Principles in antimicrobial therapy: The ABCs

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Disclosure

- Medical Director, Otsuka Philippines Pharmaceuticals Inc.
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- No CME activities in any form have been received by the speaker

Is there anything beyond BE?

- Four important parameters should be observed before writing an antibiotic prescription:
  - SAFETY
  - AFFORDABILITY
  - NEED/SUITABILITY
  - EFFICACY

YES THERE IS!

AND IT SIMPLY MEANS WE GO BACK TO BASICS…THE *A B C* OF ANTIBIOTIC THERAPY

Objectives

- 1. Review the basic principles in selection of optimal antimicrobial therapy in pediatrics
- 2. Provide an update on the epidemiologic basis for antibiotic selection
- 3. Provide guidelines for SANE-based prescription in the current scenario of generic equivalents

Selecting Optimal Antimicrobial Therapy

(adapted from Principles of Anti-infective Therapy by John Bradley and Sarah Long in Principles & Practice of Pediatric Infectious Diseases)

Questions pertinent to choosing antimicrobial therapy appropriately
1. What is the clinical syndrome/site of infection? Pathogens are predictable by site
2. Does the child have normal defense mechanisms (in which case causative agents are predictable) OR are they impaired by underlying conditions, trauma, surgery, or a medical device (in which case causative agents are less reliably predictable)?
3. What is the child's age? Pathogens are predictable by age
4. What clinical specimen(s) should be obtained to guide empirical/definitive therapy?
5. Which antimicrobial agents have activity against the pathogens considered, and what is the current range of susceptibilities for each antibiotic against these pathogens in the practitioner's hospital or clinic?

Selecting Optimal Antimicrobial Therapy

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Questions pertinent to choosing antimicrobial therapy appropriately
6. What special pharmacokinetic and pharmacodynamic properties of a therapeutic agent are important regarding the site of the infection host?
7. For any given infection site, what percent of children require effective antimicrobial therapy with agents first selected for treatment? *Bacterial meningitis requires 100%, whereas 75% may be acceptable for impetigo.*
8. What empiric therapy and what definitive therapy would be optimal? *Agents with a broad spectrum of activity may be appropriate for empiric therapy, whereas those with a narrow spectrum of activity are preferred for definitive therapy*.
9. What special considerations exist regarding drug allergy, drug interaction, route of administration, cost, alteration of flora, or selective pressure in an environment?

Step 1: Predicting the infection organism

- Bacteria are tropic for tissues locally following invasion; certain species have a proclivity for causing serious infections; while others can be dismissed in some infections when the site is already identified
  - Examples:
    - Meningitis: *N. meningitidis, grp B strep, S. pneumoniae, Hib (?)*
    - AOM: *S. pneumoniae, H. influenzae, M. catarrhalis*
    - Cellulitis, pyogenic arthritis, osteomyelitis: *S. aureus, S. pyogenes*

Acute Otitis Media

Macrolides or b-lactams?

Step 2. Consider host defense mechanism

- If the host is healthy with intact immunity and normal integumental barriers to infection, the causative pathogens are predictable
- If the host is healthy with intact immunity but with trauma to skin, mucous membranes, recent surgical procedure, or indwelling medical device, a variety of relatively nonpathogenic commensals can be causative pathogens, mandating therapy with broader spectrum antibiotic
- If the host is immunocompromised – REFER!

Step 3. Consider the age of the child

- Predictability based on child's age and age-specific exposures
  - Newborn period (*L. monocytogenes, GBS, E. coli*)
  - Developmental maturity of immune system provides improved recognition of polysaccharide-encapsulated pathogens (*S. pneumoniae, Hib*) as infants approach 3 y/o.
  - Group childcare exposures in young infants are linked to carriage of, and infection by*, antibiotic-resistant strains of S. pneumoniae*
  - School-related exposure to *S. pyogenes* and older children to atypical pathogens (low in young infants)
  - Adolescent exposure to STIs

Step 4. Perform diagnostic tests

- Every effort should be made to prove the etiology of the infection and obtain an isolate for susceptibility testing ESPECIALLY when you need to prescribe an antibiotic (particularly very broad spectrum coverage which can result in altered culture findings later on)
- Difficult in the local setting, but try to DELAY having to start antibiotic therapy, unless warranted clinically.

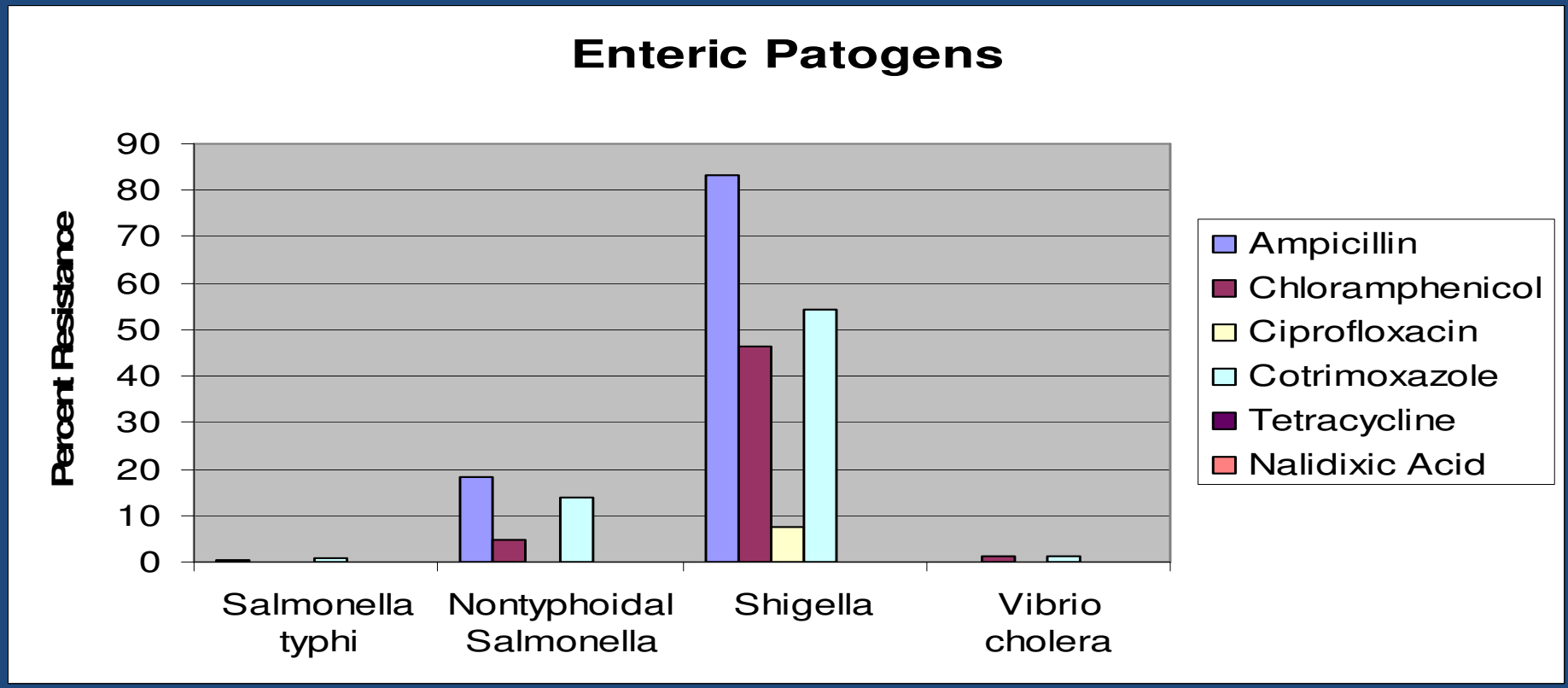
Step 5. Consider antibiotic susceptibilities of suspected pathogens

