Bugs, Drugs and Babies – New Decade, New Strategies?

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Disclosure

- I have nothing to disclose

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Objectives

Evaluate the AAP recommended changes to ampicillin dosing in neonates

Recognize dosing strategies that may start to be utilized more frequently in the neonatal/infant population

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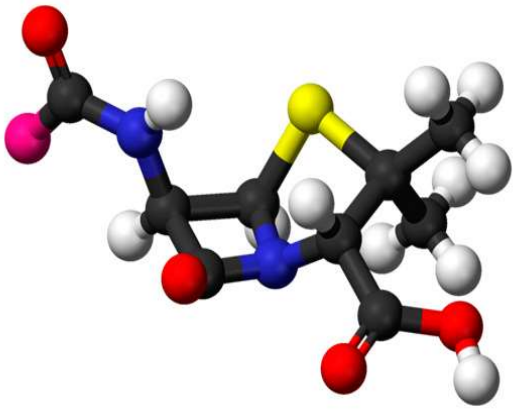
Ampicillin



- Binds to penicillin binding proteins, inhibiting cell wall synthesis
- Efficacy
  - T>MIC
  - [Free Drug] > MIC for ≥ 40-50% of the dosing interval

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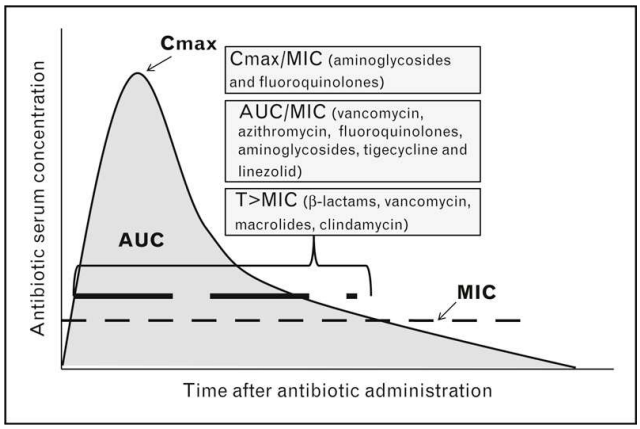
Pharmacodynamic Parameters

- Ampicillin
- Multiple dosing references providing a variety of dosing recommendations
- Based on very limited PK data
- Particularly in patients ≤ 32 weeks at birth



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AAP/Redbook Dosing Recommendations

TABLE 1 Recommended Intravenous Antibiotic Treatment Regimens for Confirmed Early- and Late-Onset GBS Bacteremia and Meningitis

	GA ≤34 wk		GA >34 wk	
	PNA ≤7 d	PNA >7 d	PNA ≤7 d	PNA >7 d
Bacteremia				
Ampicillin	50 mg/kg every 12 h	75 mg/kg every 12 h	50 mg/kg every 8 h	50 mg/kg every 8 h
Meningitis				
Ampicillin	100 mg/kg every 8 h	75 mg/kg every 6 h	100 mg/kg every 8 h	75 mg/kg q 6 h

Adapted from Table 4.2. Antibacterial Drugs for Neonates (<28 Postnatal Days of Age). In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:915-919. GA, gestational age; PNA, postnatal age.

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1. Puopolo KM, et al. *Pediatrics* 2019; 144(2):1-17.

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Population PK of Ampicillin in Neonates

- Prospective multicenter from the Pediatric Trials Network

TABLE 1 Demographic characteristics[a]

	Value for the indicated gestational age (wk) and PNA (days)				
	≤34		>34		
Parameter	≤7	8–28	≤7	8–28	Total
Group no.	1	2	3	4	
n	21	7	27	18	73
Postnatal age (days) at day of first plasma PK sample					
Mean (SD)	2.6 (2.3)	15.4 (4.0)	2.9 (2.6)	13.4 (5.4)	6.6 (6.4)
Median (minimum, maximum)	1.0 (0.0, 7.0)	16.0 (9.0, 21.0)	2.0 (0.0, 7.0)	12.5 (8.0, 25.0)	5.0 (0.0, 25.0)
Gestational age (wk)					
Mean (SD)	30.3 (3.4)	26.9 (2.5)	38.2 (2.0)	38.4 (1.8)	34.9 (5.0)
Median (minimum, maximum)	32.3 (24.0, 34.0)	26.1 (25.0, 32.0)	38.0 (34.0, 41.0)	38.8 (35.0, 41.0)	36.1 (24.0, 41.0)

