

Antibiotic Dosing Considerations in Children

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Objectives

- Define and differentiate between pharmacokinetics, pharmacodynamics, and PKPD targets
- Discuss means to optimize dosing for various antibiotics based on PKPD, products, and patient factors
- Identify alternative beta-lactam options in setting of amoxicillin allergy

I'M SO EXCITED!



I GET TO TALK NERDY!

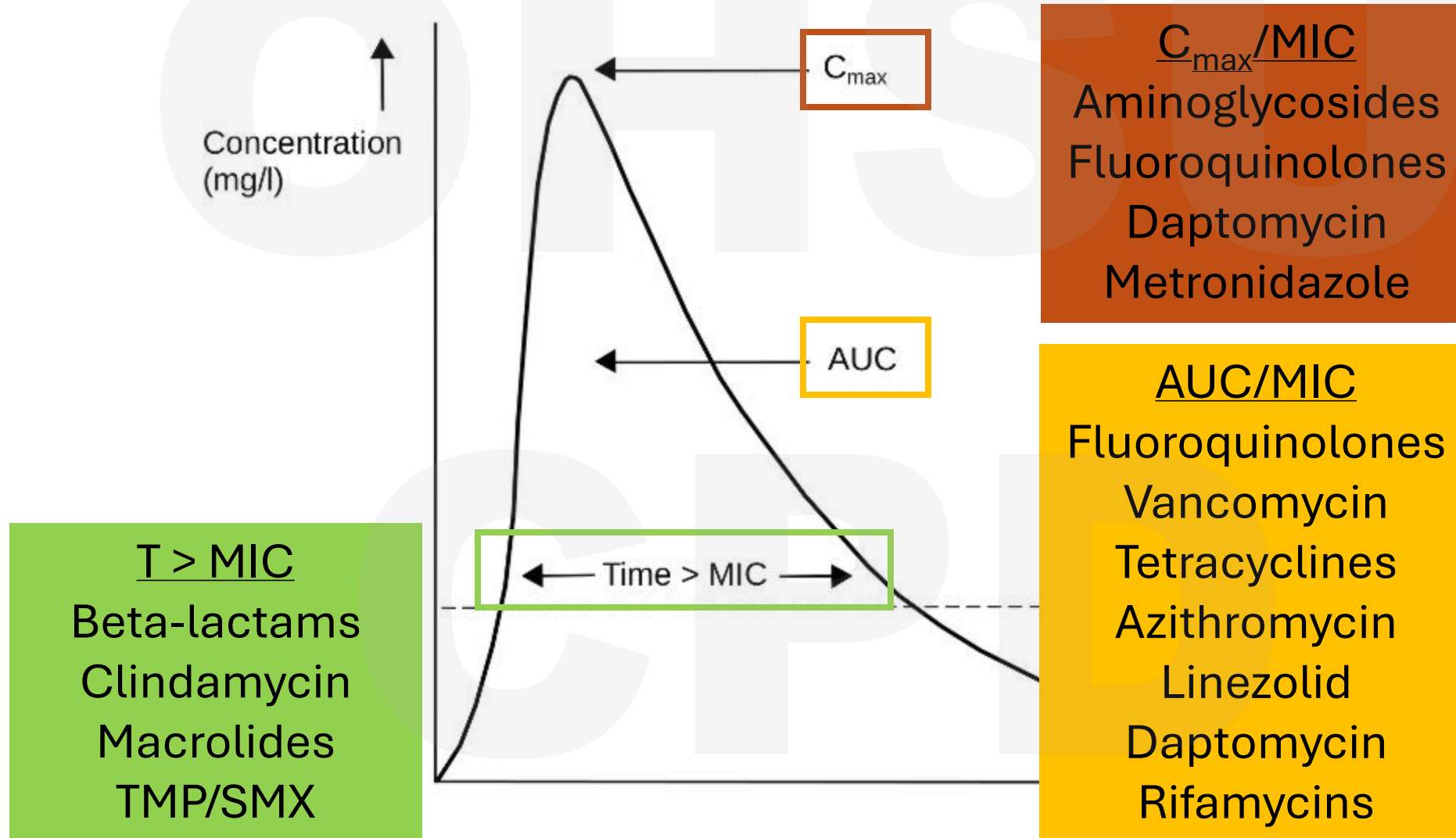
Pharmacokinetic Overview

Parameter	Implication
Absorption	How well the drug absorbed? First pass?
Distribution	Where does the drug go? Protein bound?
Metabolism	How is the drug broken down?
Excretion	How does the drug leave the body?
Toxicity	What toxicities does the drug have?

