Antibiotics for Early Onset Sepsis

Lois Lee, PharmD, BCPPS
MDPQC Neonatal Antibiotic Stewardship Workgroup
February 14, 2023

How Did We Get Here?

May 2021

MDPQC Neonatal Antibiotic Stewardship Kick-Off

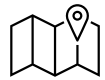
Fall 2021 – Spring 2022

Workgroup developed
Monthly meetings

June 2022

Neonatal Education Toolkit launched at MDPQC Summer Conference

February 2023



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Neonatal Education Toolkit

- Help implement neonatal antibiotic stewardship initiatives
- Divided into chapters:
  - Antibiotic Stewardship Basics
  - Implementing Antibiotic Stewardship
  - Neonatal Sepsis
    - Antibiotics
  - Early Onset Sepsis Calculator
  - Interpreting Data
  - Program Sustainability

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Neonatal Sepsis and Antibiotic Treatment

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Objectives

- Compare key characteristics of neonatal EOS and LOS
- Explain the rationale behind the use of common antibiotics for neonatal sepsis
- Understand the concepts of time and concentration-dependent antibiotics
- Identify optimal antibiotic regimens for EOS based on key clinical circumstances

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Neonatal Sepsis

- *Clinical syndrome in an infant 28 days of life or younger, manifested by systemic signs of infection and isolation of a bacterial pathogen from the bloodstream*

- Low incidence of culture proven neonatal sepsis in the US
- Early signs of sepsis are non-specific
  - Order diagnostic studies & initiate treatment
- High mortality due to untreated sepsis
  - Most clinicians will treat while awaiting results

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Puopolo KM, et al. *Pediatrics*. 2018;142(6):e20182894
Cohen-Wolkowiez M, et al. *Pediatr Infect Dis J*. 2009;28(12):1052-1056

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Classification of Neonatal Sepsis

Early Onset Sepsis

- Symptom onset ≤ 3 days of life
- Vertical transmission
  - Ascending amniotic fluid infection
  - Birth canal colonization
- Common pathogens: GBS, *E.coli*
  - *Listeria monocytogenes*
  - *Haemophilus influenzae*

Late Onset Sepsis

- Symptom onset > 3 days of life
- Exposure to pathogens during NICU stay
  - Mechanical ventilation
  - Presence of IV lines
  - Recent procedures
- Coagulase-negative staphylococcus
  - MRSA
  - *Pseudomonas aeruginosa*
  - *E.coli*

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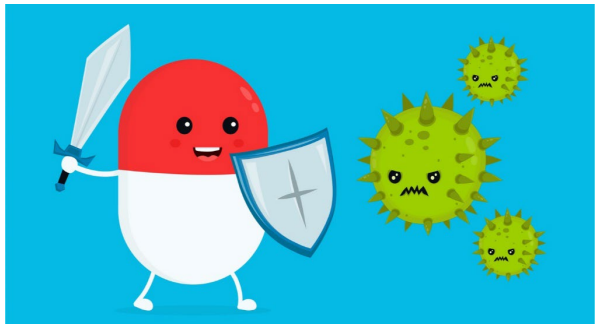
Bugs and Drugs



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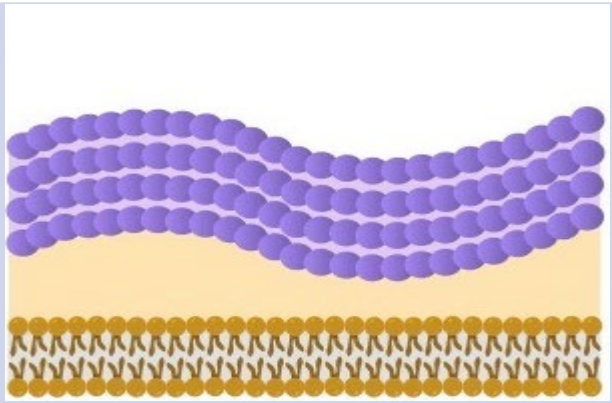
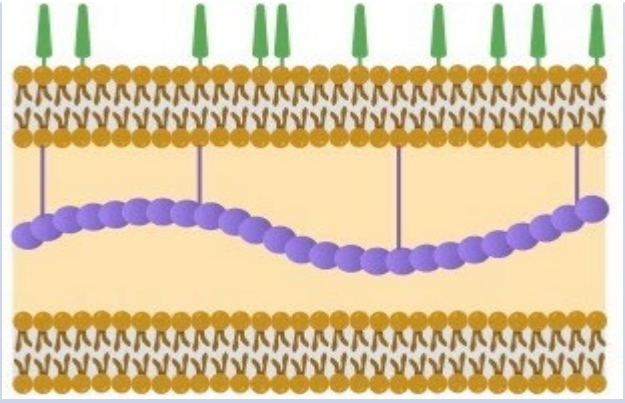
Bacterial Structure