- Antimicrobial Resistance Surveillance (Jan. – Dec. 2008)

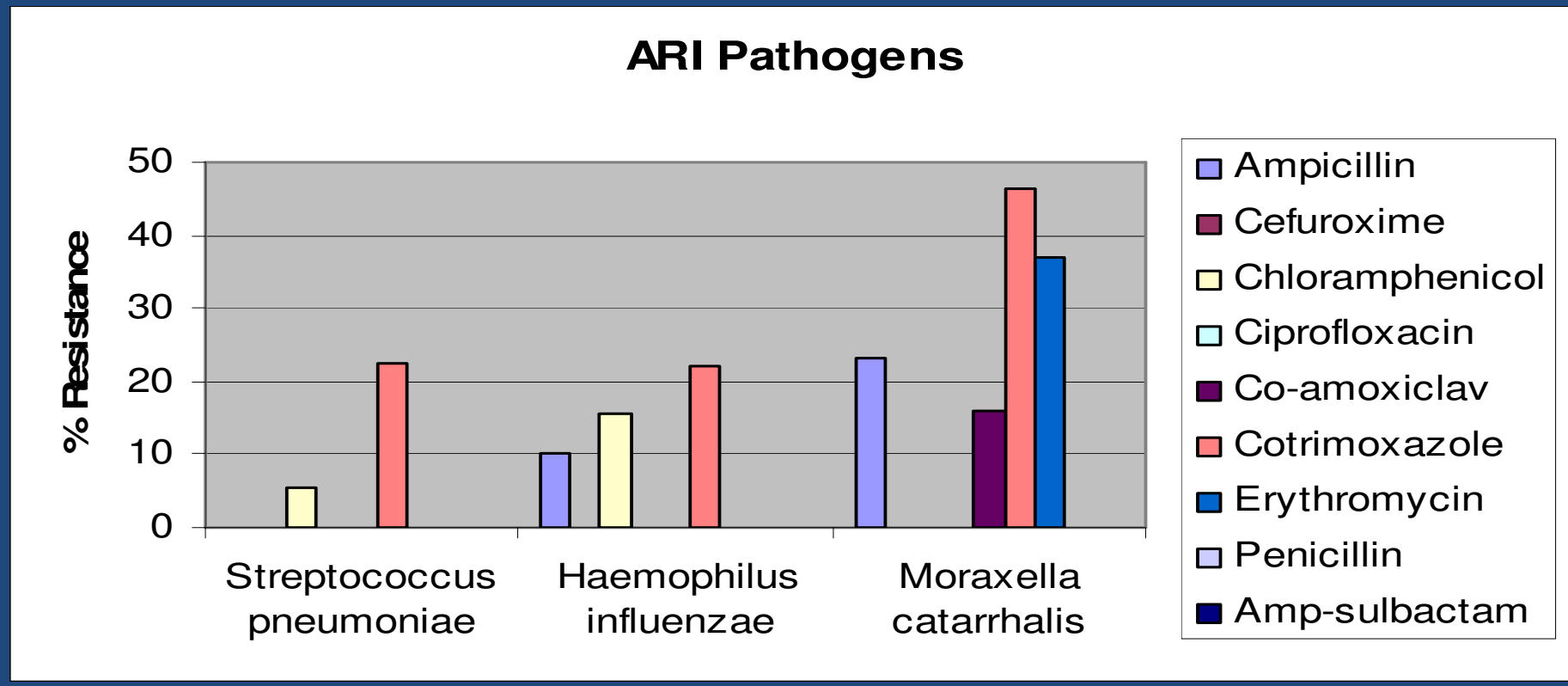
Research Institute for Tropical Medicine