PK: Children – Not Just “Little Adults”

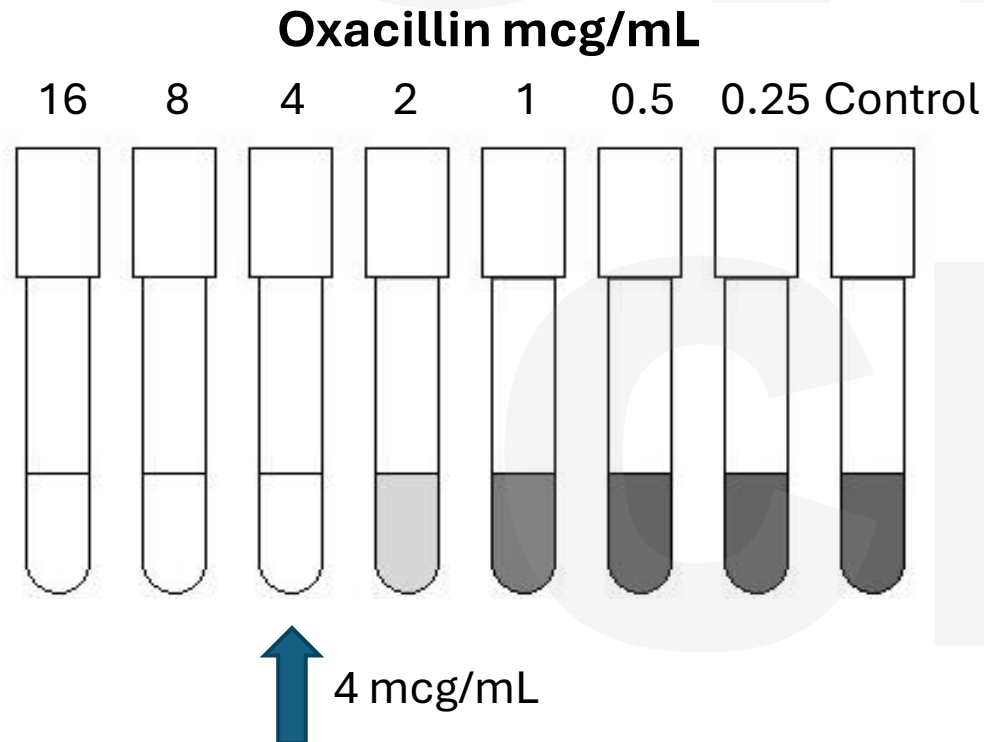
Parameter	Pediatrics vs. Adults
Absorption	Bioavailability (F) – may depend on age (↓ if young)
Distribution	Volume of Distribution (V_d) – generally larger
Metabolism	Phase I – sulfate conjugation first Phase II – increases with age Clearance generally faster
Excretion	Renal function – reaches ~adult GFR by 1 year Clearance, half-life ($t_{1/2}$) – generally faster

Pharmacokinetics/Pharmacodynamics



Minimum Inhibitory Concentration

- Lowest concentration of agent to inhibit growth



Clinical Breakpoint

- Defines if organism is susceptible or non-susceptible to a given antibiotic
 - Varies with drug-bug combination
- Determined by
 - Distributions of MIC
 - PK of antibiotic
 - Clinical outcome

