VANCOMYCIN THERAPY IN PEDIATRIC PATIENTS: "LEVELING UP"

Carlina Grindeland, PharmD, BCPS

Mentored by:

Anne Meyer, PharmD, BCPS, CACP

PATIENT CASE

- K.L., a 28 month old female with no significant medical history, is admitted to the Sanford pediatric ICU with respiratory distress, and a chest x-ray consistent with pneumonia. She is febrile with a white blood cell count of 17k, and a Scr of 0.4 mg/dL. You are consulted to dose vancomycin. She is 88cm, 12kg, and her crcl is 138 ml/min.
- Would you…?
  - A) Initiate 30 mg/kg/day divided q8h
  - B) Initiate 45 mg/kg/day divided q8h
  - C) Initiate 70 mg/kg/day divided q6h
  - D) Initiate 60 mg/kg/day divided q6h
  - E) Initiate linezolid, as vancomycin is unsafe in pedaitric patients

PATIENT CASE

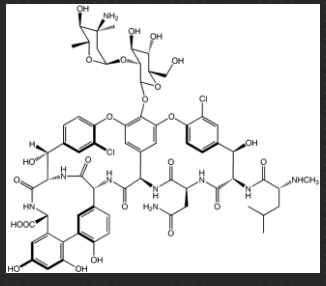
- What goal trough would you target?:
  - A) 15-20 mcg/mL
  - B) 10-15 mcg/mL
  - C) 10-20 mcg/mL
  - D) 7-10 mcg/mL

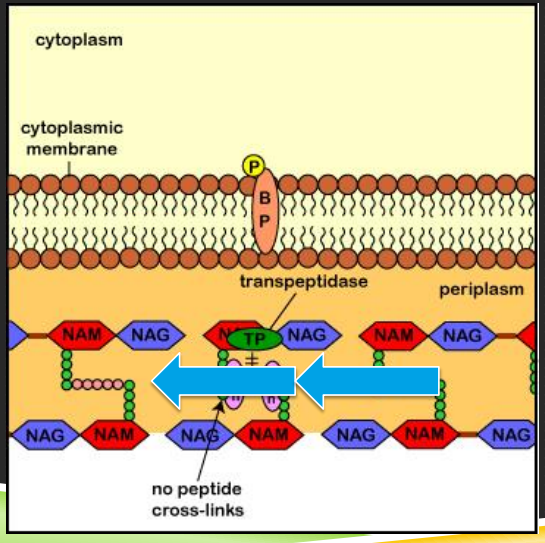
OBJECTIVES

- 1. Describe the pharmacokinetics and monitoring of vancomycin
- 2. Assess the efficacy of current vancomycin dosing and monitoring strategies.
- 3. Identify incidence and risk factors for vancomycin-associated nephrotoxicity in the pediatric population.

OBJECTIVE 1: PHARMACOKINETICS

VANCOMYCIN





http://faculty.ccbcmd.edu/~gkaiser/SoftChalk%20BIOL%20230/Bacterial%20Genetics/chemical_control/antibiotics/antibiotics_print.html

VANCOMYCIN PHARMACOKINETICS

- 1st order
- Protein-bound
- Vd = 0.5-0.9 L/kg
- T1/2 ~6h

VANCOMYCIN ADME

- Absorption:
  - 100% IV
- Distribution:
  - Widely distributed
- Metabolism:
  - None apparent
- Excretion:
  - 90% renal

VANCOMYCIN ADME

- In pediatrics:
  - Renal Clearance

Age (y)	1-2	3-4	5-9	10-11	12-13	14-15	16+
Scr (mg/dL)	0.1-0.4	0.1-0.5	0.2-0.6	0.3-0.7	0.4-0.8	0.5-0.9	0.8-1.3