Antimicrobial Resistance Surveillance Pattern

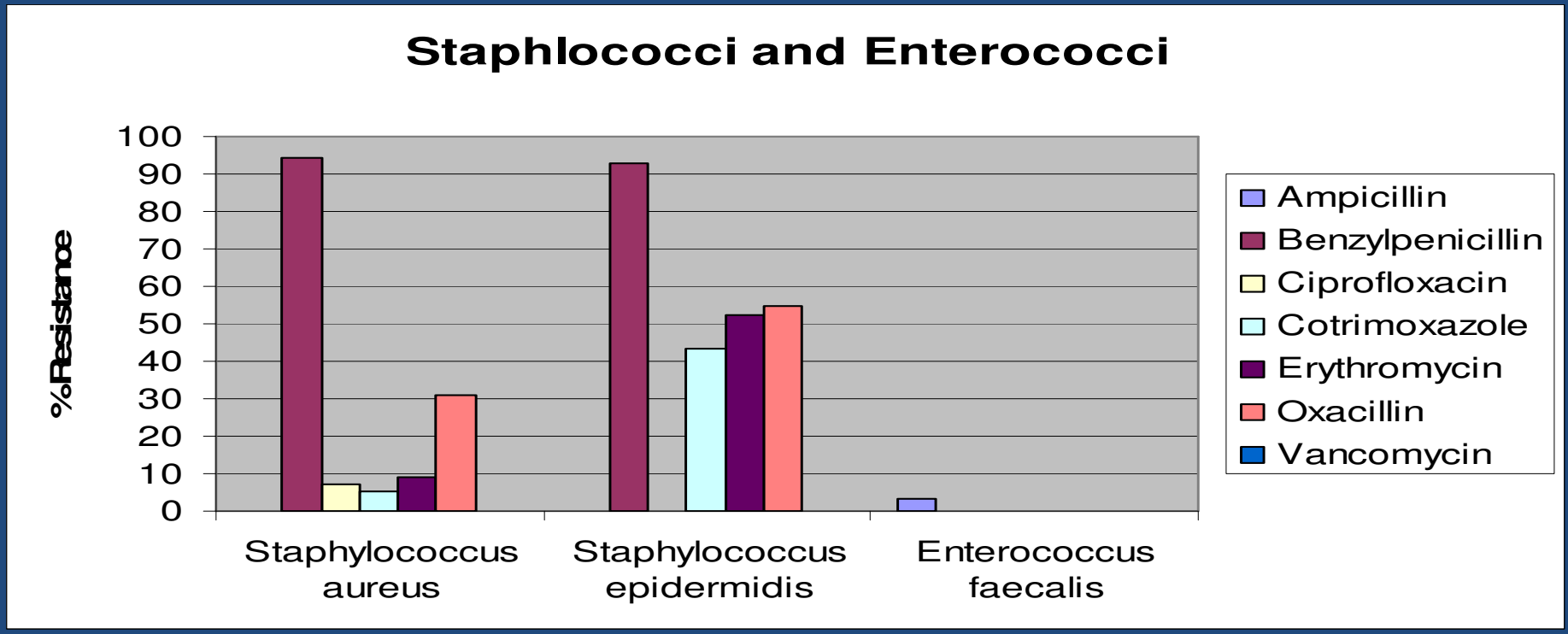
Antimicrobial Resistance Surveillance (Jan. – Dec. 2008)



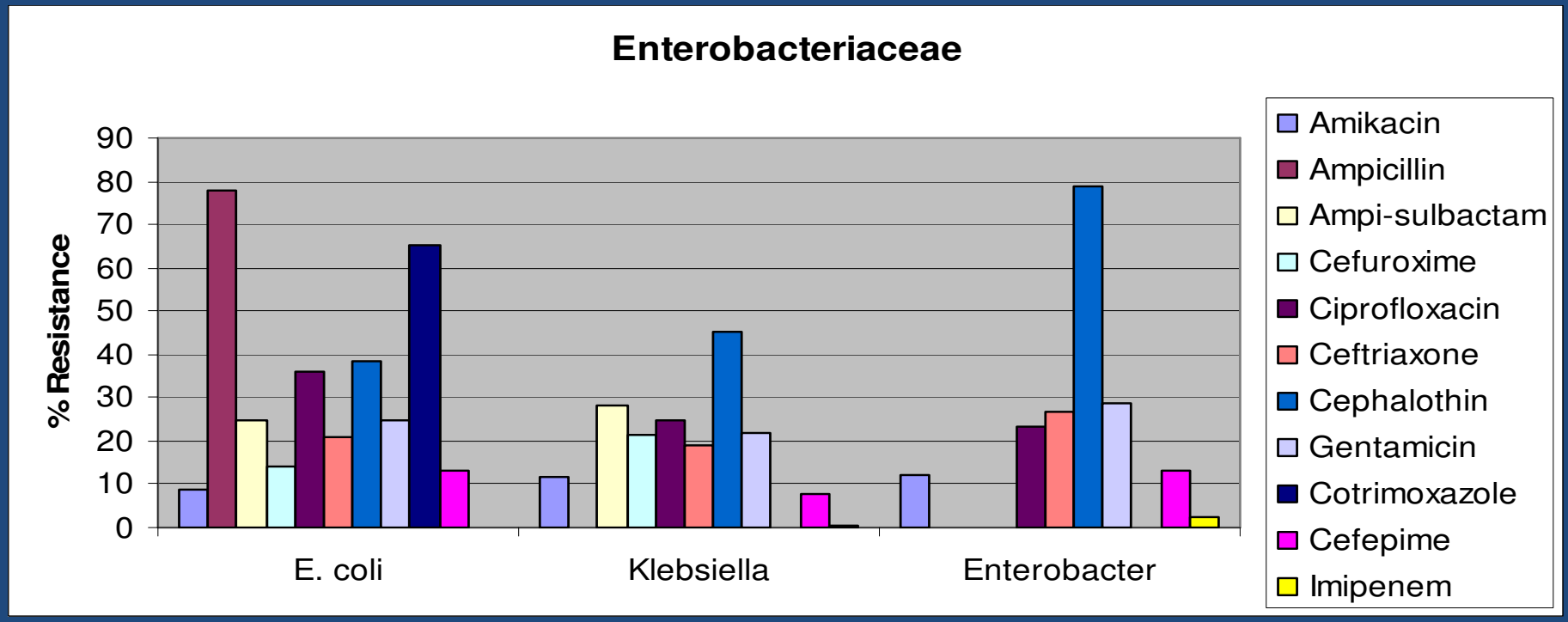
%R (Number Tested)						
	Ampicillin	Chloramphenicol	Ciprofloxacin	Cotrimoxazole	Tetracycline	Nalidixic Acid
Salmonella typhi	0.4 (252)	0 (248)		0.9 (219)		
Nontyphoidal Salmonella	18.3 (71)	4.6 (65)	0 (74)	13.9 (36)		
Shigella	83.3 (12)	46.2 (13)	7.7 (13)	54.5 (11)		0 (12)
Vibrio cholera		1.1 (89)		1.1 (90)	0 (89)	