1. Tremoulet A, et al Antimicrob Agents Chemother 2014;58(6):3013-3020.

POP PK Dosing

TABLE 2 Ampicillin as prescribed by primary physician

Group	*n*	Daily dose (mg/kg/day)[a]	Amt per dose (mg/kg)[a]	Dosing interval	Typical POPS[b] dose
1	21	200 (161–303)	100 (81–109)	19% every 8 h, 81% every 12 h	100 mg/kg every 12 h
2	7	185 (113–194)	93 (57–97)	100% every 12 h	100 mg/kg every 12 h
3	27	218 (100–307)	100 (43–102)	59% every 8 h, 41% every 12 h	75 mg/kg every q 8 h
4	18	282 (184–350)	92 (46–100)	44% every 6 h, 28% every 8 h, 28% every 12 h	100 mg/kg every 8 h
Overall	73	200 (100–350)	98 (43–109)	11% every 6 h, 34% every 8 h, 55% every 12 h	100 mg/kg every 12 h

[a] Numbers represent median (range).
[b] POPS, NIH-funded study supporting this work that focuses on pharmacokinetics of understudied drugs administered to children per standard of care.

- Simulations performed using PK model from the above dosing
- Also performed using info from Neofax, Harriet Lane
- High concentrations were seen so lower doses were also evaluated

1. Tremoulet A, et al Antimicrob Agents Chemother 2014;58(6):3013-3020.

Achievement of Adequate T>MIC

TABLE 6 Probability of target attainment from Monte Carlo simulations using the final pharmacokinetic model

	% of subjects meeting MIC target of:					
	2 μg/ml			8 μg/ml		
Group[a]	50% *T*>MIC[b]	75% *T*>MIC	100% *T*>MIC	50% *T*>MIC	75% *T*>MIC	100% *T*>MIC
Harriet Lane						
1	100	100	100	100	100	99.8
2	100	100	100	100	100	99.8
3	100	100	98.8	100	100	90.2
4	100	100	100	100	100	99.2
Neofax						
1	100	100	1	100	100	98.1
2	100	100	99.8	100	100	96.9
3	100	100	98.8	100	100	90.2
4	100	100	99.2	100	100	90.2
Typical POPS doses						
1	100	100	100	100	100	99.2
2	100	100	100	100	100	97.1
3	100	100	99.6	100	100	98.1
4	100	100	100	100	100	98.3

[a] Group numbers refer to the age group categories defined in Table 1.
[b] *T*>MIC, time above MIC.

1. Tremoulet A, et al Antimicrob Agents Chemother 2014;58(6):3013-3020.

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Bacteremia Dosing

- Dosing for ≤ 7 days did not change
- Dosing for > 7 days decreased dosing intervals
  - Based on longer $t_{1/2}$ compared to other studies

	≤ 34 weeks; ≤ 7 days	≤ 34 weeks; > 7 days	>34 weeks; ≤ 7 days	>34 weeks; > 7 days
Previous Dosing	50 mg/kg q 12 hrs	50 mg/kg q 8 hrs	50 mg/kg q 8 hrs	50 mg/kg q 6 hrs
New Dosing	50 mg/kg q 12 hrs	**75 mg/kg q 12 hrs**	50 mg/kg q 8 hrs	**50 mg/kg q 8 hrs**

1. Tremoulet A, et al Antimicrob Agents Chemother 2014;58(6):3013-3020.

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Ampicillin and CNS Penetration

Primary study was conducted in 1974	CNS penetration reported 2-39% of [serum]	Updated dosing based on old data
• Range of 11-65% reported with 120-200 mg/kg/day in infants < 1 year with meningitis	• Higher with IV versus IM administration • Higher with positive CSF culture vs negative	• Other studies that discuss the variability in CNS penetration

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1. Sullins AK, et al. Pediatr Drugs 2013;Apr 15(2):93-117.
2. Kaplan JM, et al. J Pediatr 1974; 84:571-577.

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Ampicillin with Meningitis

- Unknown where the new recommendations originated from
- Dosing is higher than the single CNS study
  - No new studies have been published
  - Many institutions have used 100 mg/kg every 12 or 8 hours for the first 48 hours while ruling out meningitis

New Recommendation	Previous Dosing	% Difference	Line entries
100 mg/kg/dose IV q 8 hours	100 mg/kg/dose IV q 12 hours	33% difference	3 vs 2
75 mg/kg/dose IV q 6 hours	100 mg/kg/dose IV q 8 hours	No difference	4 vs 3

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1. Tremoulet A, et al Antimicrob Agents Chemother 2014;58(6):3013-3020.