  - Total body water changes with growth
  - Vd changes with growth

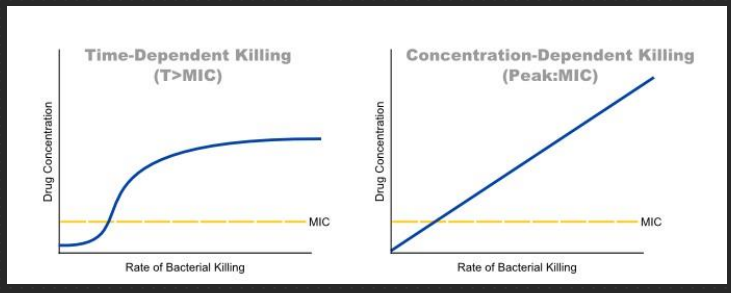
Mayo Medical Laboratories, 2015

PEDIATRIC PATIENTS

Age Group	Definition	Vd (L/kg)	Clearance (ml/kg/min)
Neonates	1st month of life, regardless of gestational age	0.57 – 0.69	1 (0.63 – 1.5)
Infants	1 month to 2 years	0.26 – 1.05	1.2 (0.33 – 1.87)
Children	>2 years to <13 years		
Adolescents	13 years to 17 years	0.5 – 0.9	1 (0.71 – 1.31)
Adults	18 years or greater		

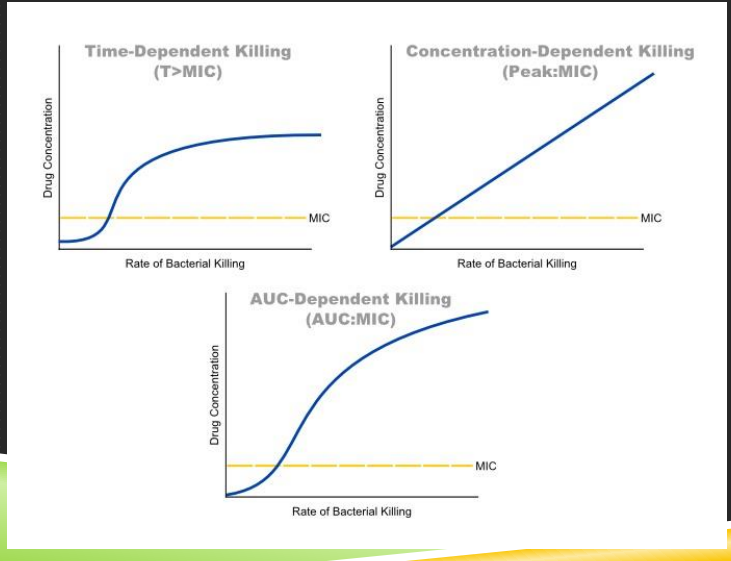
Micromedex "Vancomycin" 2015, Lexicomp Pediatric Drug Information "Vancomycin" 2015

VANCOMYCIN



http://clincalc.com/blog/2012/04/vancomycin-aucmic-versus-tmic/

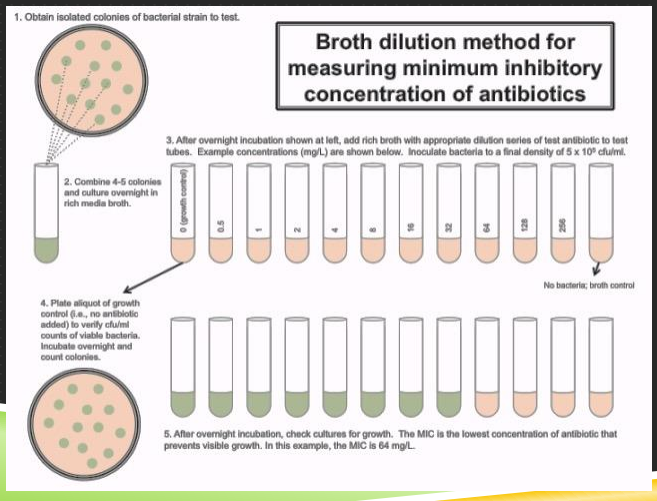
VANCOMYCIN



http://clincalc.com/blog/2012/04/vancomycin-aucmic-versus-tmic/

VANCOMYCIN MICS

- MIC: broth microdilution



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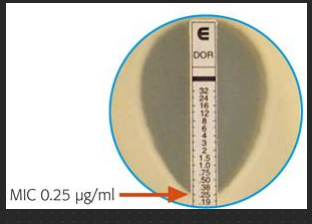
VANCOMYCIN MICS

- Etest



- VITEK (2)

http://www.biomerieux-usa.com/clinical/vitek-2-healthcare, http://aws.labome.com/figure/te-127-5.png