%R (Number Tested)						
	Ampicillin	Chloramphenicol	Co-amoxiclav	Cotrimoxazole	Erythromycin	Penicillin
Streptococcus pneumoniae		5.3 (113)		22.6 (115)		0 (116)
Haemophilus influenzae	10.3 (97)	15.4 (91)		22 (82)		
Moraxella catarrhalis	23.3 (437)		16.1 (453)	46.4 (425)	36.8 (459)	

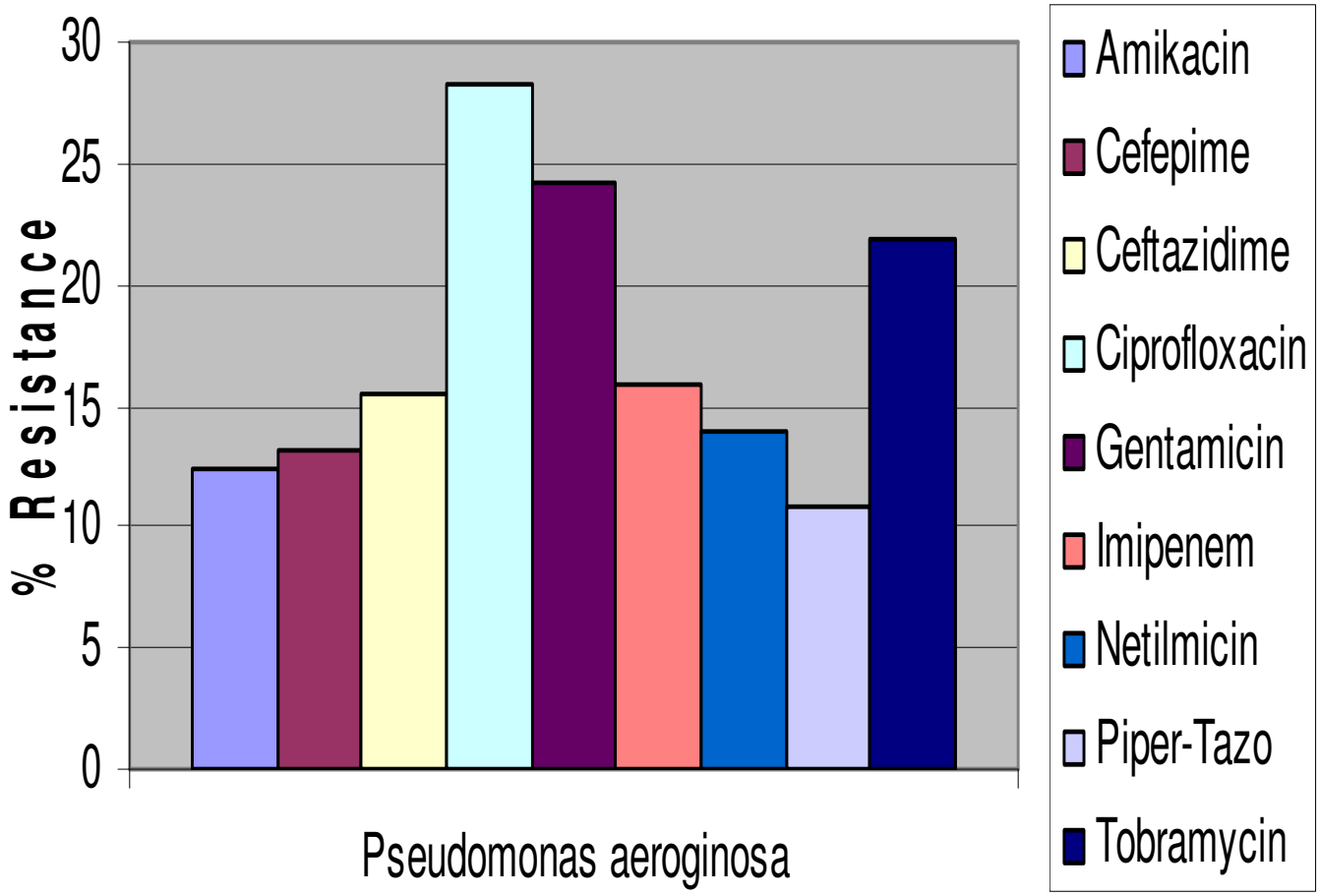


%R (Number Tested)							
	Ampicillin	Benzylpenicillin	Ciprofloxacin	Cotrimoxazole	Erythromycin	Oxacillin	Vancomycin
Staphylococcus aureus		94.3 (1115)	7 (969)	5.2 (993)	8.9 (1140)	31 (1141)	0 (1132)
Staphylococcus epidermidis		92.7 (341)		43.1 (320)	52.2 (343)	54.8 (332)	0 (349)
Enterococcus faecalis	3.4 (179)						0 (225)

