Enterobacteriaceae**

Peterson LR. Clin Infect Dis. 2009;49:992

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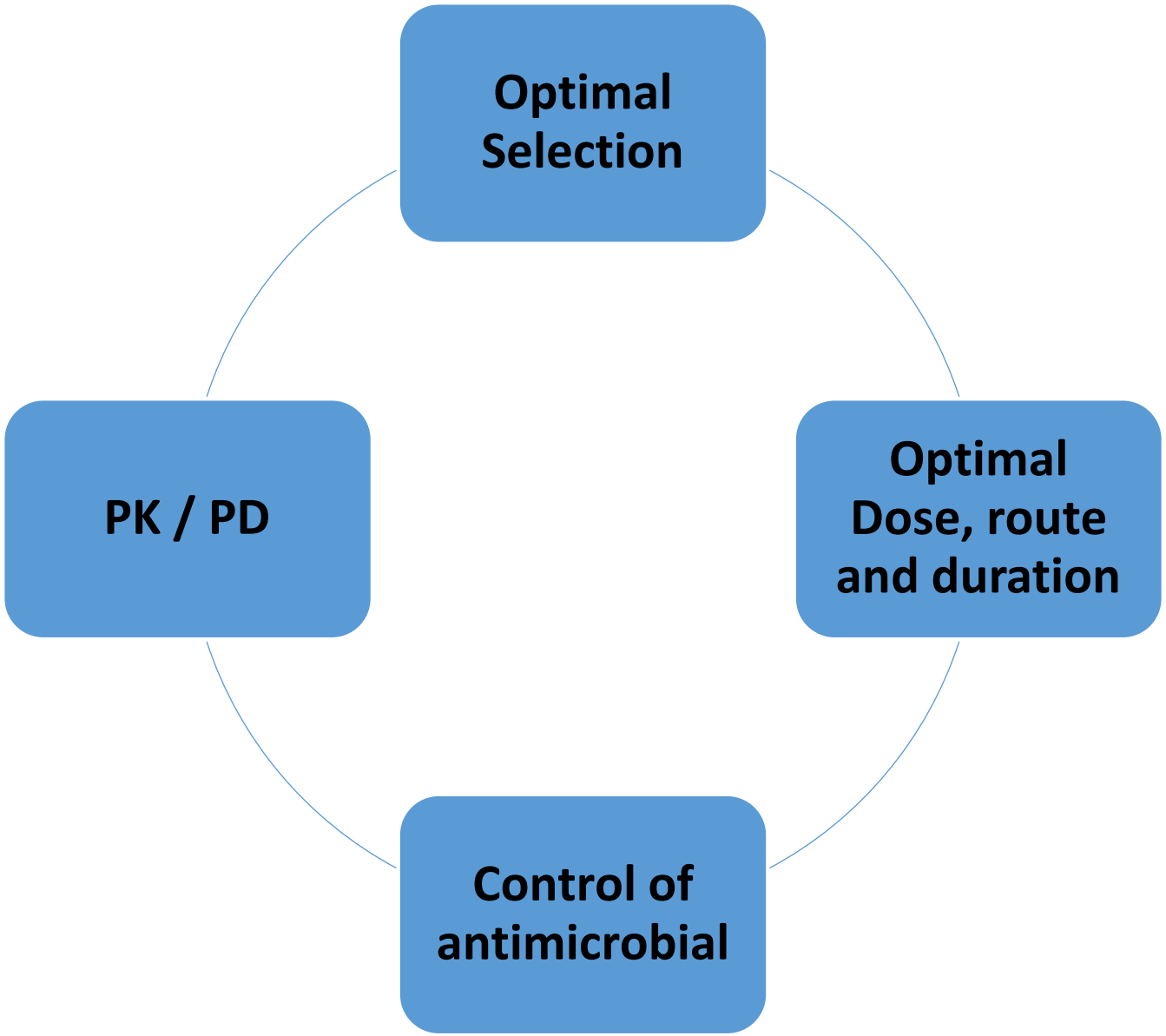
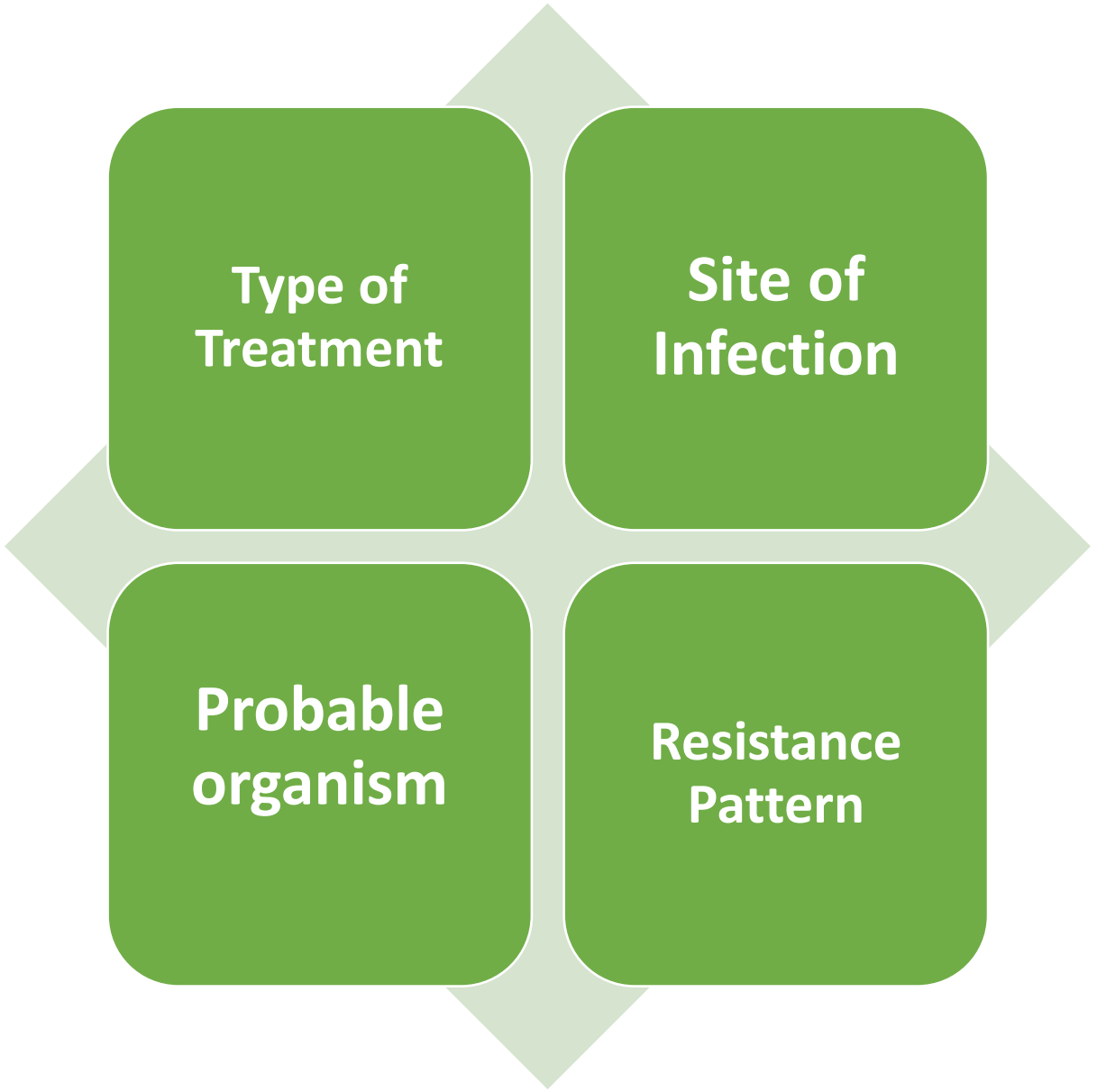