Gram-POSITIVE	Gram-NEGATIVE
	
1. No outer membrane 2. Thick peptidoglycan layer (purple)	1. Outer membrane • Difficult to penetrate 2. Thin peptidoglycan layer
GBS *Staphylococcus aureus* (MSSA and MRSA) Coagulase-negative Staphylococcus *Listeria monocytogenes*	*E. coli* *Pseudomonas aeruginosa* *Klebsiella spp.*

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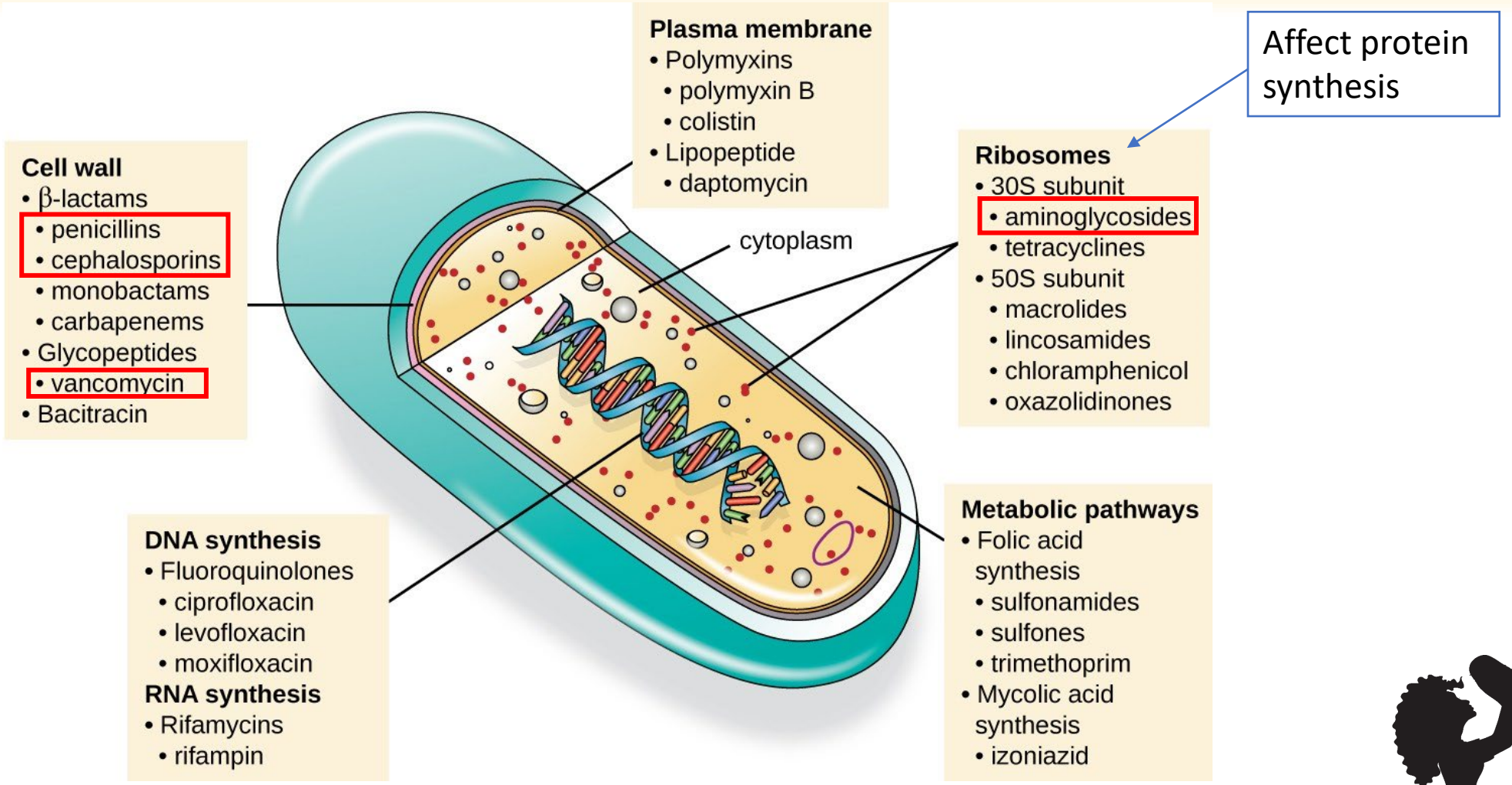
Sites of Antibiotic Action