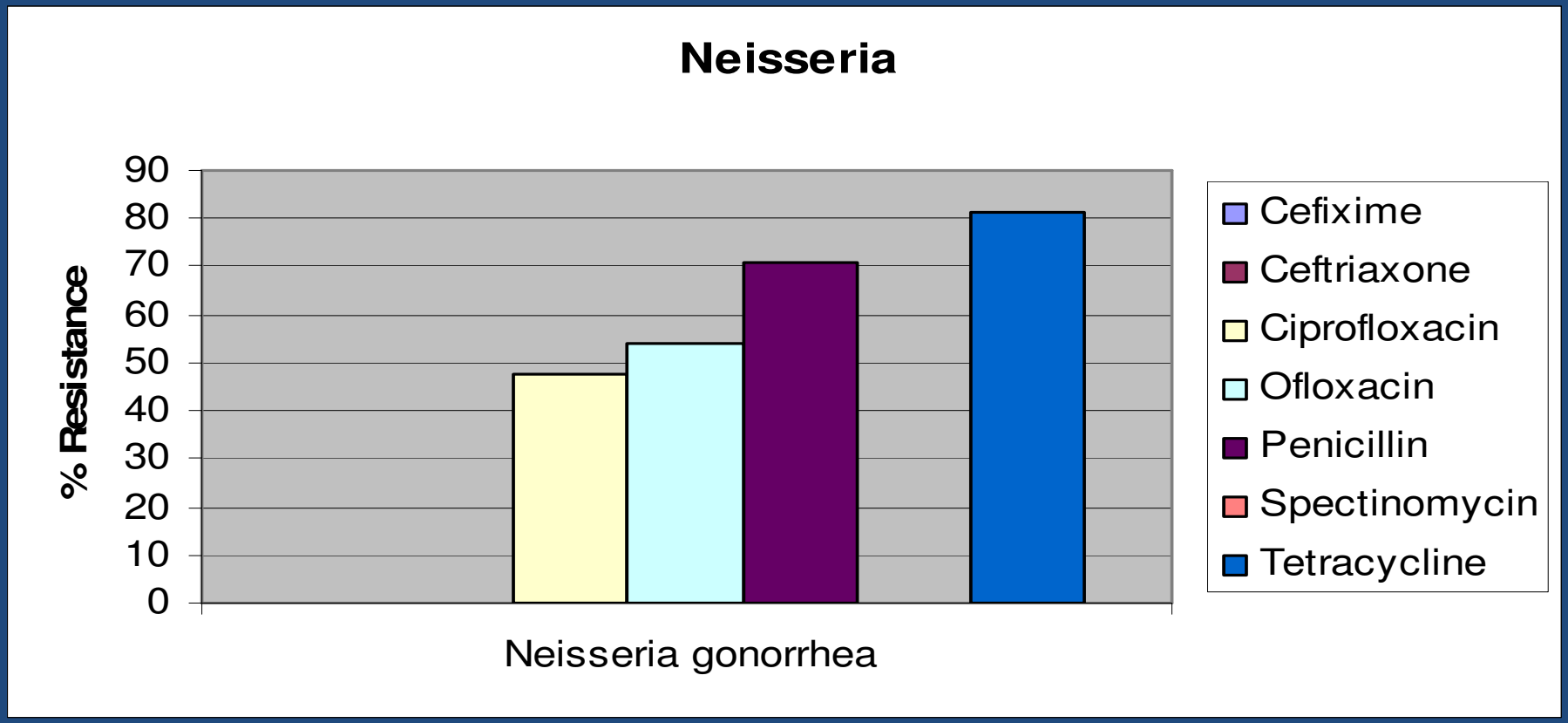


%R (Number Tested)						
	Amikacin	Ampicillin	Ampi-sulbactam	Cefuroxime	Ciprofloxacin	Ceftriaxone
E. coli	8.7 (2433)	77.7 (2825)	24.6 (2259)	13.9 (1590)	36.2 (2595)	21.1 (2435)
Klebsiella	11.8 (1943)		28 (1538)	21.2 (1092)	24.6 (1992)	19.2 (1929)
Enterobacter	12.4 (1429)				23.2 (1416)	26.6 (1400)
	Cephalothin	Gentamicin	Cotrimoxazole	Cefepime	Imipenem	
E. coli	38.6 (1361)	24.7 (2561)	65 (2504)	13.1 (2365)		
Klebsiella	45.3 (1065)	21.9 (1975)		7.8 (1858)	0.6 (2085)	
Enterobacter	78.7 (863)	28.9 (1452)		13.2 (1360)	2.3 (1374)	

Gram negative, non-fermentative bacilli



%R (Number Tested)
Pseudomonas aeroginosa
Amikacin
12.4 (1828)
Cefepime
13.1 (1710)
Ceftazidime
15.4 (1709)
Ciprofloxacin
28.3 (1709)
Gentamicin
24.1 (1707)
Imipenem
15.9 (1696)
Netilmicin
14 (344)
Piper-Tazo
10.8 (928)
Tobramycin
21.8 (1692)



Number Tested							
	Cefixime	Ceftriaxone	Ciprofloxacin	Ofloxacin	Penicillin	Spectinomycin	Tetracycline
Neisseria gonorrhea	0 (75)	0 (82)	47.8 (69)	54.1 (74)	70.7 (75)	0 (70)	81.4 (70)

Step 6. Consider PK/PD properties of drugs

- Critical information to guide the selection of both drug and drug dosage in antimicrobial therapy:
  - 1. route of administration
  - 2. absorption
  - 3. tissue distribution of antibiotic at site of infection
  - 4. drug elimination characteristics

PD antibacterial effect of antimicrobial agents by primary bacterial target and by antibiotic class

Primary target	Antibacterial class	Pharmacodynamics	Intracellular activity
Cell wall	B-lactams - penicillins - cephalosporins - monobactams - carbapenems Glycopeptides - vancomycin - teicoplanin	Bactericidal Time-dependent PAE only against G(+) organisms Carbapenems PAE against G(+) & G(-) organisms	Not generally effective
Cell membrane	Lipopetides - Daptomycin Polymyxins - Polymyxin B - Colistin	Bactericidal Concentration-dependent Long PAE (Daptomycin) PAE (polymyxins)	Not known

PD antibacterial effect of antimicrobial agents by primary bacterial target and by antibiotic class

Primary target	Antibacterial class	Pharmacodynamics	Intracellular activity
Ribosome	Macrolides, azalides, ketolides	Bacteriostatic or –cidal (ketolides) Time- and concentration-dependent Long PAE	Yes
	Tetracyclines, glycylcyclines	Bacteriostatic Time-dependent Long PAE	Yes
	Lincosamides (Clindamycin)	Bactericidal or –static Time-dependent PAE	Yes

PD antibacterial effect of antimicrobial agents by primary bacterial target and by antibiotic class

Primary target	Antibacterial class	Pharmacodynamics	Intracellular activity
Ribosome	Aminoglycosides	Bactericidal Concentration-dependent PAE	Not effective partially
	Oxazolidinones	Bacteriostatic (except against S. pneumoniae) Concentration-dependent PAE	Not effective partially
	Rifamycins	Bactericidal Long PAE	Yes

PD antibacterial effect of antimicrobial agents by primary bacterial target and by antibiotic class

Primary target	Antibacterial class	Pharmacodynamics	Intracellular activity
Ribosome	Quinolones	Bactericidal Concentration-dependent Long PAE	Yes
	Streptogramins	Bactericidal (except against Enterococcus faecium) Concentration-dependent PAE	Yes

PD antibacterial effect of antimicrobial agents by primary bacterial target and by antibiotic class