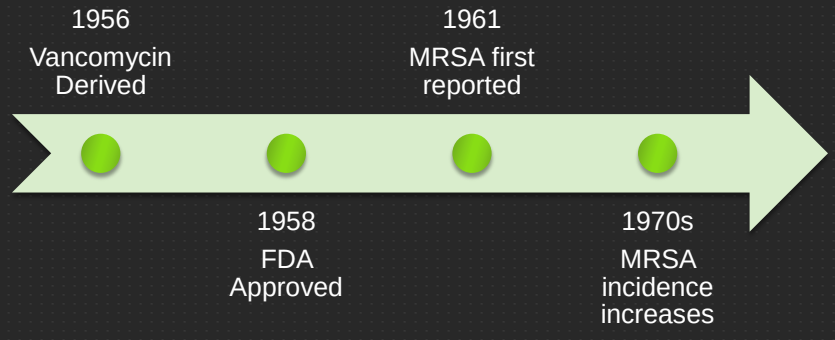
VANCOMYCIN

- Invasive gram positive infections
- Spectrum:

Gram – Positive	Anaerobes
Streptococcus sp. (Group A,B,C,G) Step. Pneumoniae E. Faecalis Staph. Aureus (MSSA, MRSA) S. epidermidis	Actinomyces C. Difficile Clostridium sp. Peptostreptococcus sp.

Sanford Guide, 2014

VANCOMYCIN HISTORY



VANCOMYCIN HISTORY

1981
Moellering
nomogram

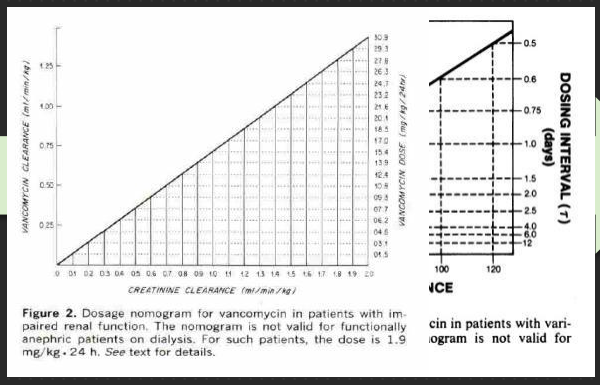


Figure 2. Dosage nomogram for vancomycin in patients with impaired renal function. The nomogram is not valid for functionally anephric patients on dialysis. For such patients, the dose is 1.9 mg/kg · 24 h. *See* text for details.

cin in patients with vari-
ogram is not valid for

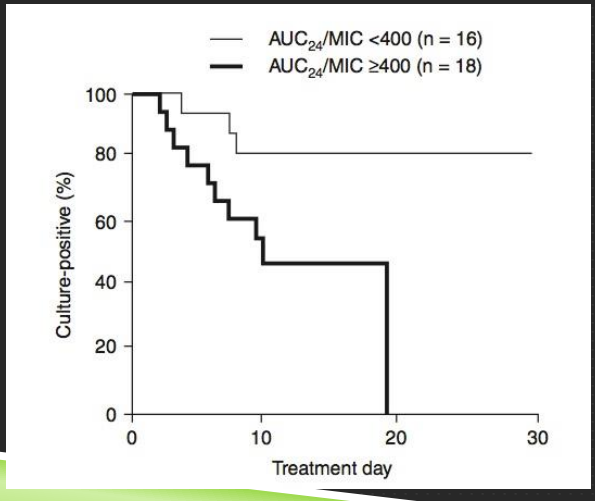
Pharmacodynamics of Vancomycin and Other Antimicrobials in Patients with Staphylococcus Aureus Lower Respiratory Tract Infections

Moise-Broder PA, Forrest A, Birmingham MC et al,
Clinical Pharmacokinetics 2004.