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Ampicillin

- Beta-lactam antibiotic (penicillin-derivative)
- First line agent for EOS
  - In combination with gentamicin for broad coverage and synergistic effects
- May be considered for LOS as <u>targeted therapy for susceptible organisms</u>

Mechanism of Action	Inhibits cell wall formation of bacteria, leading to bacterial death (bactericidal)
Spectrum of Activity	• GBS • *Listeria* • Few strains of *Haemophilus influenzae* & *E.coli* • Increasing resistance concern
Dosing	Varies per age and indication (see next slide)
Duration	Rule-out period: 24-36 hours Treatment • Bacteremia: 10 days • Meningitis: 14 days • Longer durations may be necessary for prolonged or complicated courses

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Puopolo KM, et al. *Pediatrics*. 2019;144(2):e20191881

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Ampicillin

SAMPLE Policy: May be different by institution

- GBS bacteremia

Gestational Age	Postnatal age	
	≤ 7 days	> 7 days
≤ 34 weeks	50 mg/kg Q12H	75 mg/kg Q12H
> 34 weeks	50 mg/kg Q8H	

- GBS meningitis

Postnatal age	Dosage
≤ 7 days	100 mg/kg Q8H
> 7 days	75 mg/kg Q6H

Frequency of administration matters

Time-dependent bactericidal activity

- Maximize effects by maintaining drug concentrations above a certain level (MIC) for **longer periods of time**
  - More frequent dosing intervals (Q6-8H)
  - Relatively lower mg/kg doses
- Rationale for **continuous infusion** in other populations and severe infections
- Dosing recommendations based on changes in renal function in neonates

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Ampicillin in: NeoFax®
Puopolo KM, et al. *Pediatrics*. 2019;144(2):e20191881

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Gentamicin

- Aminoglycoside
- Preferred first line agent for EOS
  - In combination with ampicillin for broad coverage and synergistic effects
- Often used in combination with vancomycin for LOS
  - Caution: nephrotoxic and ototoxic!

Mechanism of Action	Inhibits bacterial protein synthesis (bacteriostatic)
Spectrum of Activity	Gram-negative organisms • *E.coli* • *Pseudomonas species* • *Klebsiella* species
Dosing	Varies per age, indication, and dosing strategy (see next slide)
Duration	Rule-out period 24-36 hours Treatment • Bacteremia: 10 days • Meningitis: 14 days • Longer durations may be necessary for prolonged or complicated courses

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Puopolo KM, et al. *Pediatrics*. 2019;144(2):e20191881
Gentamicin in: NeoFax®

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Gentamicin

SAMPLE Policy: May be different by institution

- Standard dosing

PMA (weeks)	Postnatal age (days)	Dose (mg/kg)	Interval (hours)
≤29	0 to 7 8 to 28 ≥29	5 4 4	48 36 24
30 to 34	0 to 7 ≥8	4.5 4	36 24
≥35	ALL	4	24