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Why Decrease After R/O Meningitis?

1. Published dosing and PK suggests that our previous dosing of 100 mg/kg IV q 12hrs is MORE than adequate for treatment of bacteremia
2. New dose recommendations target very high levels compared to previous
   - Neonates < 7 days: Peak > 274 and 318 mcg/mL for each GA group
3. Same dose is recommended for PNA < 7 days regardless of GA
   - Doesn't match the PK data; $T_{1/2}$ was almost 2x as long in patients ≤ 34 weeks at birth

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Adverse Effects With Ampicillin

- Seizures (1-2%)
  - Accumulation of drug; B-lactam ring inhibits GABA → CNS excitation
  - [>140 mcg/mL] was associated with a 1.76 greater odds of seizure
    - Increase in seizure not associated with increase mg/kg/day

TABLE 5 Individual empirical Bayesian *post hoc* parameter estimates[a]

Group	*n*	Clearance (liters/h/kg)	Volume (liters/kg)	Half-life (h)	Steady-state concn (μg/ml)	
					Minimum	Maximum
1	21	0.055 (0.03–0.07)	0.40 (0.40–0.40)	5.0 (3.9–9.4)	77 (36–320)	318 (244–563)
2	7	0.070 (0.03–0.07)	0.40 (0.40–0.41)	4.0 (3.8–8.3)	33 (21–145)	266 (159–368)
3	27	0.086 (0.04–0.13)	0.40 (0.40–0.40)	3.2 (2.2–6.2)	48 (5–173)	274 (127–413)
4	18	0.11 (0.06–0.13)	0.40 (0.40–0.41)	2.4 (2.1–4.7)	28 (5–129)	246 (138–203)
Overall	73	0.072 (0.03–0.13)	0.40 (0.40–0.41)	3.3 (2.1–9.4)	47 (5–320)	281 (127–563)

[a] All values are medians and ranges.

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1. Hornik CP, et al. J Pediatr 2016; 178:125-129.

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Adverse Effects With Ampicillin

- Prolonged bleeding time
  - Reversible inhibition of platelet agonists (ADP, von Wildebrand) and irreversible effects on calcium influx
  - VLBW (n=20); 100 mg/kg IV q 12 hrs
  - No difference in bleeding time first 2-4 days; prolonged from 166 vs 284 seconds (p=0.0001) at the end of treatment

1. Hornik CP, et al. J Pediatr 2016; 178:125-129.
2. Sheffield MJ, et al. J Perinatol 2011;31(7):477-480.

Summary

- New AAP recommendations for ampicillin dosing provides for higher, sometimes more frequent dosing, despite new evidence
- Many institutions are adopting the new dose recommendations are references are being updated to reflect them
- Stepping down from CNS dosing to bacteremia dosing may be reasonable

Same Drugs New Tricks?

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Why Consider Other Dosing Strategies?

- Prolonged or continuous infusions of time can increase probability of attaining PK/PD targets
  - B-lactams pharmacodynamic efficacy target is t>MIC
    - Typically ≥ 50% of the dosing interval
      - 60-70% for cephalosporins
      - 50% for penicillins
    - Adults/peds suggested to be 100% in immunocompromised patients
      - Do premature infants fit into "immunocompromised" patients?
- Can be useful with difficult to treat pathogens
  - Higher MICs make it more difficult to attain target

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1. Cohen-Wolkowiez M, et al. Ther Drug Monit 2012; Jun 34(3):312-319.
2. Rybak MJ. Clin Infect Dise 2006;42(S1):S35-S39.
3. Demirel B, et al. J Neonatal Perinatal Med 2015;8:149-155.

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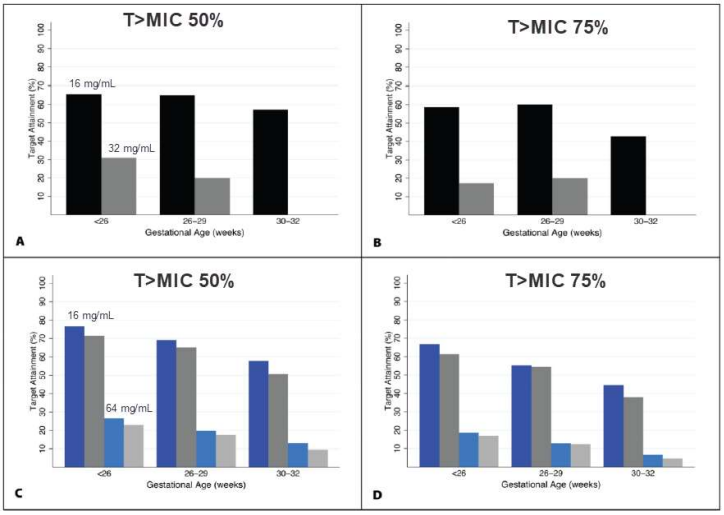
Pipercillin/Tazobactam