Polk. Clin Infect Dis 1999;29:264-



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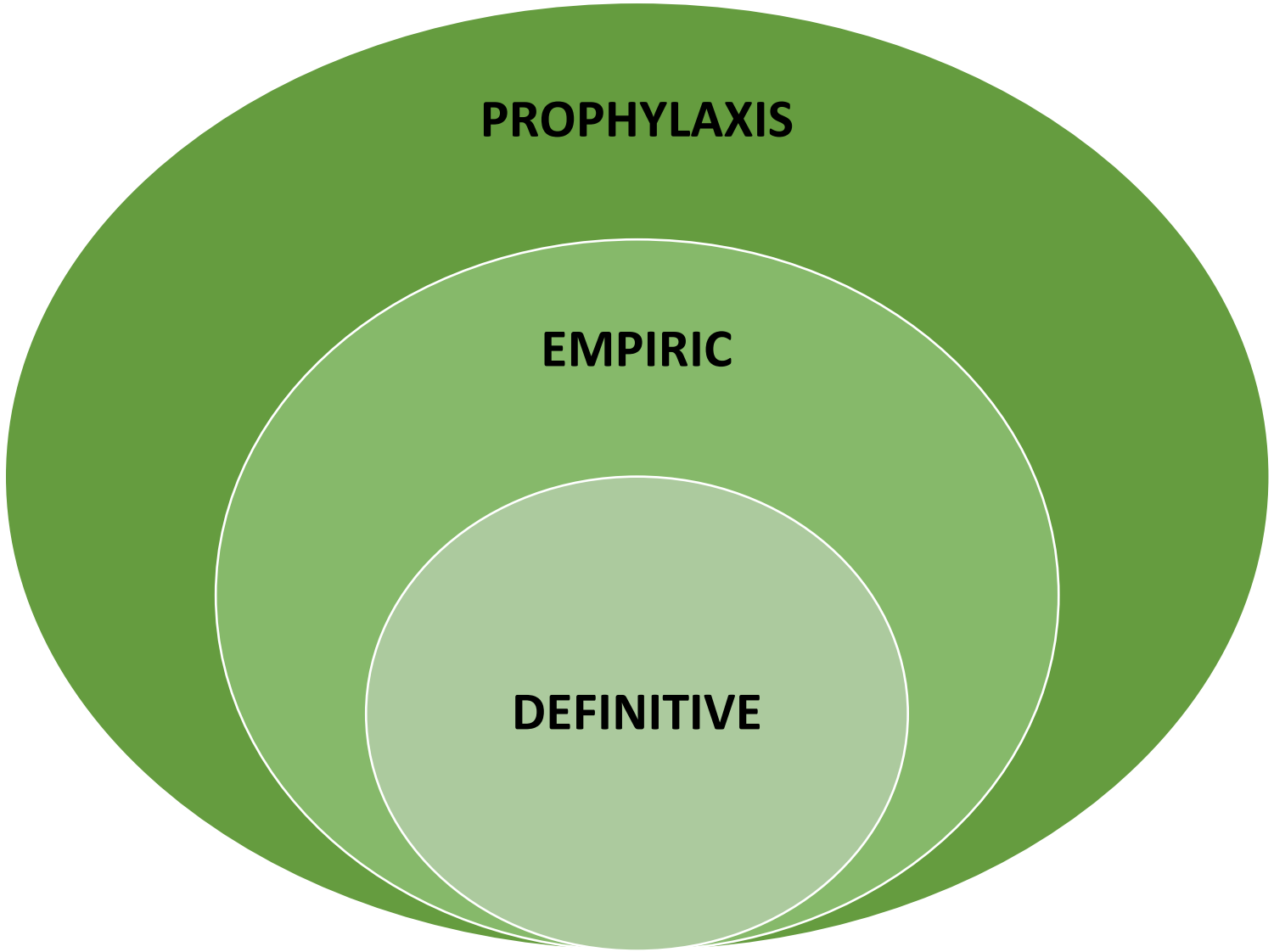
TYPES OF TREATMENT



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TYPE OF TREATMENT	DEFINITION
Prophylaxis	Antibiotics used to prevent infection
Empiric	Organism is unknown Syndrome is known
Definitive: Pathogen – directed	Organism is known Susceptibility is unknown
Definitve: Susceptibility – guided	Organism is known Susceptibility is known

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Local Antibiotic Resistance Data

<u>Antimicrobial Resistance Surveillance Program – Philippines Data Summary Report 2015</u>

- 50,895 isolates
- 8% increase when compared to 2014
- came from the 22 sentinel sites of the program which represents 14 regions of the Philippines
- The most common specimen types comprising the 2015 ARSP data were respiratory, blood, wound and urine specimens
- **For 2015, *Klebsiella* species, followed by *Escherichia coli***

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Klebsiella pneumoniae

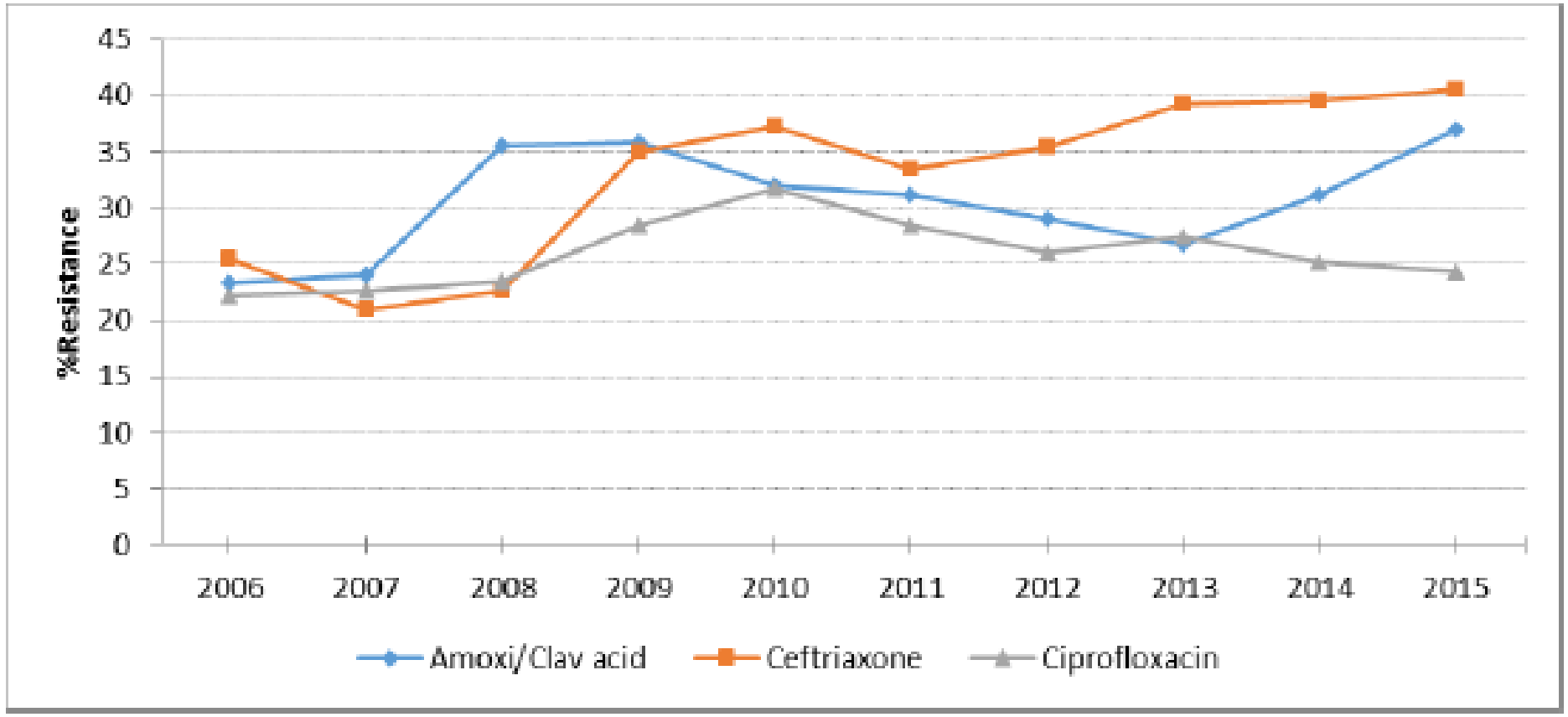

Figure 49. Yearly amoxicillin-clavulanic acid, ceftriaxone and ciprofloxacin resistance rates of *Klebsiella pneumoniae*, ARSP, 2006-2015