Primary target	Antibacterial class	Pharmacodynamics	Intracellular activity
Nucleic Acid	Metronidazole	Bactericidal Concentration-dependent PAE	Yes
	Sulfamethoxazole-trimethoprim	Bactericidal Concentration-dependent	Yes
	PAE – postantibiotic effect OR the observation of delay in regrowth of organisms following removal of antibiotic from the media		

PK/PD basis of optimal antibiotic therapy

(adapted from Michael N. Neely and Michael D. Reed in Principles & Practice of Pediatric Infectious Diseases, 2008)

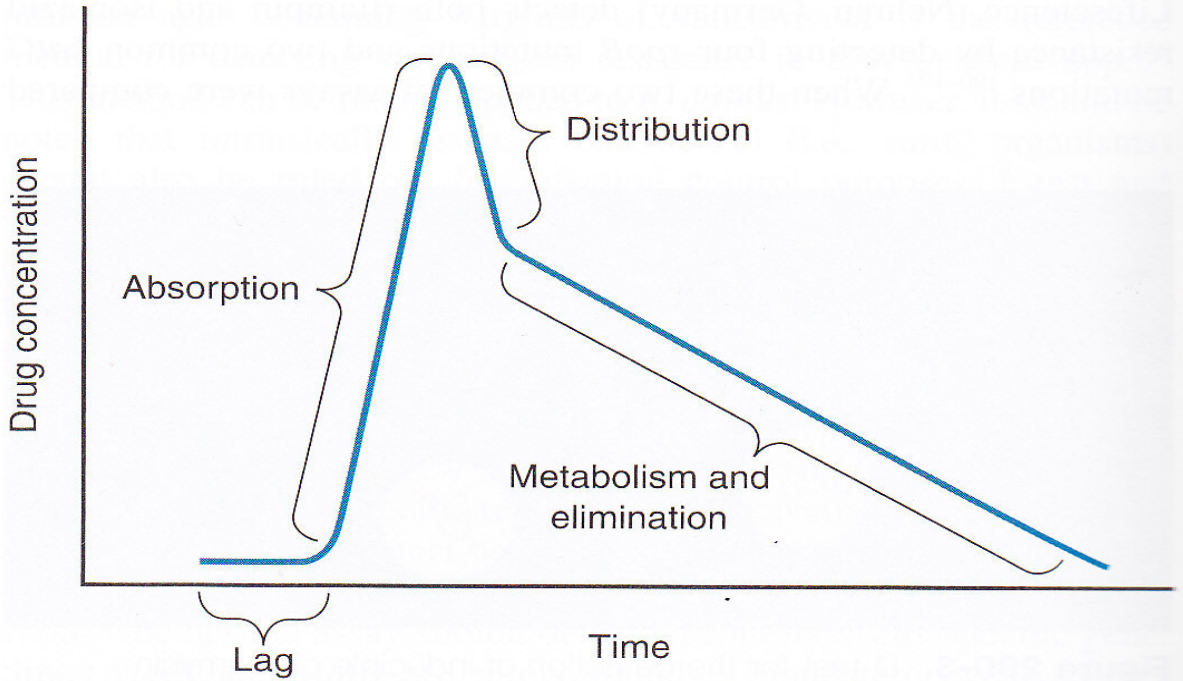


Figure 291-1. Overall biologic fluid (e.g., serum) drug concentration–time curve after extravascular drug administration. Each important process of drug disposition is indicated. Although these processes are compartmentalized graphically in the figure, in reality they occur simultaneously (see text for details).

Drug disposition in specific patient populations

TABLE 291-1. Physiologic Changes in Children That Affect the Pharmacokinetic Characteristics of Drugs[2,3]

Parameter	Neonates	Approximate Age Approaching Adult Level
ABSORPTION		
Gastric pH	↑	3 months
Gastric emptying	↓	6–8 months
Pancreatic function	↓	9 months
DISTRIBUTION		
Body water	↑[a]	Adolescence
Protein binding	↓	12 months
METABOLISM		
Hepatic drug-metabolizing	↓	Adolescence
ELIMINATION		
Renal function	↓	Glomerular filtration: 3–5 months
		Tubular secretion: 8–9 months

[a]The distribution of body water depends on age: the total body water (TBW) of neonates is about 75% of body weight, with about 50% intracellular (IC) and 50% extracellular (EC). A gradual decrease in TBW and a shift to IC distribution occur until adult values of 50% to 60% TBW, 33% EC, and 66% IC are reached at puberty.