VANCOMYCIN

- 108 patients with lower respiratory tract infection
- Outcomes:
  - Time to bacterial eradication
  - Time to clinical improvement

VANCOMYCIN



Moise-Broder et al, Clinical Pharmacokinetics, 2004

VANCOMYCIN

- AUC/MIC ≥ 400 correlated to troughs of 10-15
- ADULT data

Moise-Broder et al, Clinical Pharmacokinetics, 2004

VANCOMYCIN

Children ≠ **Little Adults**

OBJECTIVE 2: DOSING AND MONITORING

BACKGROUND

Red Book	Sanford Fargo	IDSA
45 - 60 mg/kg/day Q 6 - 8 hours	30 - 60 mg/kg/day Q 6 - 8 hours	60 mg/kg/day Q 6 hours

- "Data are limited to guide vancomycin dosing in children. IV vancomycin 15 mg/kg/dose every 6 hours is recommended in children with invasive disease" (B-III) - IDSA

BACKGROUND

POP QUIZ!

How many pediatric vancomycin studies were included in IDSA guideline?

VANCOMYCIN DOSING INADEQUACY

- Frymoyer 2009
  - Only vancomycin dosing study cited
  - Conclusion: 60 mg/kg/day > 40 mg/kg/day
- Eiland 2011
- Nassar 2012
- DaSilva 2013 (Hem Onc)
- Madigan 2013

CURRENT RECOMMENDATIONS

- What dose will reliably reach AUC/MIC goals?
- What troughs correspond to adequate treatment?
- What are the outcomes?

Improved Vancomycin Dosing in Children Using Area-Under-the-Curve Exposure

Le J, Bradley JS, Murray W et al,
Pediatric Infectious Disease Journal, 2013.

PK-PD TRIAL: METHODS

Inclusion	Exclusion
3 m. to 12 y. of age	Neonates
Vancomycin therapy	Premature
>48h of treatment	Neonatal Intensive Care Patients
9/1/11 to 7/30/2013	Hemodialysis
Trough at <96h	Interfering meds

1631 screened

929 excluded

702 included

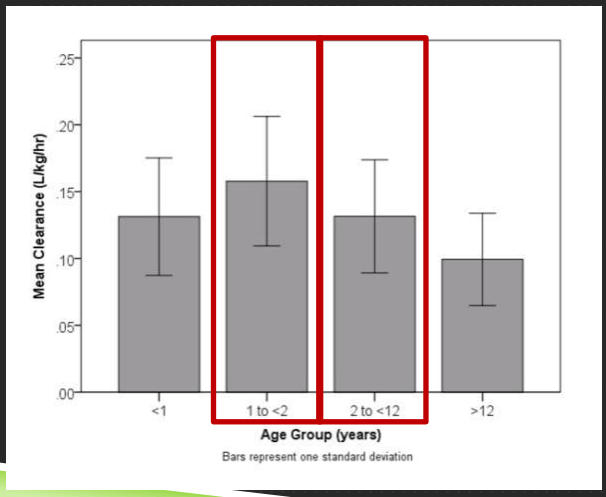
Lee et al, Pediatr Infect Dis J, 2013

PK-PD TRIAL: METHODS

- Population-based pharmacokinetics:
  - Non-linear mixed effect modeling
- Monte Carlo Simulations

Lee et al, Pediatr Infect Dis J, 2013

PK-PD TRIAL: RESULTS



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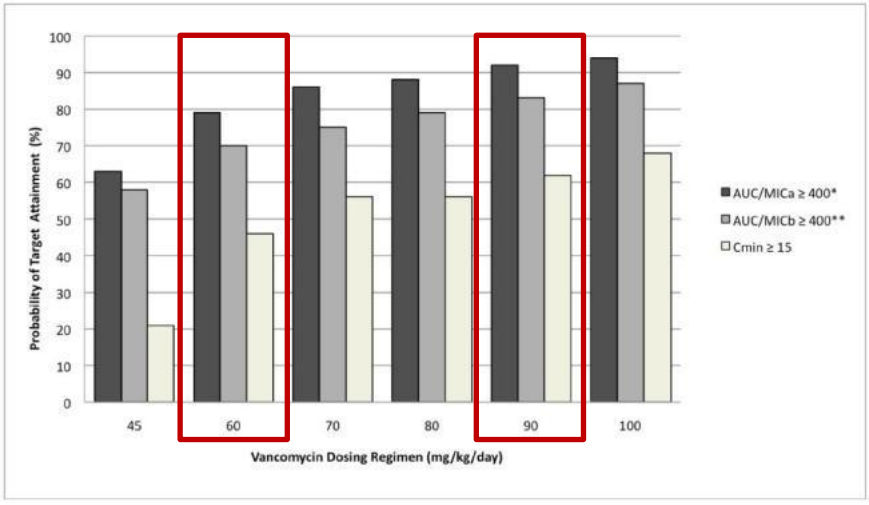
PK-PD TRIAL: RESULTS