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Escherichia coli

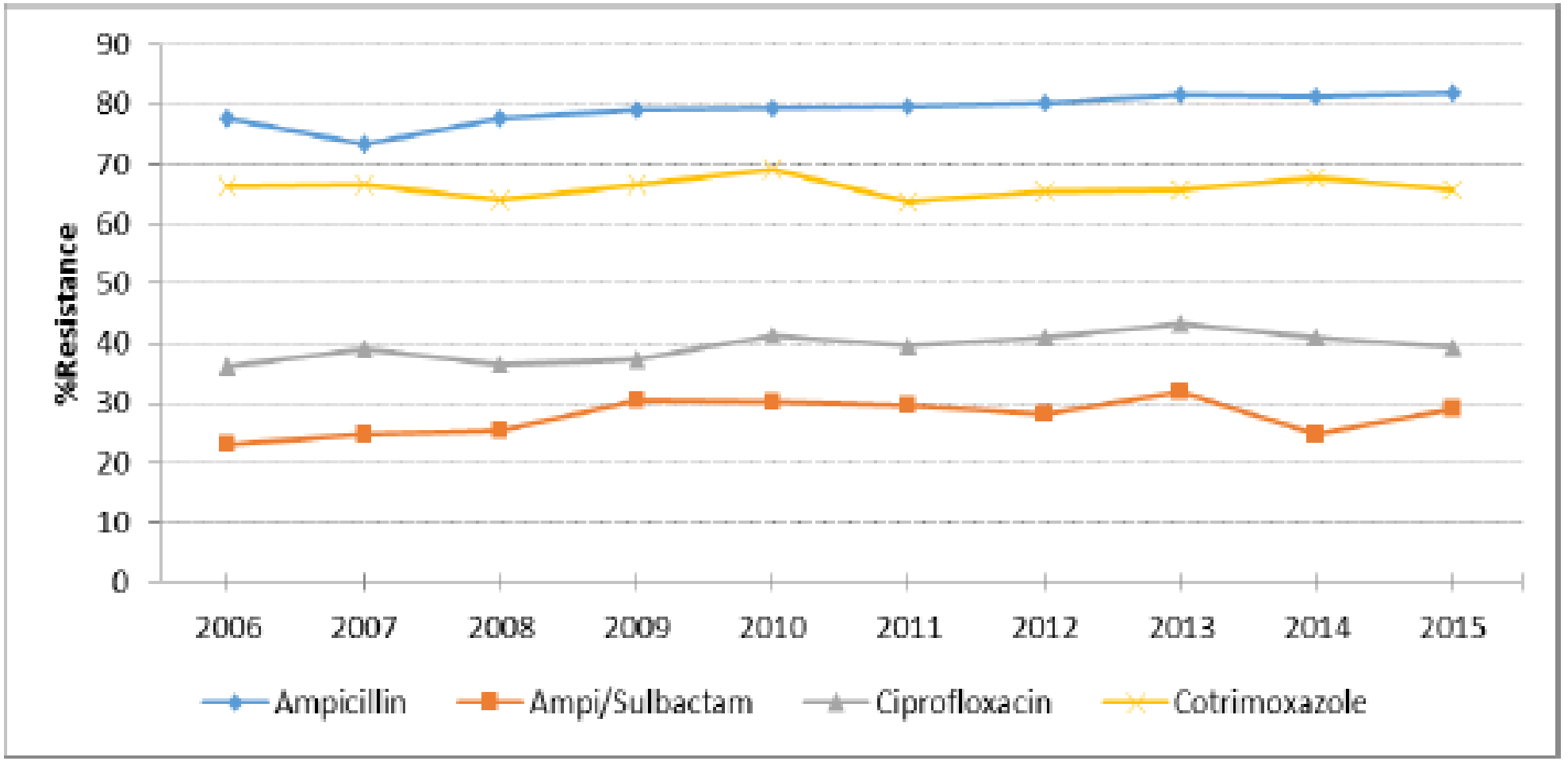

Figure 44. Yearly ampicillin, ampi-sulbactam, ciprofloxacin and co-trimoxazole resistance rates of *Escherichia coli*, ARSP, 2006-2015

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WHO Advisory

- WHO issued an advisory on ***stewardship program*** to minimize or prevent **unwanted consequences** of AMR.
  - Program to monitor use of antibiotics
  - Coordinated effort between pharmacist and medical team

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Pharmacokinetics (PK)

- Encompasses all the ways that the body manipulates a drug
- Science of the rate of movement of the drug within biological systems
- BODY → DRUG

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Pharmacodynamics (PD)

- Describes the biochemical and physiologic effects of the drug and its mechanism of action
- Study on the action of drugs on living organisms
- DRUG → BODY

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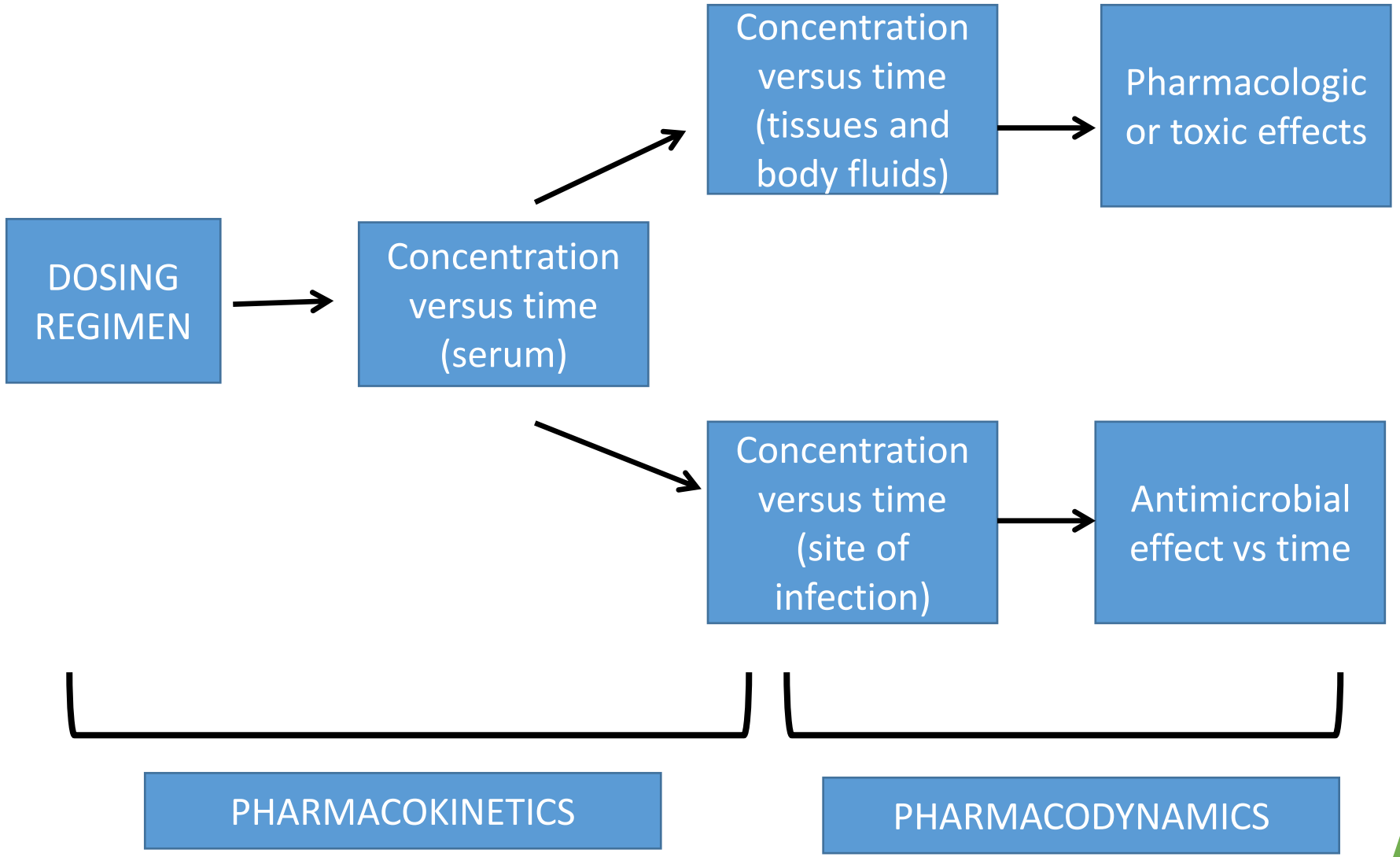
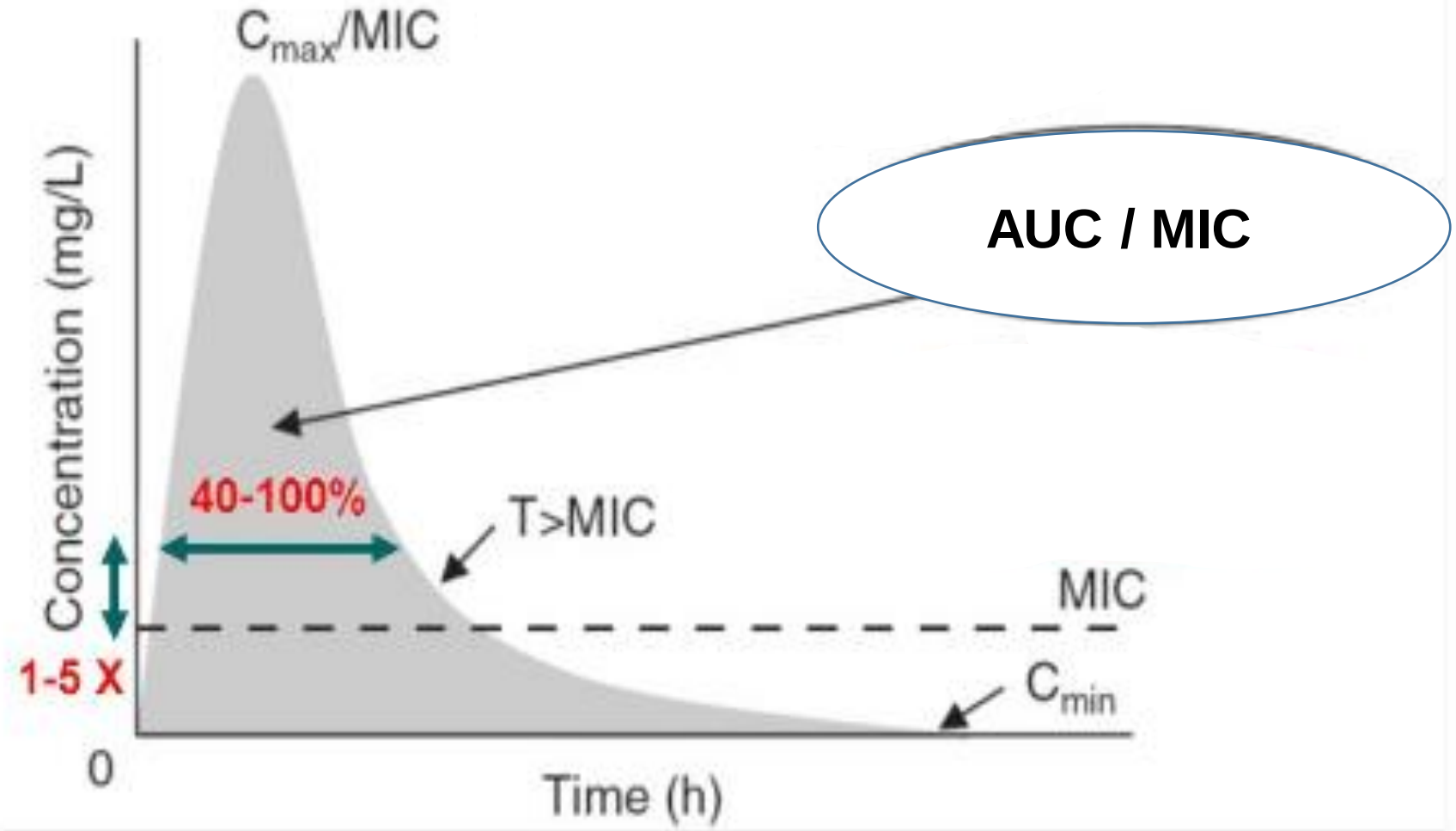
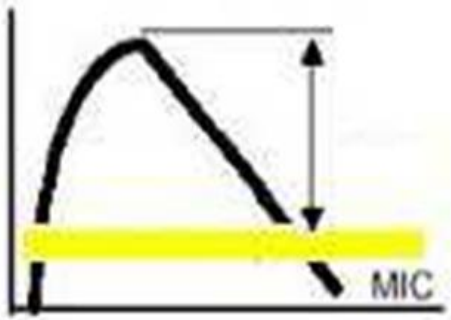