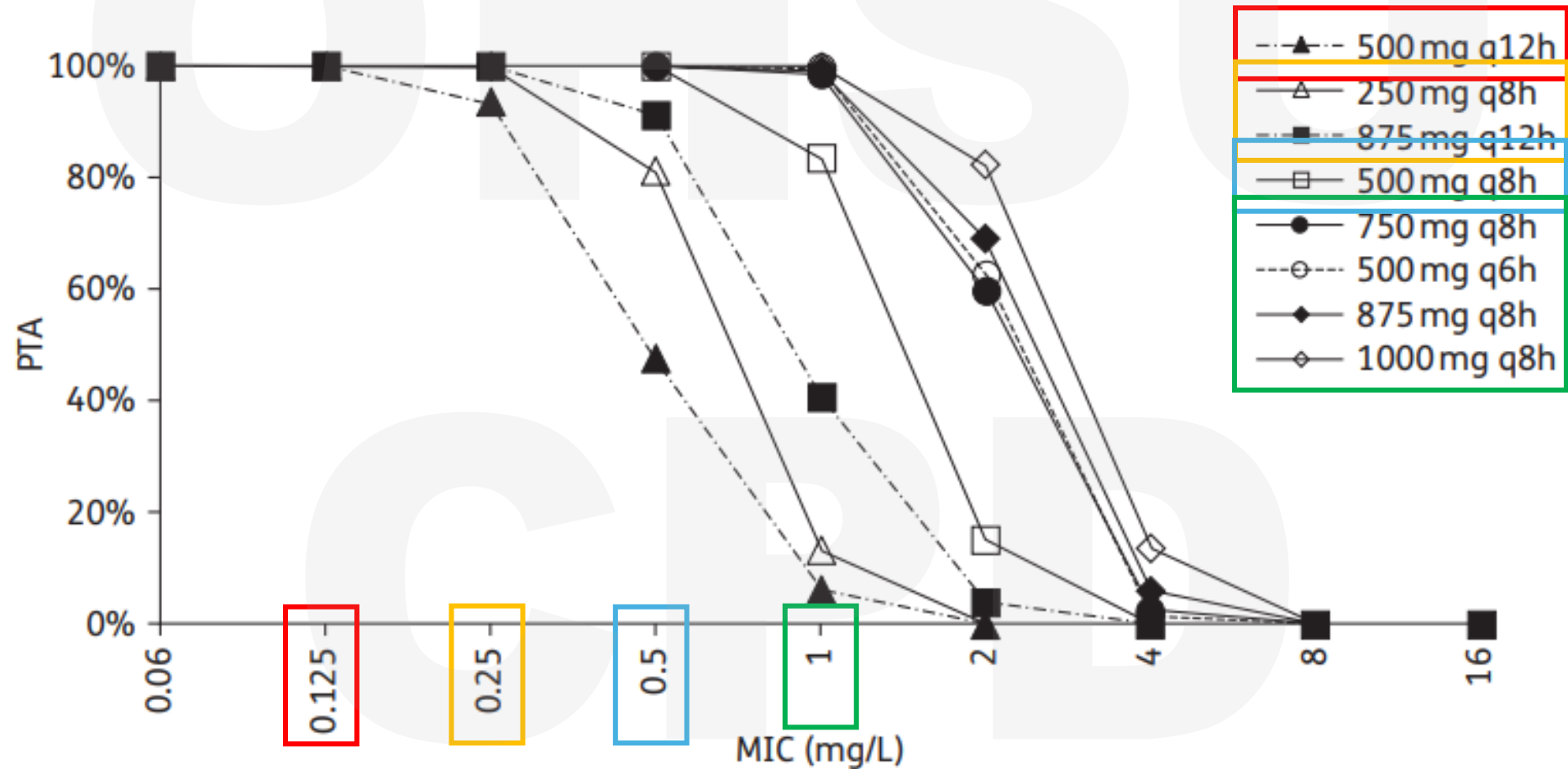
S. pneumoniae PK/PD

Antibiotic	Absorption (%)	Protein Binding (%)	T _{1/2} (h)	Break-point	T>MIC
Ideal agent	>80	Low	Long	N/A	>35-50

S. pneumoniae PK/PD

Antibiotic	Absorption (%)	Protein Binding (%)	T _{1/2} (h)	Break-point	T>MIC
Ideal agent	>80	Low	Long	N/A	> 35-50
Amoxicillin, HD	89	~20	1-1.5	2	33
Cefpodoxime	50	21-33	2-3	0.5	33
Cefdinir	16-25	60-70	1.7	0.5	10

Probability of Target Attainment



S. pneumoniae PK/PD

Antibiotic	Breakpoint	PSSP ¹ MIC50/MIC 90 % susceptible	PRSP ¹ MIC50/MIC 90 % susceptible	All SP ² MIC50/MIC 90 % susceptible
Amoxicillin, SD	0.5			<0.06/<2 74
Amoxicillin, HD	2	<0.015/<0.015 100	1/4 90	<0.06/<2 89