Schematogram of sites of action for various antibiotics

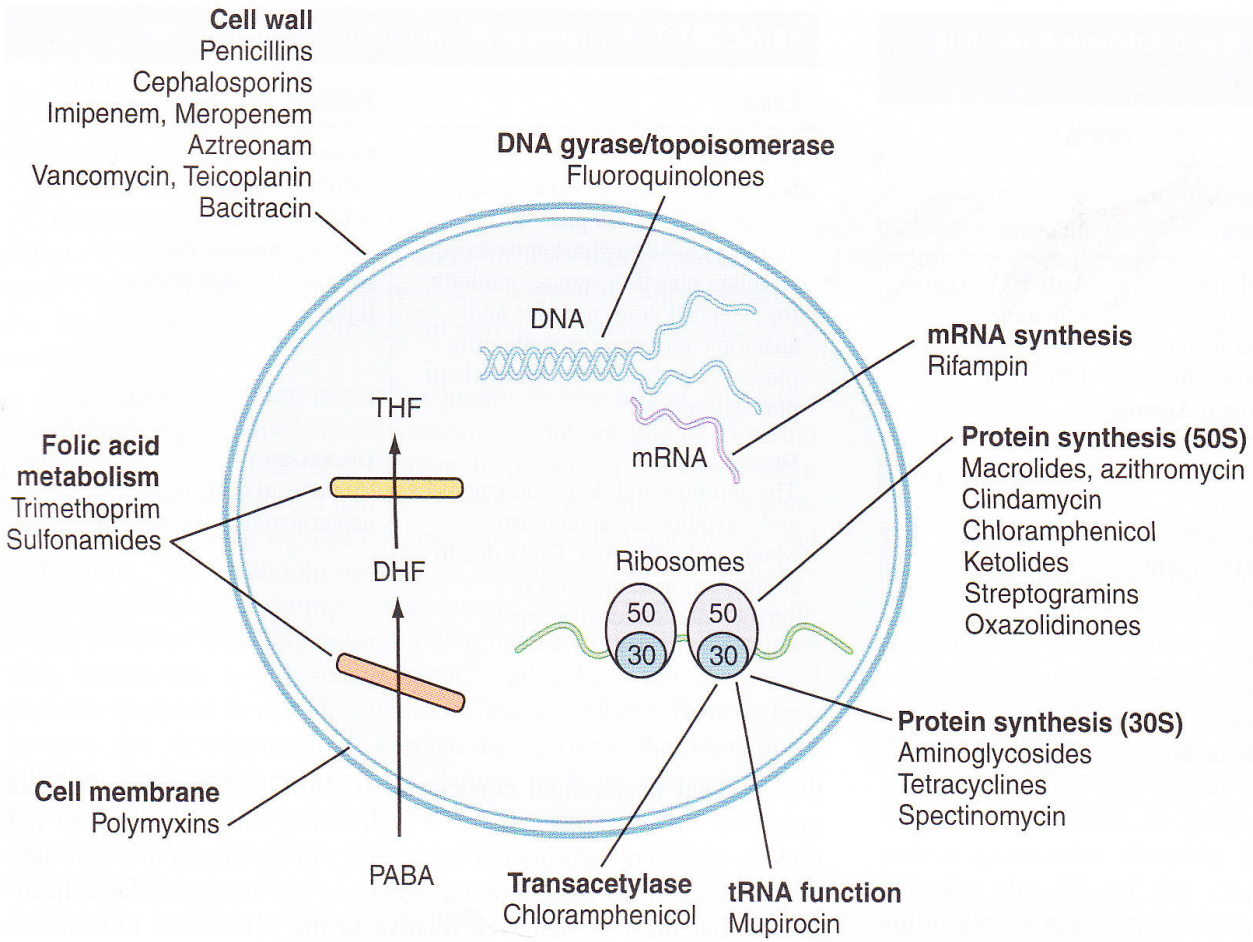


Figure 291-2. Sites of action for major antibacterial drugs. DHF, dihydrofolate; PABA, *para*-aminobenzoic acid; THF, tetrahydrofolate. (Adapted from Neu HC. The crisis in antibiotic resistance. Science 1992;257:1064–1073.)

Time vs concentration-dependent antibiotics

- PD of antibiotics are based on:
  - 1. kinetics of bacterial killing
  - 2. post-antibiotic effect (PAE)
  - 3. post-antibiotic leukocyte enhancing effect (PALE)
  - 4. inoculum effect

Time vs concentration-dependent antibiotics

- Concentration-dependent antibiotics
  - Exhibit a concentration-dependent killing:
    - The higher the concentration of the drug, the greater the bactericidal effect
  - PAE: the time period after an exposure to and removal of an antimicrobial agents during which inhibition of bacterial growth persists
  - In vivo PALE: enhanced leukocyte phagocytosis and intracellular killing of bacterial during the drug-free period

Time vs concentration-dependent antibiotics

- Concentration-dependent antibiotics
  - Aminoglycosides: goal is to attain maximum serum concentrations exceeding the MIC of the organism tenfold (10)
  - Fluoroquinolones: ratio of the area under the cure/MIC (AUIC) should be greater than 125
  - GIVE TOTAL DAILY DOSE LESS FREQUENTLY

Time vs concentration-dependent antibiotics

- Time-dependent antibiotics
  - Bactericidal effect is dependent upon the length of time that the bacteria are exposed to serum concentrations which exceed the MIC of the bacteria by at least 4x.
  - All drugs exert PAE vs *S. aureus* but not all drugs exert PAE against G(-) bacilli.
  - Goal is to attain serum concentrations of at least 4x MIC of the infecting agent for at least 60% of the dosing time interval.

Time vs concentration-dependent antibiotics

- Time-dependent antibiotics
  - Most cost-effective means of attaining this is:
    - 1. administering the drug by constant infusion following an initial bolus or loading dose
    - 2. OR, choosing the drug with the longest half-life

Time-dependent vs. Concentration-dependent antibiotics

TABLE 291-8. Classification of Selected Antibiotics Based on Their Pattern of Antimicrobial Activity

Drugs for Which the Duration above the MIC ($T > MIC$) Correlates Best with Efficacy	Drugs for Which the Concentration above the MIC (peak/MIC or AUC/MIC) Correlates Best with Efficacy
Penicillins	Aminoglycosides
Cephalosporins	Fluoroquinolones
Carbapenems	Ketolides
Monobactams	Streptogramins
Macrolides	
Clindamycin	
Oxazolidinones	
Vancomycin	
Azithromycin	
Tetracyclines	

AUC, area under the curve; MIC, minimal inhibitory concentration.
Adapted from Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998;26:1–10.

Clinical use of PK/PD correlates

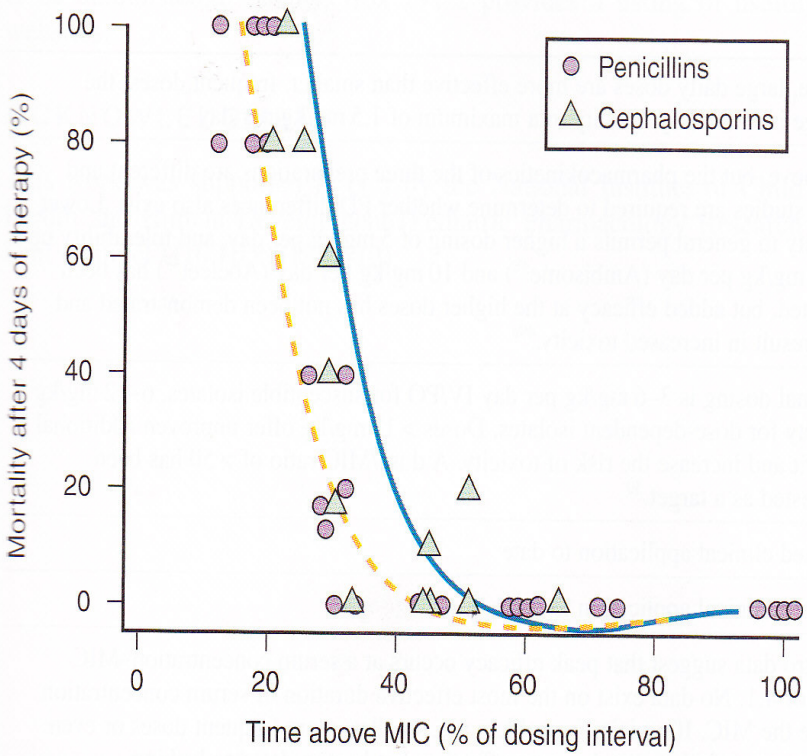


Figure 291-3. Efficacy of β-lactam antibiotics against *Streptococcus pneumoniae* in animal models. MIC, minimal inhibitory concentration. (Adapted from Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998;26:1–10.)