DOSING REGIMEN
Concentration versus time (serum)
Concentration versus time (tissues and body fluids)
Pharmacologic or toxic effects
Concentration versus time (site of infection)
Antimicrobial effect vs time
PHARMACOKINETICS
PHARMACODYNAMICS



Roberts JA, Lipman J. *Clin Pharmacokinet* 2006; 45:755-773

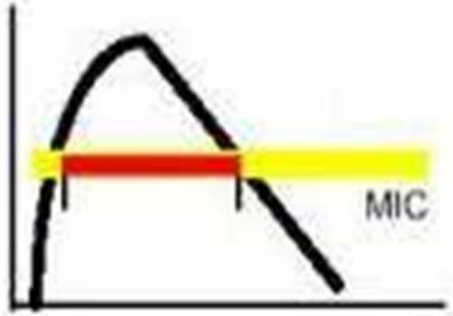
Predictors of Bacterial Eradication: Pharmacokinetic/Pharmacodynamic Profiles

Peak/MIC



- Aminoglycosides

T > MIC



- Beta-lactams
- Clindamycin
- Erythromycin
- Linezolid

24h-AUC/MIC

- Azithromycin
- Quinolones
- Vancomycin

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Post-Antibiotic Effect (PAE)

- During testing of antibiotics, there may be a delay before organisms recover and re-enter a log-growth period.
- PAE is species and drug dependent
- Mechanism is unknown

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Post-Antibiotic Effect (PAE)

- Aminoglycosides and Fluoroquinolones have prolonged PAE (2 to 6 hours for gram negative)
- Beta lactams have little or no PAE for gram negative, 2 hours for gram positive.

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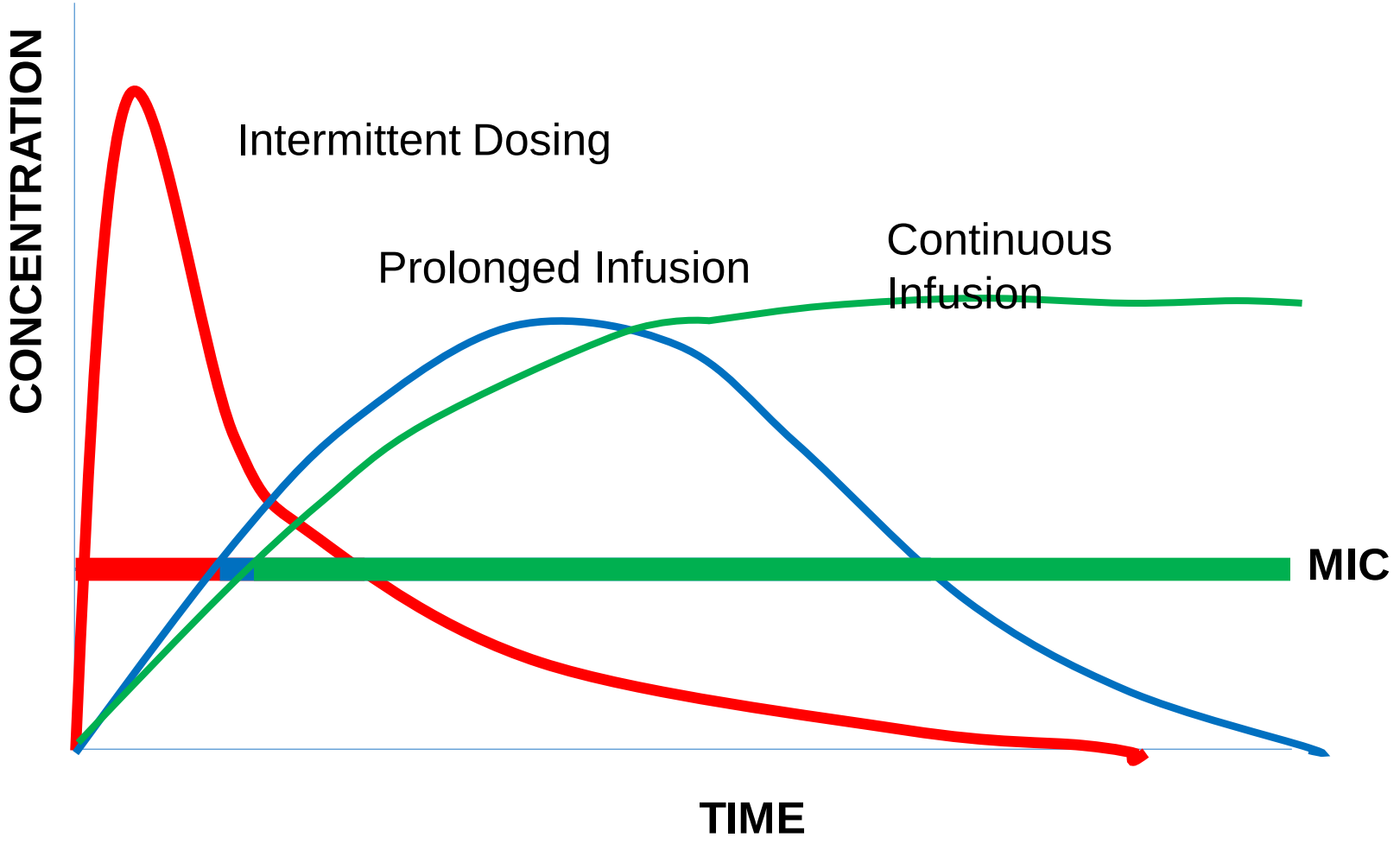
- Theoretically, an agent with long PAE can be dosed less frequently than an antimicrobial lacking PAE.