Cefpodoxime	0.5	<0.015/0.12 97	2/4 0	
Cefdinir	0.5	0.06/0.12 97	2/4 0	0.25/16 59
Ceftriaxone	1			<0.03/2 89

1. Peric M, et al. Clin Ther. 2003;25:169-77.

2. Harrison CJ, et al. J Antimicrob Chemother. 2009;63:511-9.

When to do high-dose amoxicillin?

- Standard dose amoxicillin (45 mg/kg/day divided BID or TID) is adequate for penicillin-susceptible pneumococcus
- Consider higher dose (90 mg/kg/day divided BID or TID) when rate of penicillin-NON-susceptible *S. pneumoniae* $\geq 10\%$ based on local epidemiology

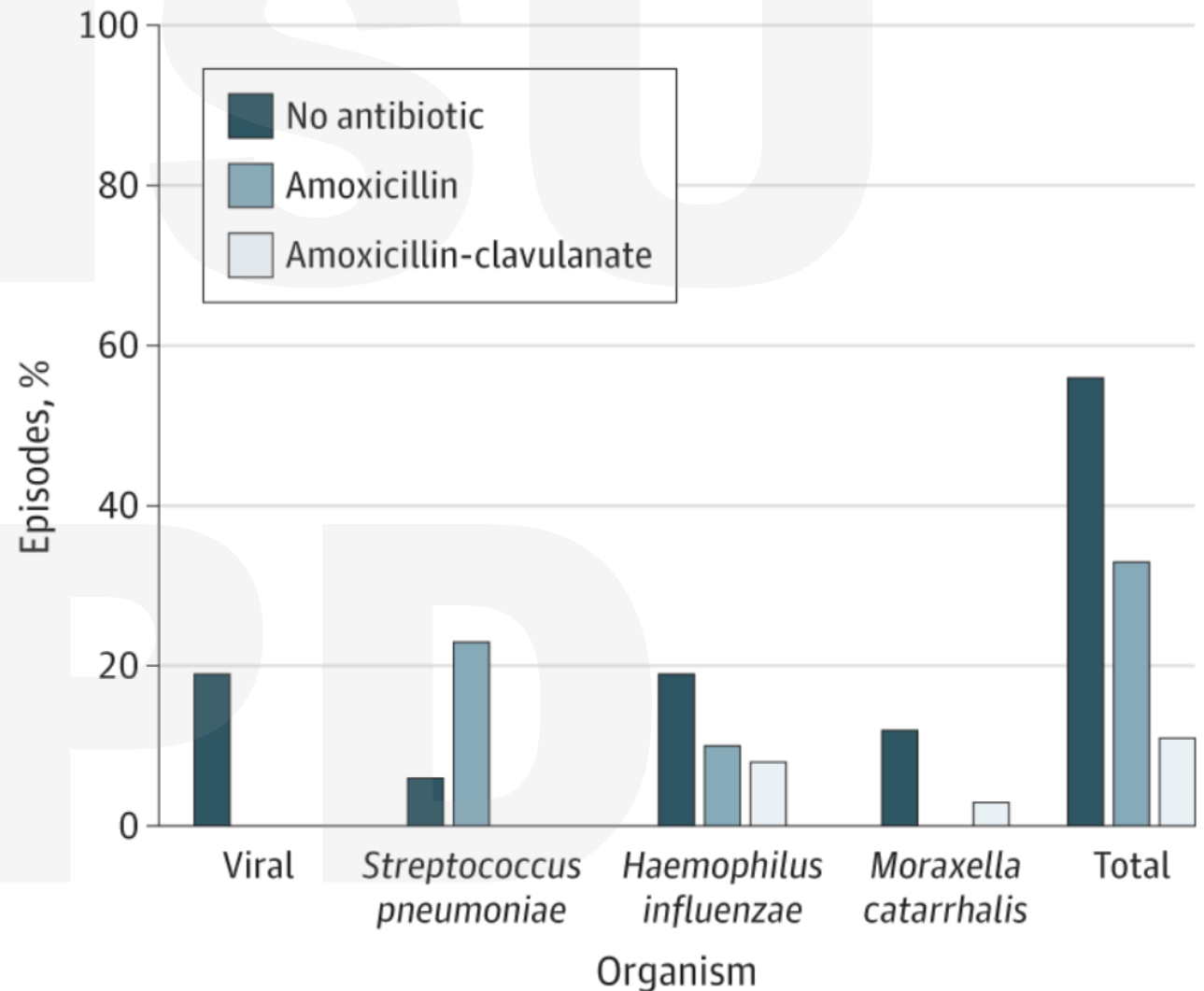
Antibiotic	PCN	CRO	ERYTH	TETRA	LEVO
% Susceptibility	84	98	69	97	100