- Extended interval dosing
  - 5 mg/kg Q36H

Concentration-dependent bacteriostatic activity

- Maximize effects by achieving a **high peak concentration** above MIC after administration
- Rationale for **larger doses** given **less frequently**
- Dosing recommendations based on changes in renal function in neonates

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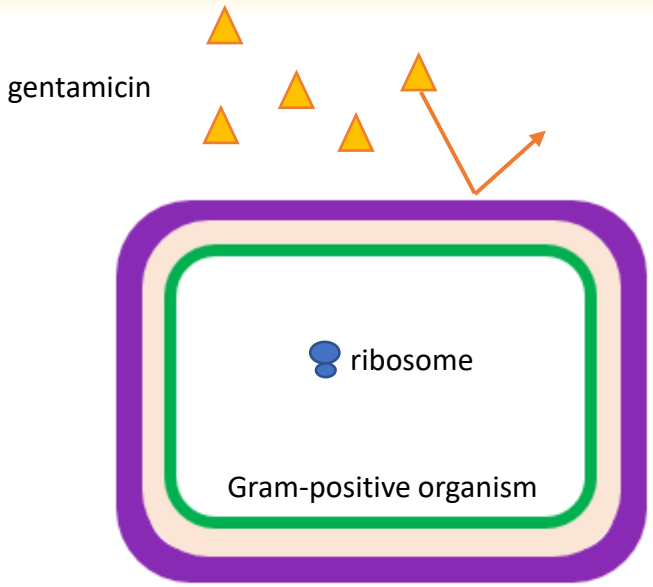
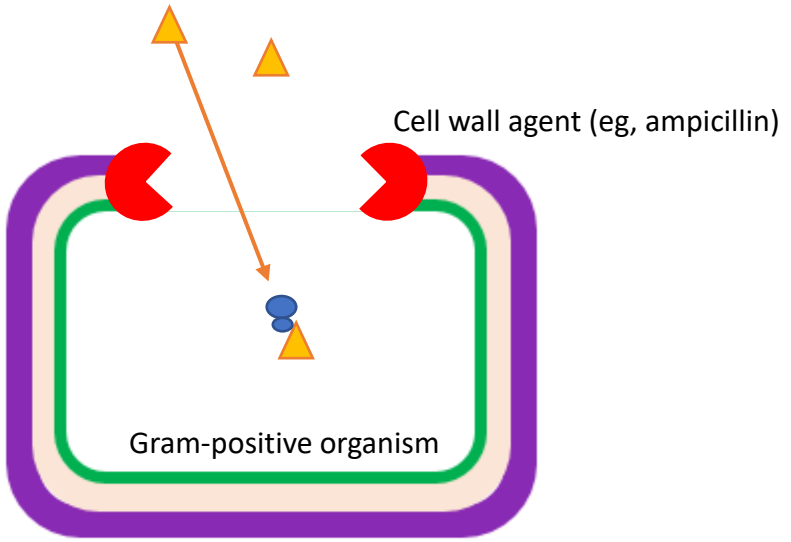
Gentamicin in: NeoFax®
Rao SC, et al. *Cochrane Database Syst Rev*. 2016;12(12):CD005091
El-Chaar GM, et al. *J Perinatol*. 2016;36(8):660-665

Ampicillin and Gentamicin Synergy



- **Gentamicin** is unable to penetrate the thick **peptidoglycan** layer of gram-positive organisms in order to reach its **target site** (**ribosome**)
- Bacteria continues to survive



- When used with an **agent that disrupts the cell wall** (eg, beta-lactams or vancomycin), **gentamicin** can freely move into the cell and attach to its **target site**, preventing bacterial protein synthesis
- Cell death follows