- If antimicrobials have little PAE, it may be most effective to be given as continuous infusion

Optimizing B-lactam Therapy: Maximizing Percent T>MIC



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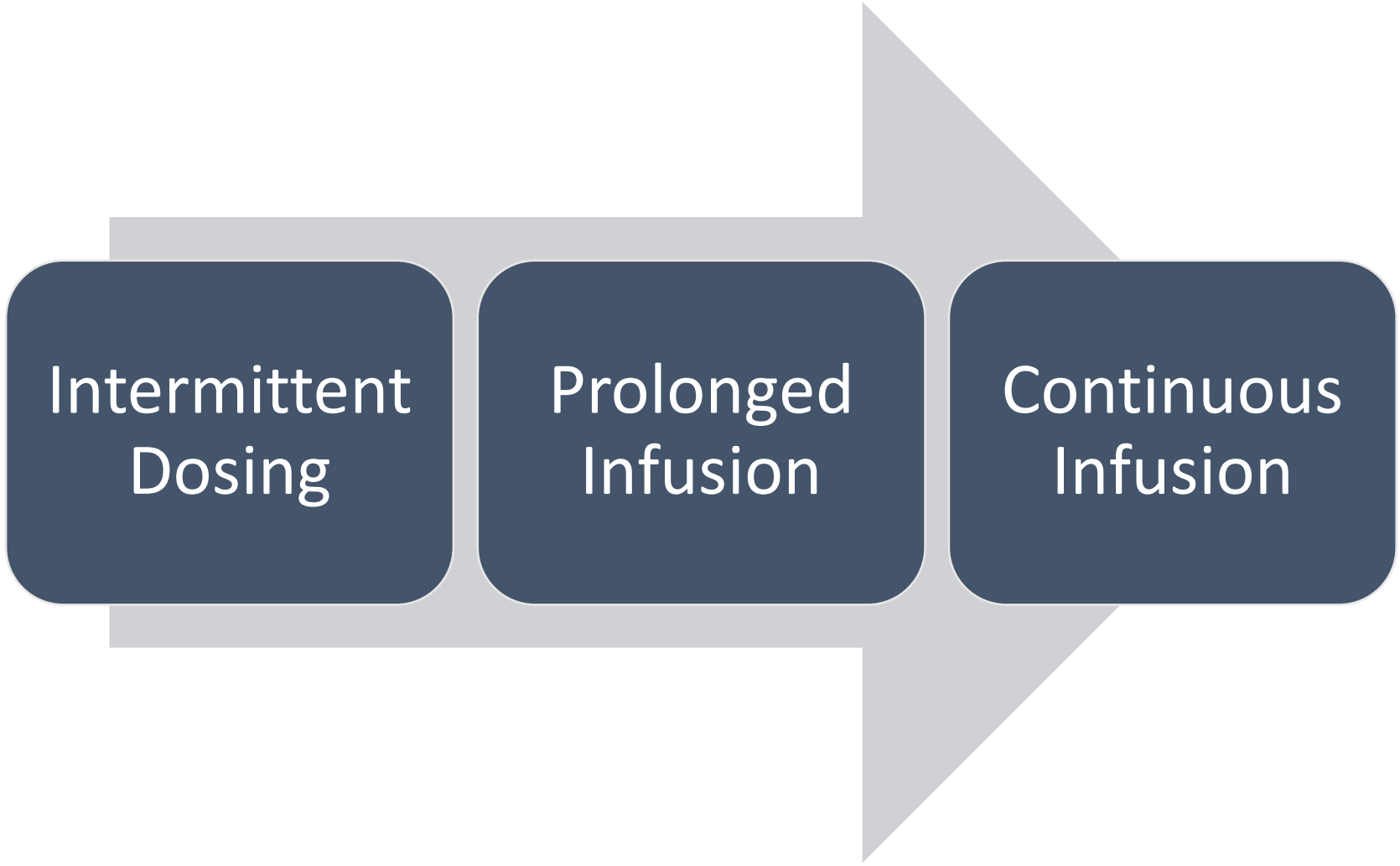
Increasing Order of Optimal Infusion



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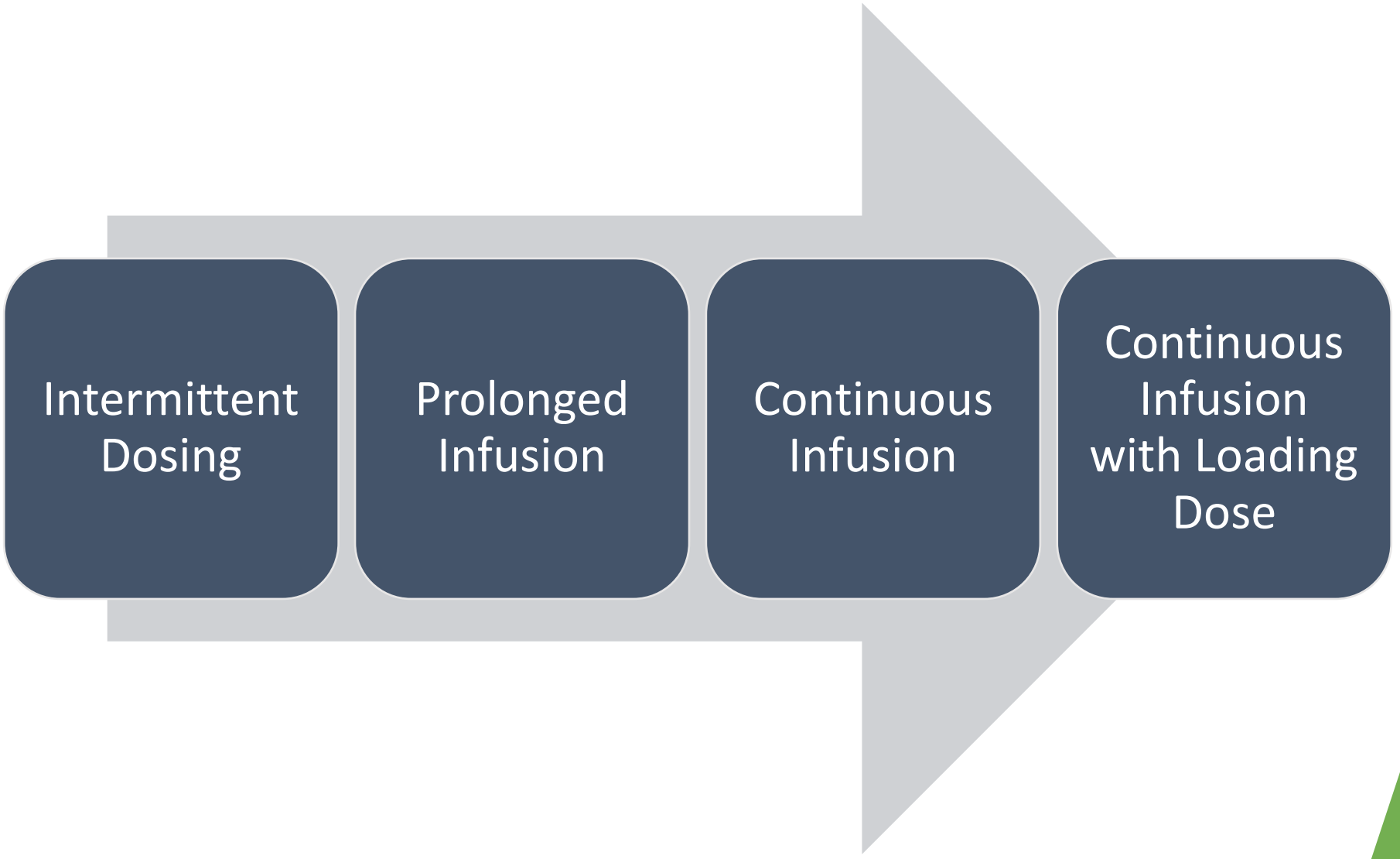

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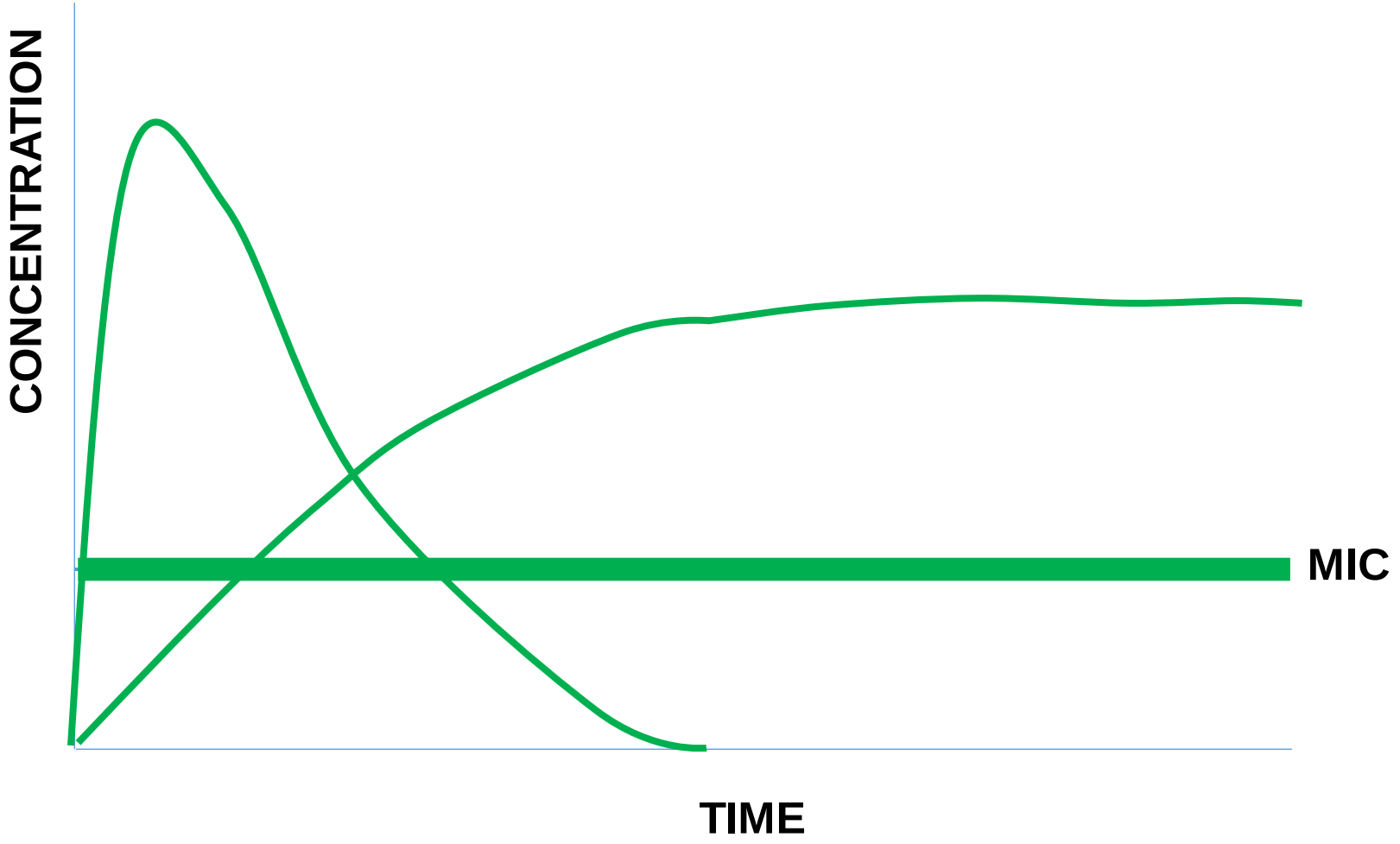
CONCENTRATION
MIC
TIME