But do I REALLY need high-dose amoxicillin?

- CAP-IT trial
- Multicenter, randomized 2X2 factorial non-inferiority trial
 - Amoxicillin dose 35-50 vs 70-90 mg/kg/day
 - Duration 3 vs 7 days
- All arms were found to be non-inferior
 - Faster resolution in cough seen in patients who received 7 days
 - Of the patients swabbed, 42% were colonized with *S. pneumoniae*
 - PCN-non-susceptible *S. pneumoniae* rate was ~7%
 - Median age: 2.5 years

But do I REALLY need high-dose amoxicillin?

- Spontaneous resolution of AOM has been observed in ~55% of cases in post-PCV era



How much amoxicillin can I give per dose?

- Maximum amoxicillin dosage per day is 4 grams
 - Why shouldn't the dose be 2 g orally twice daily then?
- Absorption rates appear to decrease as the dose increases
- Less tolerability as doses increase
- Generally have recommended that when amoxicillin dose exceeds 1000-1200 mg to divide q8h

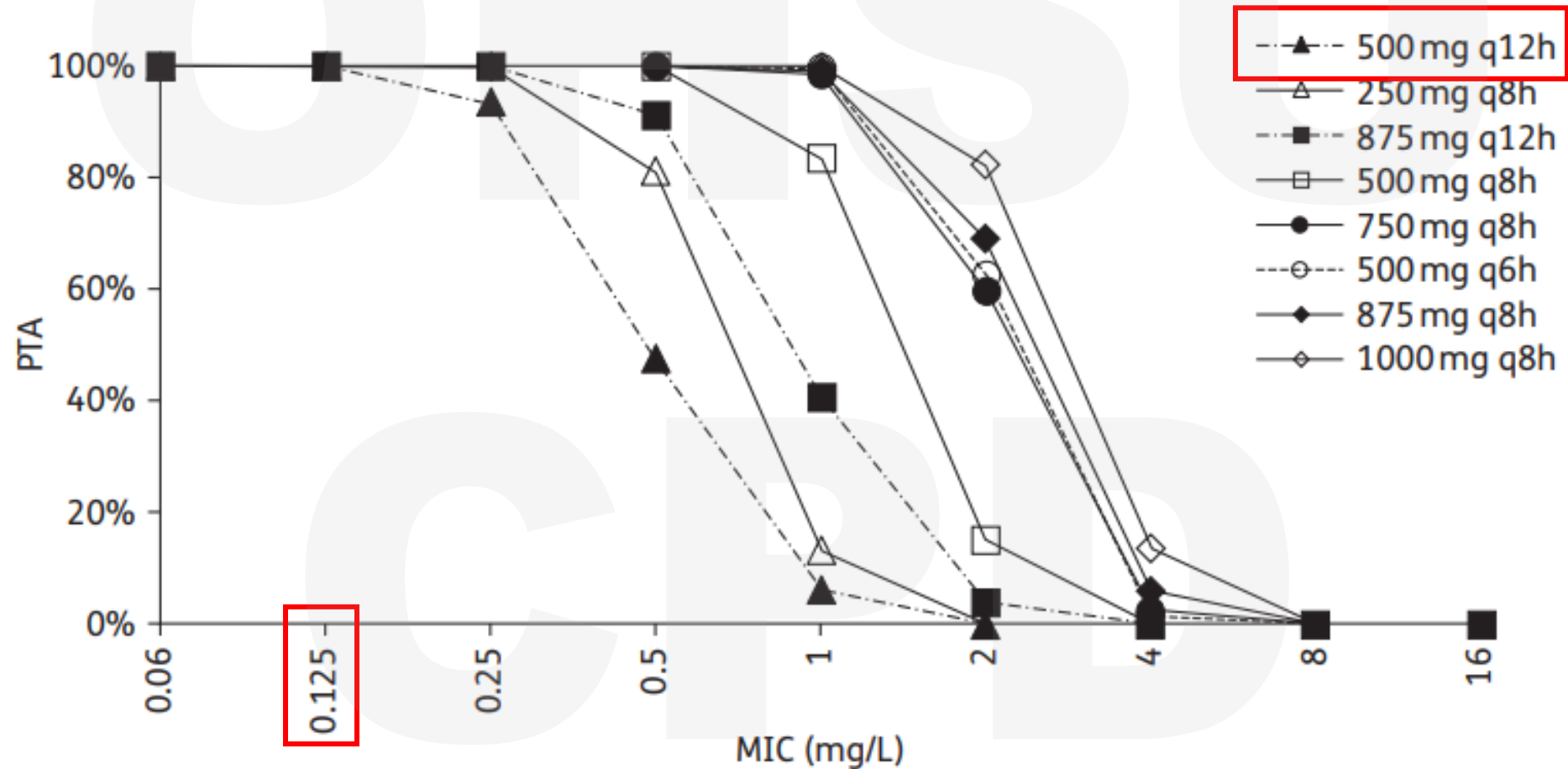
Case

- An 8-year-old child presents to clinic with fever and sore throat; parents report no cough. On exam, an exudative throat and lymphadenopathy.
- You order a rapid streptococcal test, and it results positive.
- Parents ask you if their asymptomatic sibling (who is 9 years old) should also be swabbed “just in case”.

Does GAS need high-dose amoxicillin?

- *S. pyogenes* is always susceptible to penicillin
 - MIC90 is 0.125 mcg/mL

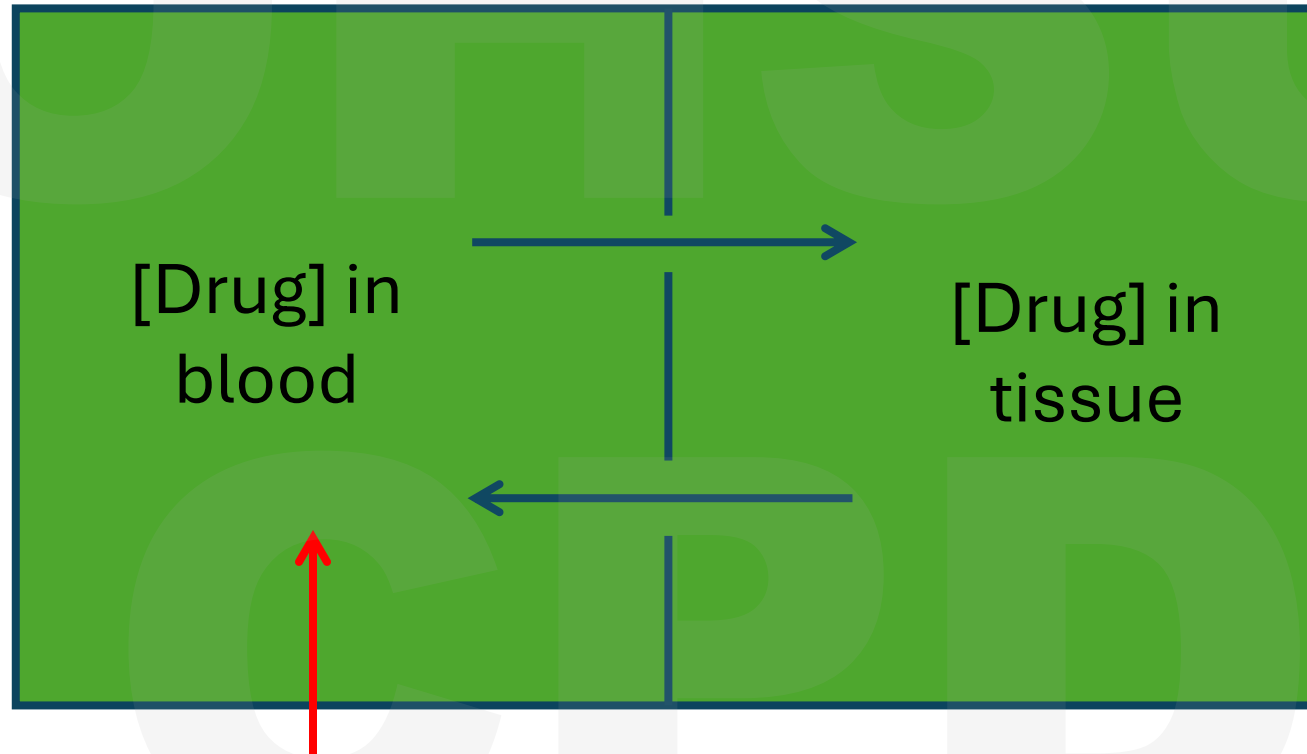
Probability of Target Attainment



Does GAS need high-dose amoxicillin?