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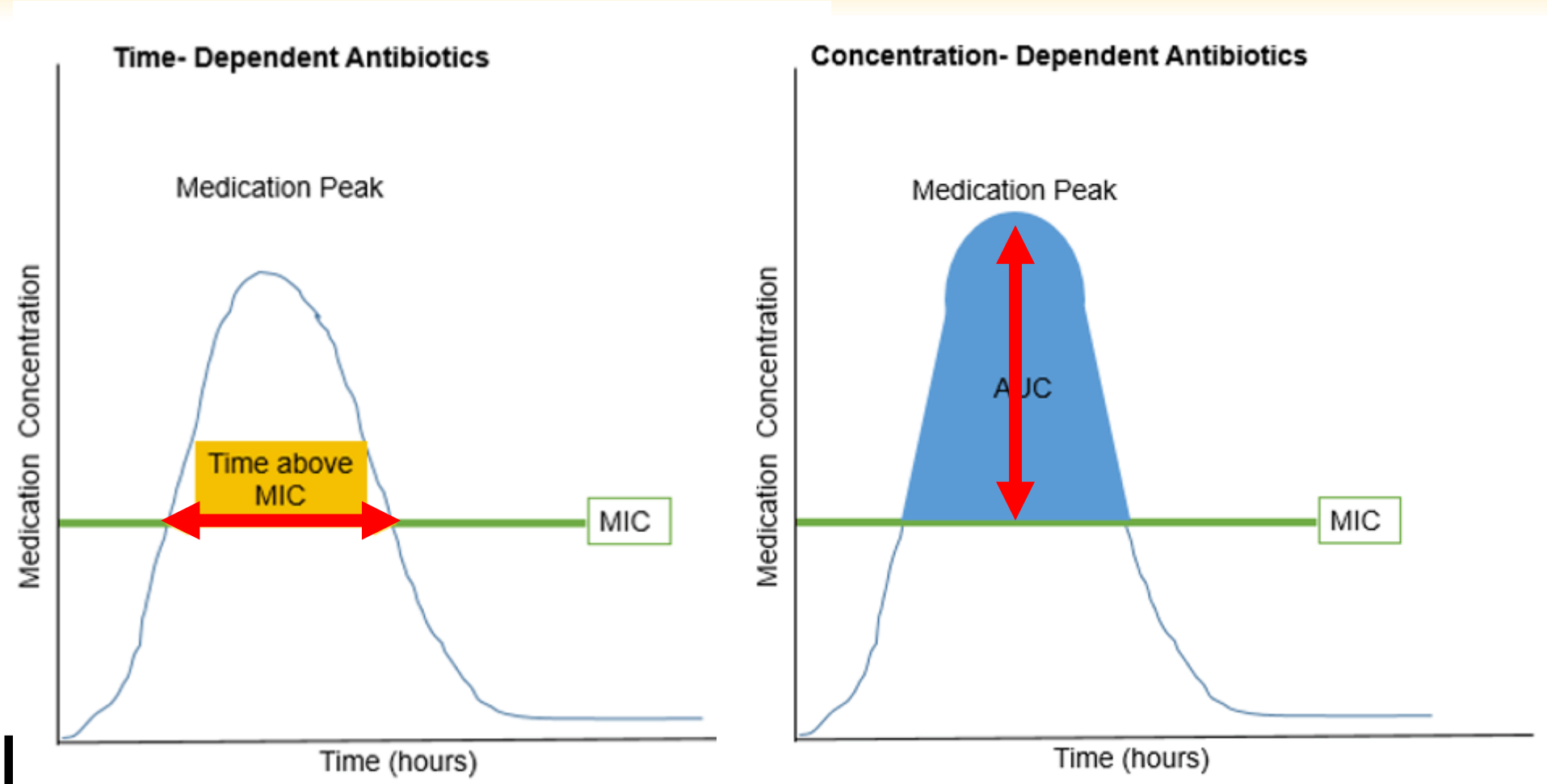
Time vs. Concentration-Dependent Antibiotics



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Time vs. Concentration-Dependent Antibiotics

Time-dependent bactericidal activity	Concentration-dependent bacteriostatic activity
Increased frequency = better	**Higher peak = better**