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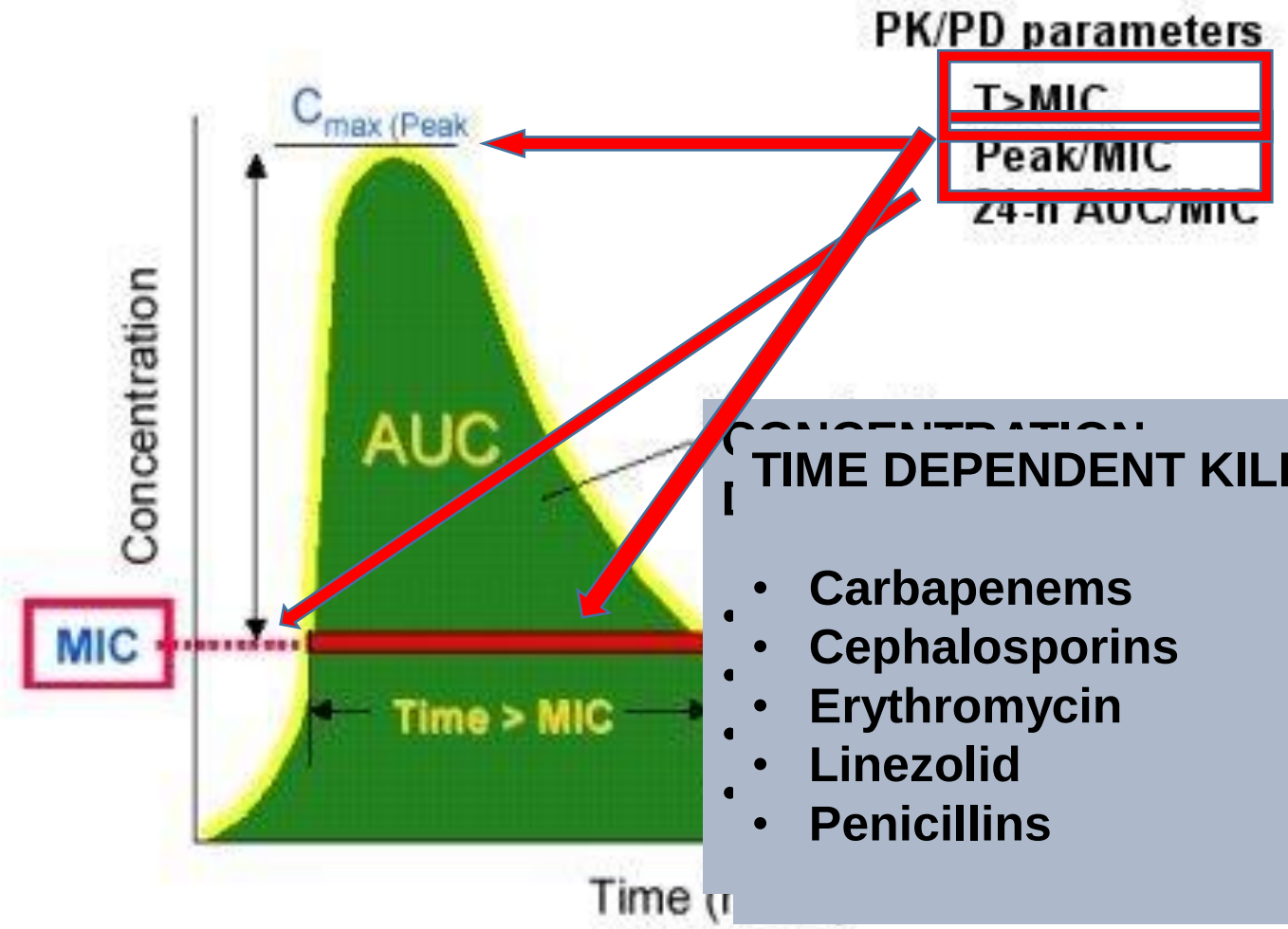
Pharmacokinetic/Pharmacodynamic Predictors of Efficacy



TIME DEPENDENT KILLING

- Carbapenems
- Cephalosporins
- Erythromycin
- Linezolid
- Penicillins

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Importance of Early Appropriate and Potent Antimicrobial Therapy