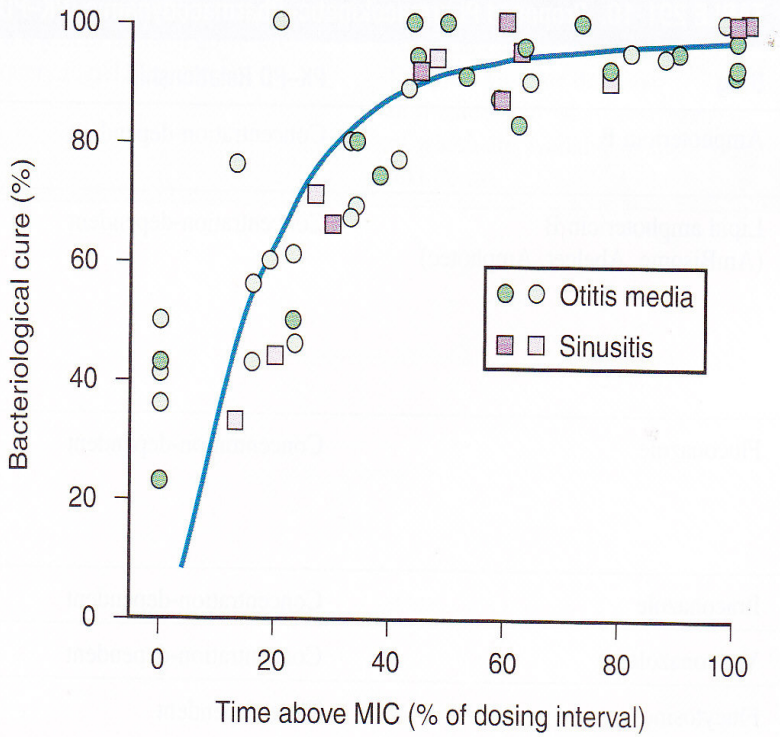


Figure 291-4. The relationship between time of antibiotic serum concentration above the minimal inhibitory concentration for 90% of organisms (MIC_{90}) and bacteriologic cure in *Streptococcus pneumoniae* (solid symbols) and *Haemophilus influenzae* (hollow symbols) otitis media and sinusitis. (Adapted from Craig WA, Andes D. Pharmacokinetics and pharmacodynamics of antibiotics in otitis media. Pediatr Infect Dis J 1996;15:255–259.)

Step 7. Consider target attainment

- In treating any child, the practitioner must assess the seriousness of the infection, and the risk or injury or death if the antibiotic is not effective.
  - Infections that are bothersome (e.g., impetigo) but non-life-threatening, a cure rate of 70-80% with a safe and inexpensive antibiotic is acceptable, especially if alternative is using a drug with a 98% success rate but has excessive risk of toxicity or high cost.

Step 7. Consider target attainment

- In treating any child, the practitioner must assess the seriousness of the infection, and the risk or injury or death if the antibiotic is not effective.
  - Infections with degree of suffering or risk or organ damage (e.g., pyelonephritis or AOM), cure rate of 80-90% is desirable.
  - Infections that are life-threatening or serious (e.g., meningitis, sepsis), a 100% cure rate is mandatory

Step 7. Consider target attainment

- No formal list of “approved” cure rates or “target attainments” exists.
- Accepted target attainment may differ between diseases, physicians, families and societies.
- Risk/Benefit ratio must always be considered
- Setting targets can help clarify decision-making regarding relative merits, risks, and cost of management.

Step 8. Separate empiric and definitive therapeutic decisions

- Empiric therapy is selected based on:
  - 1. presumed pathogens at the site of infection
  - 2. local resistance patterns of the presumed pathogens
  - 3. desired cure rates selected by the clinician

IN GENERAL, THE SICKER CHILD DEMANDS TREATMENT DOSAGES AND ANTIBACTERIAL ACTIVITY ASSOCIATED WITH A HIGHER RATE OF CURE.

Step 8. Separate empiric and definitive therapeutic decisions

- Once the pathogen is identified, a narrow-spectrum agent can frequently provide the same degree of bacterial eradication and clinical efficacy with:
  - 1. decreased toxicity
  - 2. decreased selective pressure
  - 3. decreased cost

Step 8. Separate empiric and definitive therapeutic decisions

- Switch therapy or definitive convalescent outpatient therapy of serious infections initially treated in the hospital can be acceptable if:
  - 1. risks of complications of the infection are negligible
  - 2. parents and child can adhere to well defined management plans
  - 3. follow-up or return to hospital quickly for any infection- or therapy-related problems is not a problem

Step 9. Special considerations

- 1. drug allergy for a particular agent, agents of the same type or agents in the same class impact selection
- 2. cost considerations have become a greater issue on health insurers and government agencies and the public with knowledge in doctors having “conflicts of interest” with the pharmaceutical industry

Step 9. Special considerations

- 3. Acceptable risk of failure needs to be determined by the treating physicians and medical advisors to the health plan formularies to allow families to achieve acceptable cure rates and continue to have confidence in their healthcare providers.

Take home message

- The armamentarium against bacterial infections is within our reach. The challenge to the physician is his/her ability to rationally use these drugs so that we do not create bad bugs and resort to more expensive treatment options. It is wise to remember that Bad Bugs are more often than not created by Bad use of Drugs.

Thank you for your kind attention