- *S. pyogenes* is always susceptible to penicillin
 - MIC90 is 0.125 mcg/mL
- Lower and less frequent dosing will achieve PKPD targets for pharyngitis
 - Once daily dosing found to be non-inferior to twice daily dosing
- Increased and/or three times daily dosing may be needed for deep-seated infections
 - Limited clinical data confirming ideal dosing

Serum Concentrations $\neq$ Site Concentrations



Sampling Compartment for [Drug]

Serum Concentrations ≠ Site Concentrations

- Otitis media, amoxicillin 25 mg/kg/dose PO once

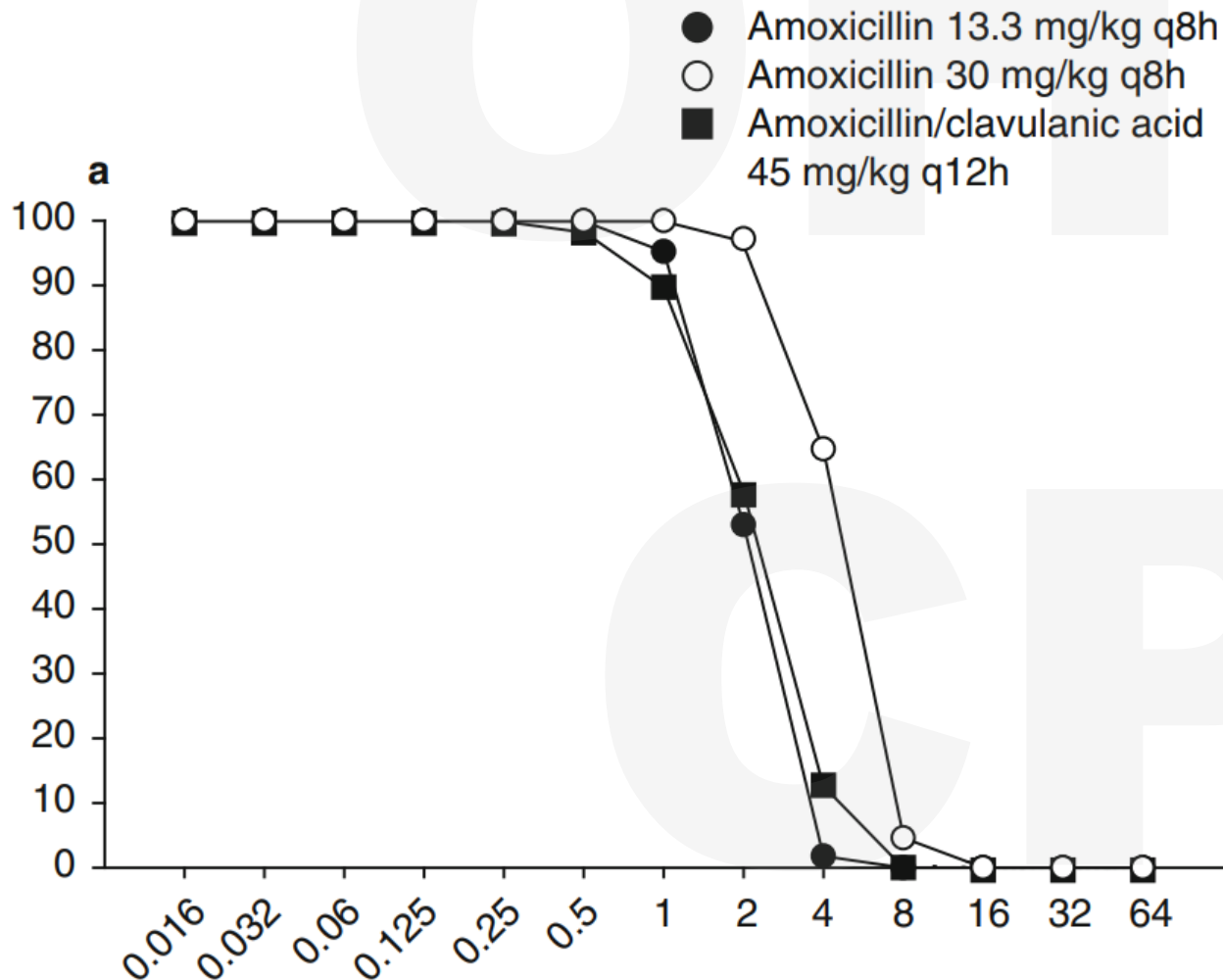
Setting	Time to Peak (hr)	Mean Peak Concentration (mcg/mL)
Serum	1-1.5	[18]
Middle ear fluid	3	9.5
Viral AOM		2.7
Bacterial AOM		5.7

Serum Concentrations ≠ Site Concentrations

- Pulmonary epithelial lining fluid (ELF) [drug]

Drug	Dose	[ELF] mcg/mL	[ELF]/ [Plasma]
Amox/clav	500 mg x 1 dose	0.89	NR
Cefdinir	600 mg x 1 dose	0.29	0.12
Azithromycin	500 mg x 1, then 250 mg/d	1.7-3.12	NR (?>>1)
Levofloxacin	500 mg x 1 dose	10.1-10.9	1.7-3.0

Amoxicillin BID vs TID Dosing



- Complicated infections (e.g. deep-seated, limited source control), TID dosing
 - Standard dosing for β HS
 - High-dose for pneumococcus
- BID dosing for less complicated infections or concerns for adherence

Adding Clavulanate – What is it good for??