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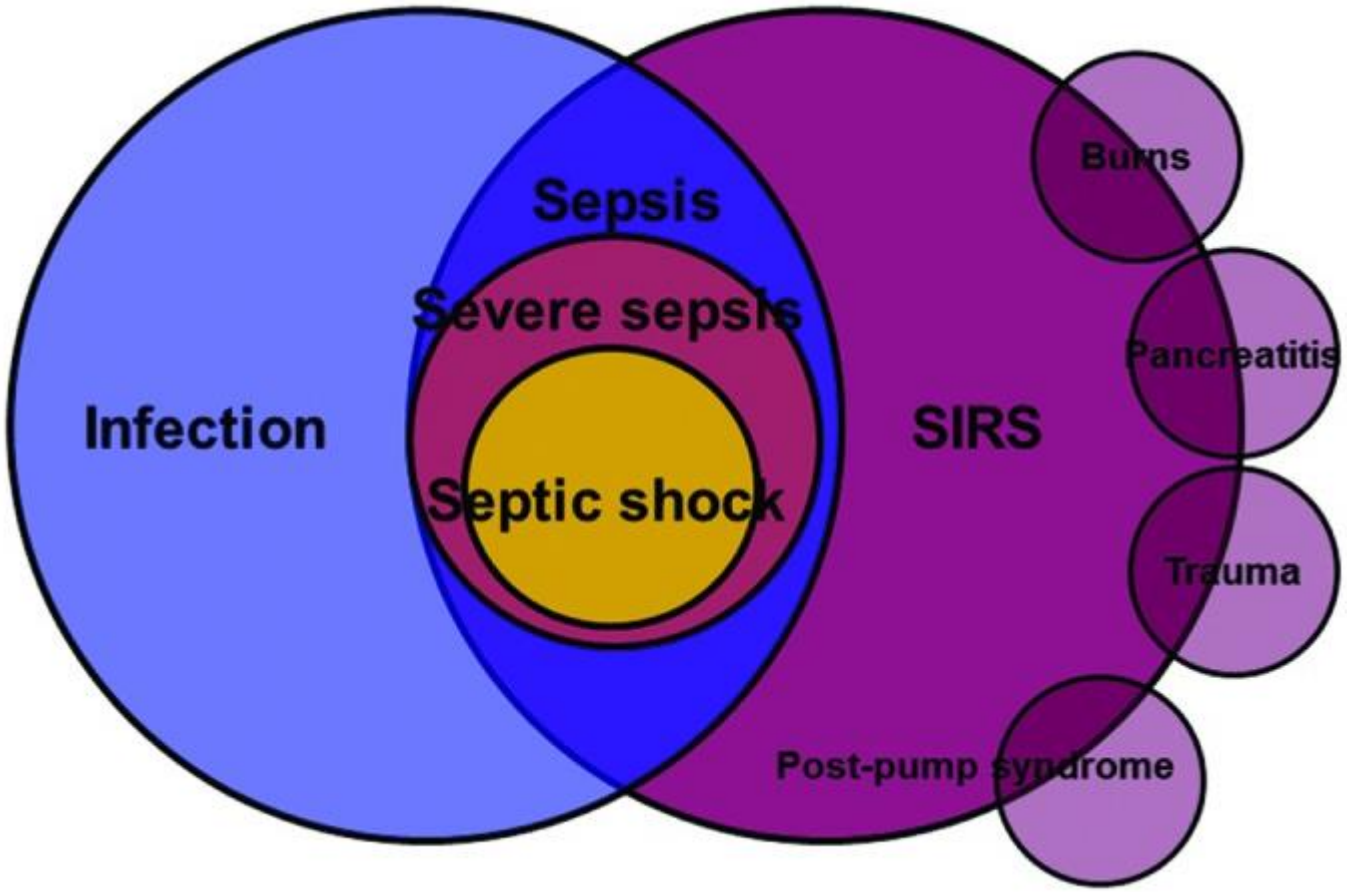
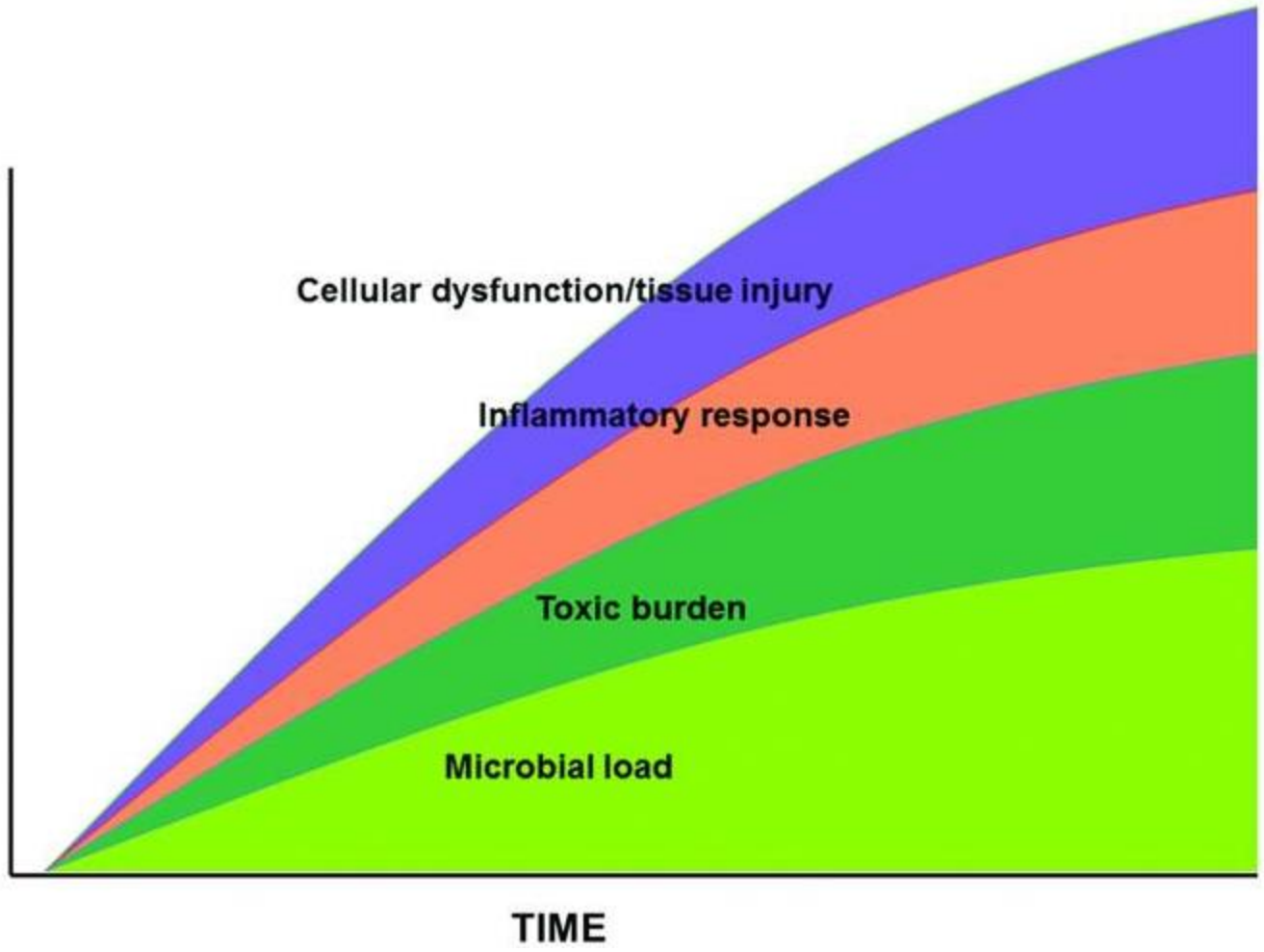


Kumar A. An alternate pathophysiologic paradigm of sepsis and septic shock. Virulence. 2013;5(1):80-97. doi:10.4161/viru.26913.



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SHOCK

- "… a syndrome resulting from depression of many functions, but in which reduction of the effective circulating volume and blood pressure are of basic importance, and in which impairment of circulation steadily progresses until it eventuates in **a state of irreversible circulatory failure**"

- Carl J Wiggers (1883 – 1963)

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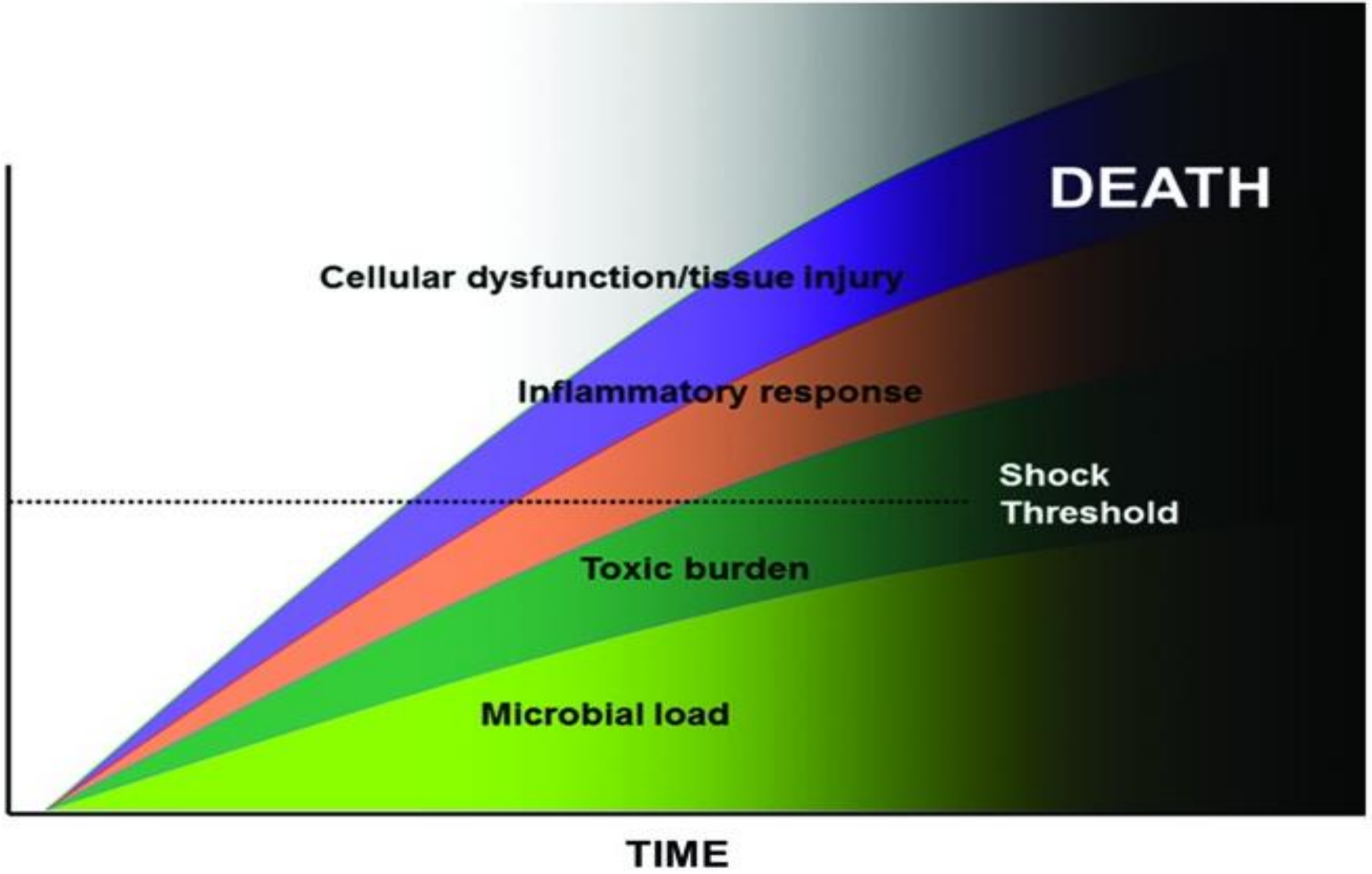