- Premature/term infants < 90 days (n=77)
- 80-100 mg/kg/dose q8hrs
- Extended infusion could improve this more without more frequent dosing
- Not correlated with clinical outcomes



1. Cohen-Wolkowiez M, et al. Ther Drug Monit 2012; Jun 34(3):312-319.

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French Guideline: B-Lactams

PK variability in B-lactams is wide

- 30% with pipercillin
- Cefepime volume of distribution varied from 0.08 to 0.55L/kg

Clearance can vary due to SIRS

- Use of fluids/vasoactives can contribute to GFR increases
- B-lactams are hydrophilic and are eliminated renally

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1. Guilhaumou, et al. Crit Care 2019;23:104.

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French Guidelines for B-Lactams

- Suggest targeting free plasma B-lactam concentration for 100% of the dosing interval vs 50-70%
  - Improvement in cure with cefepime/ceftazidime
  - 100% vs 33% eradication with infections caused by E.coli and Klebsiella
  - Some data that 4-6x MIC is needed; 4-8x to maximize prevention of development of resistance
    - Pediatric data suggests 4x (limited)

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1. Guilhaumou, et al. Crit Care 2019;23:104.
2. Mouton, JW, et al. Curr Opin Crit Care 2007; 13:598-606.

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French Guidelines for B-Lactams

- Suggest loading doses before prolonged or continuous infusions of B-lactams

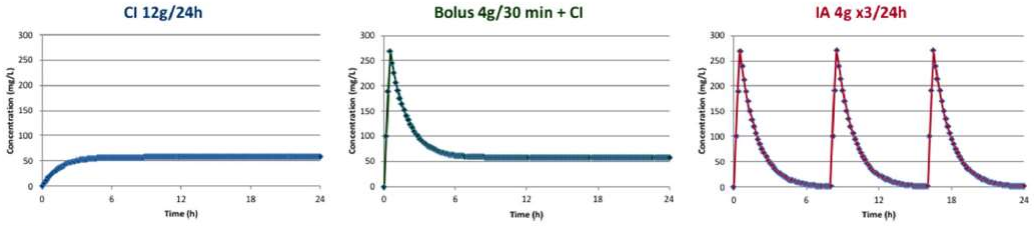

Fig. 1 Simulated plasma concentrations obtained for a 12 g piperacillin daily dose delivered as intermittent administrations (IA, right) or continuous infusion without (CI, left) or with a loading dose (Bolus+CI, middle). The continuous infusion preceded by a loading dose is the regimen that achieves the greatest % $fT \geq MIC$. The trough concentration before the next injection falls below the MIC in the discontinuous administration regimen, while the concentration may remain below the MIC for several hours after the beginning of the infusion in the case of continuous administration without a loading dose.

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1. Guilhaumou, et al. Crit Care 2019;23:104.

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Prolonged/Continuous Infusion Neonates/Infants

	Design	Dose	Population	Outcomes	Mortality
Shabaan AE, et al. Pediatr Infect Dis 2017	Single center RCT	Meropenem 60 mg/kg/day (30 min vs 4 hours)	102 neonates with late onset sepsis	Clinical success: 61% (EI) vs 33%(II) ; p =0.009 Eradication at day 7: 82% (EI) vs 57%; p = 0.009	Mortality: 14%(EI) vs 31%; p = 0.03
Padari H, et al. AAC 2012	Prospective, open label	Meropenem 40 mg/kg/day (30 min vs 4 hours)	19 neonates (<23 weeks, < 1.2 kg)	80% (EI) vs 100% achieved T>MIC for 100% (MIC 2)	Mortality 1/10 (EI) vs 1/9

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1. Shabaan AE, et al Pediatr Infect Dis 2017;36:358-363.
2. Padari H, et al. Antimicrob Agents Chemother 2012; 56:4760-4764.

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Why Consider Other Dosing Strategies - Vancomycin?