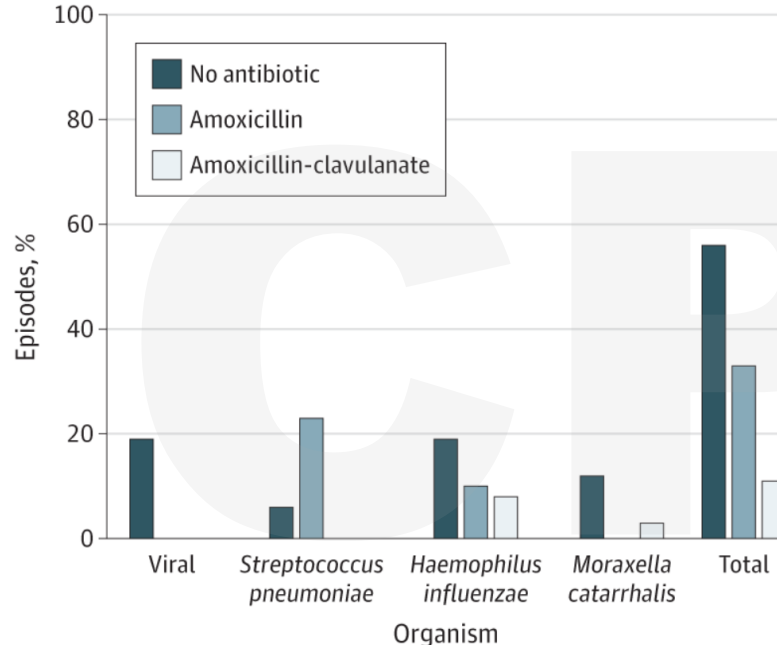
- Clavulanate increases coverage of
 - *S. aureus*
 - *H. influenzae*, *M. catarrhalis*
 - *E. coli*, *K. pneumoniae*, *Proteus*
 - *B. fragilis*
- Clavulanate does NOT increase coverage of
 - *S. pneumoniae*
 - Other streptococci
 - Enterococcus spp. (generally)

Clavulanate definitely **increases** the risk of diarrhea

Do I need high-dose amox-clav for H. flu?

- Guidelines recommend high-dose amoxicillin with clavulanate for AOM if concerned for H. influenzae
 - E.g., no response to amoxicillin, otoconjunctivitis

And remember...



H. influenzae PK/PD

Antibiotic	H. flu CLSI Breakpoint	All H. flu MIC50/MIC 90	% Susceptible
Amoxicillin, SD	2	0.5/16	55
Amoxicillin, HD	4	0.5/16	58
Amox-clav, SD	2/1	0.5/1	100
Amox-clav, HD	4/2	0.5/1	100
Cefdinir	1	0.25/1	100
Ceftriaxone	2	0.03/0.06	100

How much clavulanate should we use?

- An “optimal” dose of clavulanate has not been established
 - Assumed to be adequate based on formulation and dosage
 - Generally, ~6-7 mg/kg/day
- To minimize side effects, suggest not to exceed:
 - 5 mg/kg/dose
 - 10 mg/kg/day
 - 125 mg per dose

Amoxicillin-Clavulanate Formulations

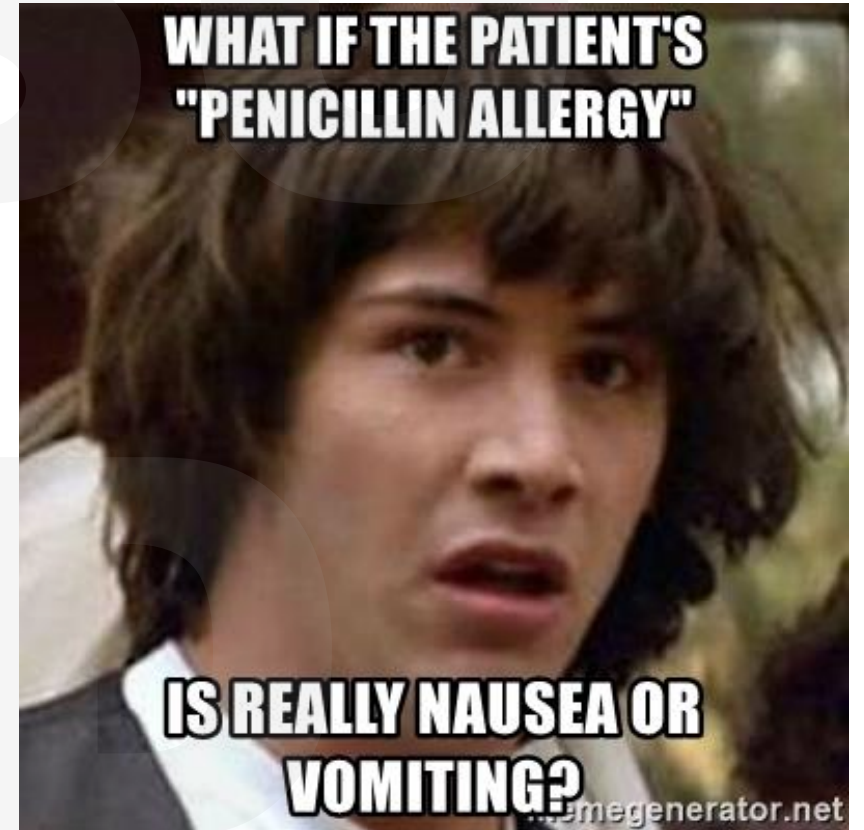
Ratio	Formulation	“Usual” Frequency	Amoxicillin mg/kg/day	Clavulanate mg/kg/day
4:1	250 mg-62.5 mg/5 mL 500 mg-125 mg tab	q8h	20-40	5-10
7:1	400 mg-57 mg/5 mL 875 mg-125 tab	q12h	25-45	3.5-6.4
14:1	600 mg-42.8 mg/5 mL	q12h	80-90	5.7-6.4
16:1	1000 mg-62.5 mg XR tab	q12h	N/A	N/A

Parent tells you that their child had a "rash" with amoxicillin 6 years ago. Which rash is more concerning?