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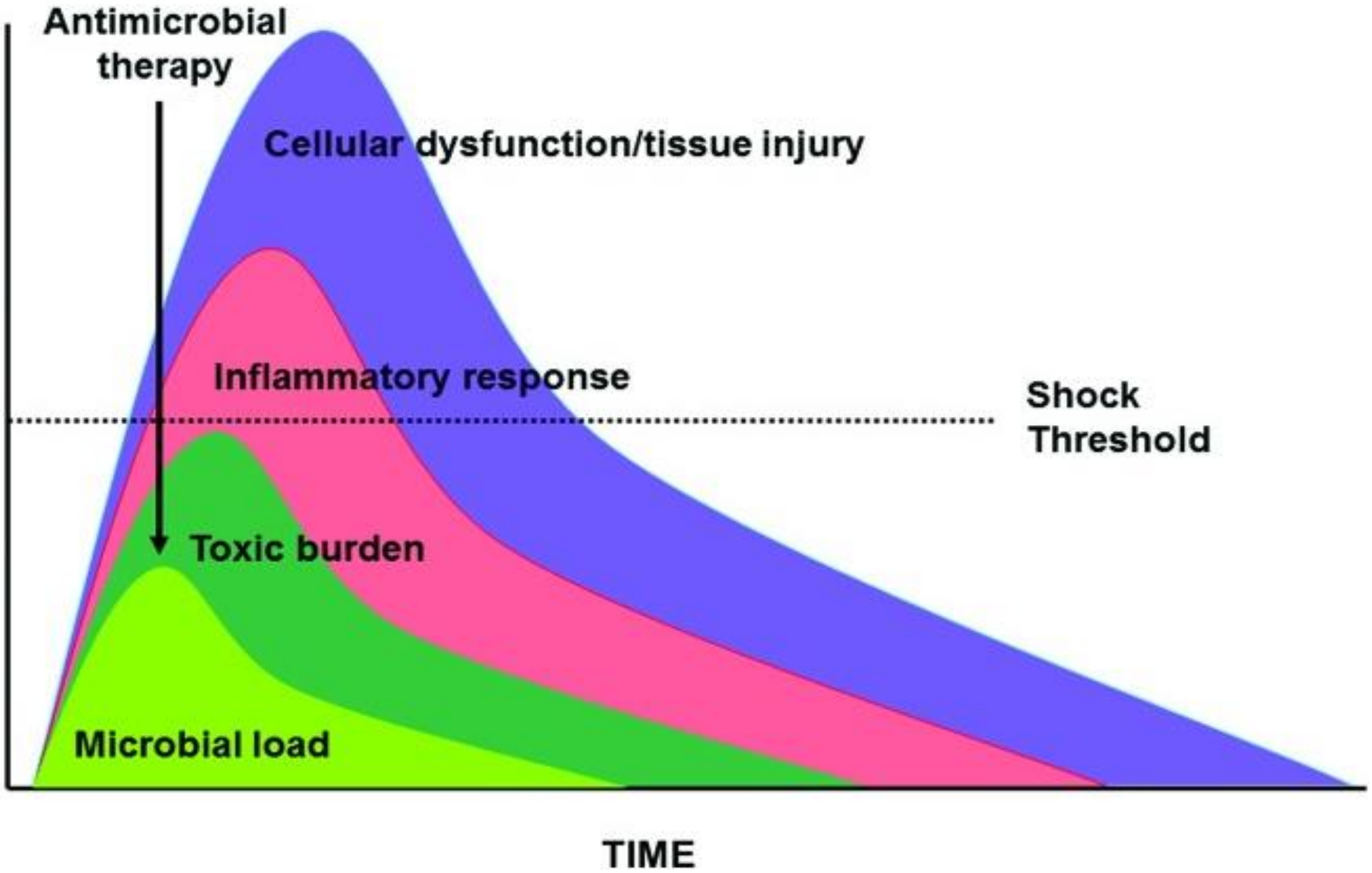

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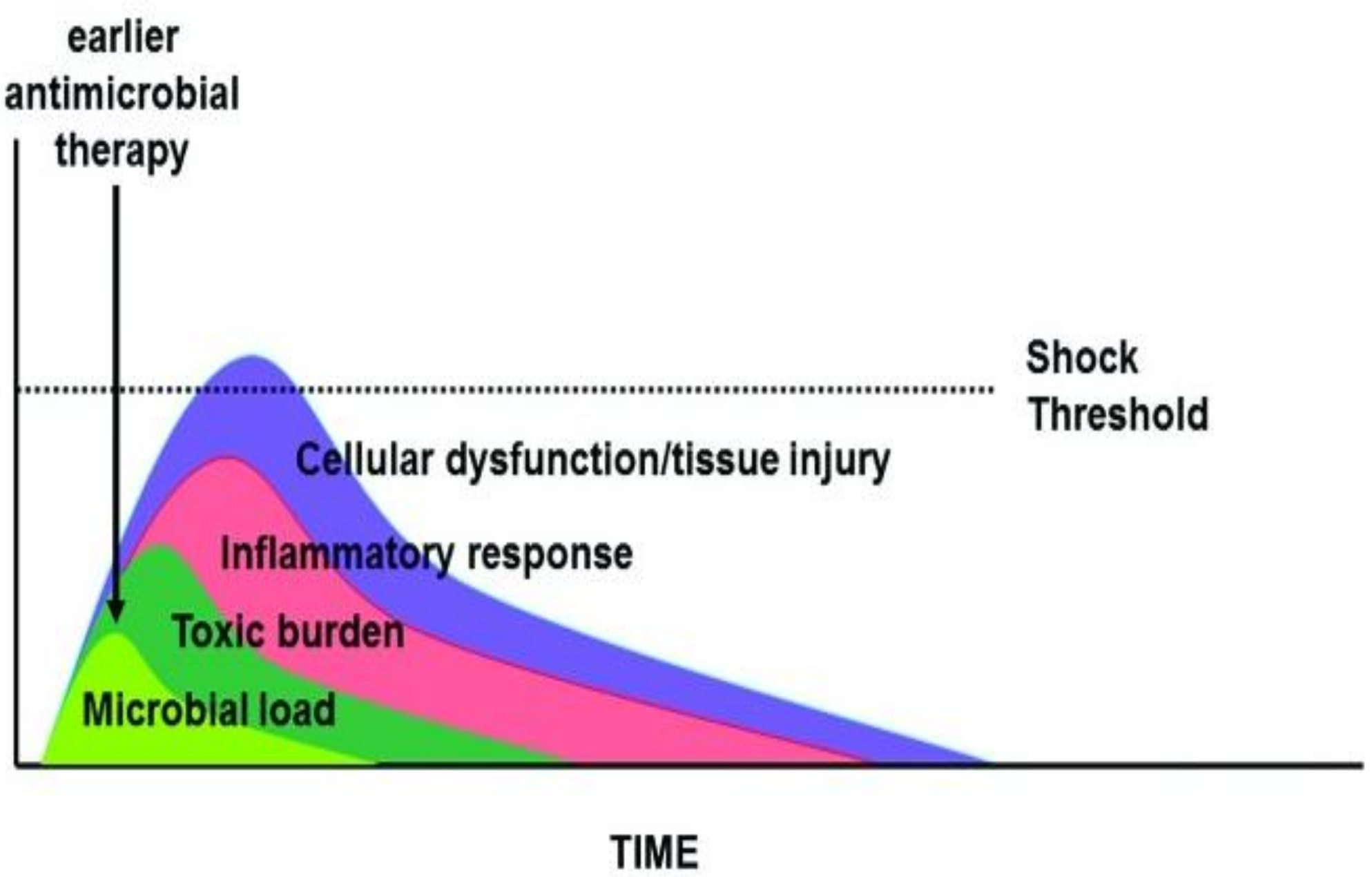

Kumar A. An alternate pathophysiologic paradigm of sepsis and septic shock. Virulence. 2013;5(1):80-97. doi:10.4161/viru.26913.

- **Time of delivery of effective antimicrobial therapy from onset of hypotension** is a surrogate marker for increasing microbial burden of organism
- **Early and Rapid clearance of pathogens** is the most important determinant of outcome in sepsis

Kumar A. An alternate pathophysiologic paradigm of sepsis and septic shock. Virulence. 2013;5(1):80-97. doi:10.4161/viru.26913.

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- Time to initiation of appropriate antibiotic therapy was the strongest predictor of survival

- **If an effective antibiotic was administered within the first hour of documented hypotension, the survival rate was 79.9%; each 1-h delay over the next 6 h decreased average survival rates by 7.6%.**

Kumar A. An alternate pathophysiologic paradigm of sepsis and septic shock. Virulence. 2013;5(1):80-97. doi:10.4161/viru.26913.

Right Drug

Right Dose

Right Time

Right Duration

Every Patient

Start Smart

then Focus on clinical review and decision documentation*

WHO and DOH Advisory

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The best way of optimizing and maximizing the benefits of antibiotics is knowing how to use them the best way possible.

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THANK YOU!

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