- National treatment guidelines recommend AUC_{24}/MIC ratio > 400
  - Invasive methicillin-resistant Staphylococcus aureus
  - Limited data in neonates; but varied:
    - Frymoyer: troughs of 7-11 mcg/mL were adequate to attain target
      - 89% of patients with a trough of 10; used MIC=1
    - Chen: troughs were predictive; but variability in achievement of AUC target
      - MIC ≤ 0.5: trough 5-10 mcg/mL
      - MIC 1: 15% attained AUC target in the 5-10 mcg/mL trough range; trough 5-15 was more predictive in attaining target AUC
    - Gwee: troughs of at least 15-20 mcg/mL were needed
      - Dosed every 6 to 8 hours

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1. Frymoyer A, et al. Antmicrobial Agent and Chemother 2014; 58(11): 6454-6461.
2. Chen Y, et al. Eur J Clin Pharmacol 2018;74(7):921-930.

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Continuous Infusion Vancomycin

Demographic and clinical features of the study population

	Group I ($n=41$)	Group II ($n=36$)	p
Gestational age (mean ± SD)	29.3 ± 2.9	28.6 ± 2.9	0.3
Birth weight (mean ± SD)	1269 ± 230	1026 ± 364	0.01
Vaginal birth (n) (%)	6 (14.6)	4 (11.1)	0.6
Male gender (n) (%)	28 (68.3)	19 (52.8)	0.1
Prolonged rupture of membranes (n) (%)	9 (22)	7 (19.4)	0.7
Ventilator treatment (n) (%)	27 (65.9)	25 (69.4)	0.7
Central venous catheter (n) (%)	23 (56.1)	23 (63.9)	0.6
Duration of treatment (median-range)	10 (4–15)	10 (3–17)	0.9
Site of infection			
Not detected (n) (%)	18 (43.9)	17 (47.2)	0.6
Bacteremia (n) (%)	13 (31.7)	9 (25)	
Meningitis (n) (%)	6 (14.6)	4 (11.2)	
VAP* (n) (%)	3 (7.4)	5 (13.8)	
UTI* (n) (%)	1 (2.4)	1 (2.8)	
Postconceptional age (median-range)	9 (4–29)	11 (4–56)	0.04

*VAP: ventilator associated pneumonia, UTI: urinary tract infection.

- Intermittent (group 1; n=41) or continuous (group 2; n=36)

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1. Demirel B, et al. J Neonatal Perinatal Med 2015;8:149-155.

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Continuous Infusion Vancomycin

Table 3
Comparison of pharmacokinetic features

	Group I ($n=41$)	Group II ($n=36$)	p
Vancomycin concentration at 48 hour (median-range)	8 (5–10.5)	17 (11–21)	<0.001
Therapeutic level at 48 hour of infusion (n) (%)	Subtherapeutic: 11 (26.8)	Subtherapeutic: 15 (41.7)	0.002
	Therapeutic:14 (34.1)	Therapeutic: 19 (52.8)	
	Supratherapeutic: 16 (39)	Supratherapeutic: 2 (5.6)	
Therapeutic level at the end of infusion (n) (%)	Subtherapeutic: 3 (7.3)	Subtherapeutic: 6 (16.8)	0.09
	Therapeutic:32 (78)	Therapeutic: 29 (80.6)	
	Supratherapeutic: 6 (14.6)	Supratherapeutic: 1 (2.8)	
Dose adjustment (n) (%)	27 (65.9)	19 (52.8)	0.2
Duration of vancomycin treatment (days) (median-range)	10 (10–14)	10 (10–13.5)	0.9
Δ Creatinine (2nd creatinine – basal creatinine) mg/dl (median-range)	–0.1 (–0.3/–0.05)	–0.15 (–0.4/–0.05)	0.74

- Intermittent: Target 5-10 mcg/mL; Continuous: Target 15-20 mcg/mL

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1. Demirel B, et al. J Neonatal Perinatal Med 2015;8:149-155.

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Summary

- Despite extensive use of antibiotics, the PKPD in this population are still limited
- Link between in vitro and in vivo PKPD properties and their extrapolation to the clinical use of drugs and impact on clinical outcome
- Prolonged or continuous infusion B-lactams appear to have a greater probability of target attainment
  - Positive clinical outcomes, tolerability, improved safety profile
  - Consideration on a case by case basis
  - Limitations: Drug stability, IV access
- Vancomycin AUC has its challenges in neonates. Consideration of who would best need AUC monitoring.

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