Lee et al, Pediatr Infect Dis J, 2013

PK-PD TRIAL: RESULTS

- AUC/MIC > 400 = Trough ~ 8 – 9 mcg/mL
- Troughs highly variable based on age, weight, interval, SCr
- Q8h dosing had lower troughs than Q6h dosing, but with similar AUC/MIC

Lee et al, Pediatr Infect Dis J, 2013

PK-PD TRIAL: STRENGTHS

- Large
- Multiple models
- Real patients
- Modeling good fit with patient data

Lee et al, Pediatr Infect Dis J, 2013

PK-PD TRIAL: WEAKNESSES

- Mean clearance differed between hospitals
- MIC distributions differed between hospitals
- E test used for MICs
- No outcomes

Lee et al, Pediatr Infect Dis J, 2013

PK-PD TRIAL: CONCLUSIONS

- Author's recommended dosing:

Dosing Regimen	Age Criteria
70 mg/kg/day	3 months to < 2 years old
70 mg/kg/day	≥2 years old, Scr < 0.45**
60 mg/kg/day	≥2 years old, Scr ≥ 0.45

** Could also consider this dosing if 30% or more MRSA isolates have MIC ≥ 1.5

Lee et al, Pediatr Infect Dis J, 2013

PK-PD TRIAL: CONCLUSIONS

- Agree with findings and dosing recommendations
- Largest pediatric PK study to date
- Best guidance so far

Desired Vancomycin Trough Serum Concentration for Treating Invasive Methicillin-resistant Staphylococcal Infection

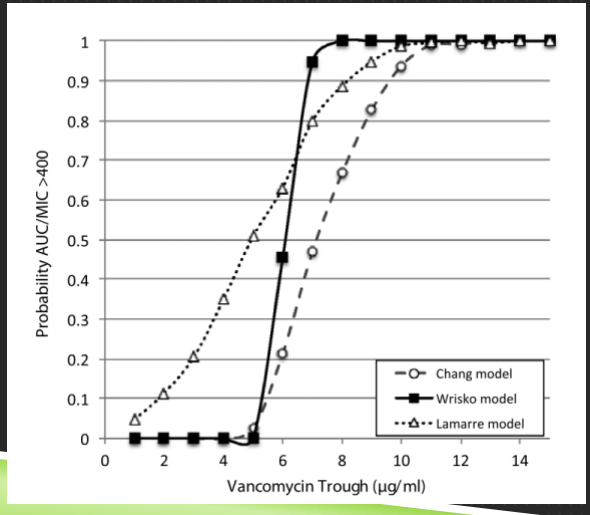
Frymoyer A, Guglielmo J, Hersh AL et al,
Pediatric Infectious Disease Journal, 2013.

TROUGH TRIAL: METHODS

- Pharmacokinetic modeling
  - Chang
  - Lamarre
  - Wrishko
- "Hypothetical" patients
- 15 mg/kg q6 hours
- Assumed MIC of 1

Frymoyer et al, Pediatr Infect Dis J, 2013

TROUGH TRIAL: RESULTS



Frymoyer et al, Pediatr Infect Dis J, 2013

TROUGH TRIAL: RESULTS

- Necessary troughs highly dependent upon MIC
- Q8h dosing had lower troughs than Q6h dosing, but with similar AUC/MIC

Frymoyer et al, Pediatr Infect Dis J, 2013

TROUGH TRIAL: STRENGTHS

- Multiple models used
- Modeled guideline-recommended dose
- Large “n”

Frymoyer et al, Pediatr Infect Dis J, 2013

TROUGH TRIAL: WEAKNESSES

- No real patients
- Did not account for infection site
- No outcomes

Frymoyer et al, Pediatr Infect Dis J, 2013

TROUGH TRIAL: CONCLUSION

- 15 – 20 mcg/mL unnecessarily high
- 7 – 10 mcg/mL predictive of AUC/MIC >400
- 60 mg/kg/day q6h is unnecessary
- “Hypothetical benefit”
- Cannot account for resistance