Penicillin Allergy

- Up to 10% of persons report an allergy to a beta-lactam
 - Clinically significant allergy occurs < 5%
- IgE-mediated reactions wane over time
- Patients with penicillin “allergies” more likely to have
 - Broad-spectrum antibiotic exposure
 - *C. difficile* infection
 - Drug-resistant organism colonization



Can I use a different β -lactam in PCN allergy?

- Cross reactivity is dependent on overlap of side chains
 - Highest risk between amino groups (e.g. amoxicillin and cephalexin)
 - <2% with 3rd generation cephalosporin
 - Nearly no risk with cefazolin or monobactams

Beta-Lactam Cross Reactivity Chart

		Penicillin						1st		2nd			3rd				4th	
		Penicillin G/V	Oxacillin	Nafcillin	Amoxicillin	Ampicillin	Piperacillin	Cephalexin	Cefazolin	Cefoxitin	Cefotetan	Cefuroxime	Cefdinir	Cefixime	Cefpodoxime	Ceftazidime	Ceftriaxone	Cefepime
Penicillin	Penicillin G/V							O										
	Oxacillin																	
	Nafcillin																	
	Amoxicillin							O										
	Ampicillin						O	X										
	Piperacillin					O		O										
1st	Cephalexin	O			O	X	O											
	Cefazolin																	
2nd	Cefoxitin											X						
	Cefotetan																	
	Cefuroxime									X					O	O	O	O
3rd	Cefdinir													X	O	O	O	O
	Cefixime												X		O	O	O	O
	Cefpodoxime											O	O	O		O	X	X
	Ceftazidime											O	O	O	O		O	O
	Ceftriaxone											O	O	O	X	O		X
	Cefepime											O	O	O	X	O	X	

Cephalexin

Bacterial Coverage

- Gram-positive
 - Methicillin-susceptible staphylococci
 - Beta-hemolytic streptococci
 - *C. acnes*
- Gram-negative
 - *E. coli*, *K. pneumoniae*, *K. oxytoca*, *P. mirabilis*
- GI anaerobic
 - None

Indications

- Skin/skin structure infections
- Musculoskeletal infections
- Urinary tract infections
- GAS pharyngitis
- FDA-approved for AOM but generally would not suggest using for AOM

Cephalexin: SSTI vs. BJI

- LexiDrug suggested dosing: 25-100 mg/kg/day divided q6-8h
- PKPD dosing studies for MSSA with cephalexin MIC = 2 mcg/mL
 - 75 mg/kg/day divided q8h
 - 90 mg/kg/day divided q12h
- Soft tissue penetration thought to be more consistent than bone
 - Can consider TID dosing for cellulitis
 - Can consider BID dosing for GAS infections
 - Limited clinical data with PKPD dosing for deep-seated infections
 - Guidelines recommend 75-135 mg/kg/day divided q6-8h

Cephalexin. In: Lexi-Drugs. UpToDate Inc. Updated October 6, 2025.

Gwee A, et al. *Pediatr Infect Dis J*. 2020;39:519-22.

Woods CR, et al. *J Pediatric Infect Dis Soc* 2021;10:801-44.

OHSU Pediatric Urine E. coli Susceptibility

Antibiotic	Susceptibility (%)
Amoxicillin	60
Amoxicillin-clavulanate	67
Ceftriaxone	95
Cefdinir	??
Cephalexin	92
Ciprofloxacin	87
TMP-SMX	75
Nitrofurantoin	98

Cephalexin: Cystitis

- Beta-lactams concentrate highly in urine for up to 6 hours
 - Pediatric: 25-50 mg/kg/day divided q6-12h
 - Adult: 500 mg PO q12h
- Can consider BID dosing
- Important to differentiate from pyelonephritis

E. coli Cefazolin Breakpoints

Source	Susceptible	Intermediate	Resistant
Non-urine	≤ 2	4	≥ 8
Urine	≤ 16	–	≥ 32

Source	Susceptible (%)
Non-urine	74
Urine	92

Cephalexin: Pyelonephritis

- Aiming for parenchymal concentrations
- Adult study suggests cephalexin 1500 mg TID will likely achieve PKPD target if $MIC \leq 4 \text{ mcg/mL}$
- Unclear PKPD data for pediatric patients
- Suggested dosing: 50-100 mg/kg/day divided q6-8h

Summary

- Dosing of antibiotics considers organism susceptibility, location of the infection, and maximizing PKPD
 - Beta-lactam antibiotics are time-dependent
- Patient adherence decreases as regimens increase in complexity
 - Thrice daily dosing should be used in more invasive infections
 - Consider twice daily dosing in less complicated infections
- Clarity in patient's amoxicillin allergy can increase appropriate antibiotic selection
 - Cross reaction with oral cephalosporins is generally low

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