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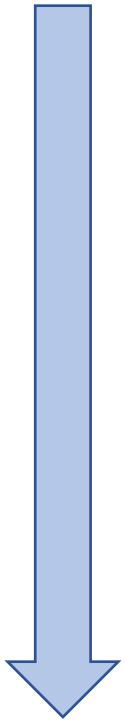
Cephalosporins

- First generation
  - Cephalexin
  - Cefazolin
- Second generation
  - Cefoxitin
- Third generation
  - ~~Ceftriaxone~~
  - ~~Cefotaxime~~
  - ★ Ceftazidime
- Fourth generation
  - ★ Cefepime
- Fifth generation
  - Ceftaroline



<u>Microbial coverage</u>

More gram positive
Less gram negative

More gram negative

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Cephalosporins

- Beta-lactam antibiotics
- First line agent for EOS associated with **meningitis**
  - Improved penetration into Blood Brain Barrier/Central Nervous System
  - In combination with ampicillin + gentamicin for broad coverage
- Also used in late-onset meningitis

Mechanism of Action	Inhibits cell wall formation of bacteria, leading to bacterial death (bactericidal)	
Spectrum of Activity	Ceftazidime • GBS • *E. coli, Haemophilus* • *± Pseudomonas*	Cefipime • GBS, MSSA • *E. coli, Haemophilus, Pseudomonas*
Dosing	Varies per age and indication (refer to Neofax/Lexicomp)	
Duration	Rule-out period: 24-36 hours Treatment • Bacteremia: 10 days • Meningitis: 14 days • Longer durations may be necessary for prolonged or complicated courses	

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Cephalosporins

- Dosing varies based on GA/PMA, postnatal age, and indication
  - Generally 30-50 mg/kg Q8-12H
  - Higher doses for meningitis or critical illness
  - Smaller doses and longer intervals for very low-birth weight neonates

Time-dependent vs. Concentration-dependent

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Special Circumstances

Circumstance	Suggested Regimen	Clinical Pearls
Meningitis (early-onset)	Ampicillin + gentamicin + cephalosporin (ceftazidime, cefepime)	• Duration of therapy typically 14-21 days
Meningitis (late-onset or ampicillin-resistant organism)	Vancomycin + gentamicin + cephalosporin (ceftazidime, cefepime)	
MRSA infections	Vancomycin	• ↑ nephrotoxicity risk with gentamicin
MSSA infections	Nafcillin Oxacillin	• May consider as 1st line for LOS in units with low MRSA prevalence or based on screening practices • Use for de-escalation or targeted therapy if vancomycin initially used
Gastrointestinal infections requiring anaerobic coverage	Ampicillin + gentamicin + metronidazole Piperacillin/Tazobactam + gentamicin Vancomycin + Piperacillin/Tazobactam Piperacillin/Tazobactam monotherapy	• Duration of therapy typically 10-14 days • Selection of empiric regimen depends on unit-specific prevalence and resistance trends
Multi-drug resistant organisms (eg, ESBL enterobacterales)	Meropenem	• Also covers anaerobes (ie, can be used for GI infections) • Can be used as monotherapy or with vancomycin if MRSA is a concern

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Summary: Bugs and Drugs

	Penicillins			Cephalosporins				C	A	G	O
	Ampicillin	Naf/Oxa	Pip-Tazo	Cefotaxime	**Ceftazidime**	Ceftriaxone	**Cefepime**	Meropenem	**Gentamicin**	Vancomycin	Metronidazole
Gram Positive											
GBS	✓	✓	✓	✓	✓	✓	✓	✓		✓	
L. monocytogenes	✓		✓								
MSSA		✓	✓	✓		✓	✓	✓		✓	
MRSA										✓	
Gram Negative											
E. coli	✓		✓	✓	✓	✓	✓	✓	✓		
Klebsiella sp.			✓	✓	✓	✓	✓	✓	✓		
H. influenzae			✓	✓	✓	✓	✓	✓			
P. aeruginosa			✓		✓		✓	✓	✓		
Anaerobes (*B. fragilis*)			✓					✓			✓

C – Carbapenem; A - Aminoglycoside; G – Glycopeptide; O - Other

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