Frymoyer et al, Pediatr Infect Dis J, 2013

TROUGH TRIAL: REBUTTAL STUDY

- Validation study
- 15 subjects, 0 – 18 years old

Trough	<5 mcg/mL (n = 2)	8 – 10 mcg/mL (n = 9)	>14.5 mcg/mL (n = 4)
AUC/MIC	100% < 400	67% > 400	100% > 400

Hahn et al, Pediatr Infect Dis J, 2013

TROUGH TRIAL: CONCLUSION

- Lower troughs may be acceptable in pediatric patients
- NO OUTCOMES
- Multiple facets to consider:
  - MIC of organism
  - Patient clearance
  - Dosing regimen
  - Site of infection (CNS)
  - Risk of nephrotoxicity

OBJECTIVE 3: NEPHROTOXICITY

VANCOMYCIN

- Toxicities
  - Infusion reaction (“Red Man”)
  - Ototoxicity
  - Nephrotoxicity
- Estimated incidence in adults: 5-40%
- Estimated incidence in children: 0-20%

Incidence and Risk Factors Influencing the Development of Vancomycin Nephrotoxicity in Children

McKamy S, Hernandez E, Jahng M et al,
The Journal of Pediatrics, 2011.

NEPHROTOXICITY

- Retrospective cohort study
- 167 children >/= 1 week old to 19 years old
- Vanco for >/= 48hours
- Similar dosing guideline to Sanford

NEPHROTOXICITY

- 14% nephrotoxicity
- Association with nephrotoxicity:
  - Trough >15
  - Furosemide use
  - Intensive care unit

NEPHROTOXICITY

Author	Population	N	Incidence	Associations
Knoderer, 2013	General, ICU	859	19.4%	ICU admission, initial trough >15
Ragab, 2013	General, ICU	265	27.2%	ICU admission, aminoglycosides
Totapally, 2013	ICU only	391	17.2%	Nephrotoxic drugs, high BUN
Cies, 2013	ICU only	113	8.8% and 5.4%	Troughs >15 NOT ASSOCIATED
Moffett, 2015	Cardiac ICU Case control	418	7.2%	Critical illness, ECMO, nephrotoxic medications

NEPHROTOXICITY

- Conclusions:
  - Conflicting results
  - Critical illness
  - Concomitant nephrotoxic drugs?
  - Troughs?

BACK TO OUR CASE…

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CONCLUSIONS

CONCLUSIONS

- Highly variable pharmacokinetics
- Dosing considerations more complex than mg/kg
- AUC/MIC > mg/kg in children
- Nephrotoxicity not as severe/common as we may have thought

CONCLUSIONS

- Reasonable to adopt Le's dosing:

Dosing Regimen	Age Criteria
70 mg/kg/day	3 months to < 2 years old
70 mg/kg/day	≥2 years old, Scr < 0.45**
60 mg/kg/day	≥2 years old, Scr ≥ 0.45

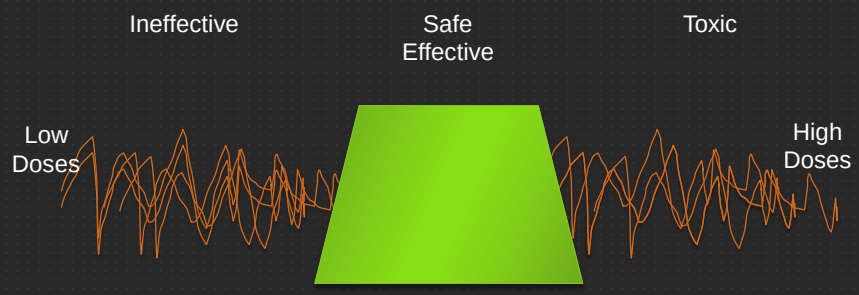
** Could also consider this dosing if 30% or more MRSA isolates have MIC ≥ 1.5

Lee et al, Pediatr Infect Dis J, 2013

CONCLUSIONS

- NO OUTCOMES DATA IN PEDIATRICS
- Requires much further study
- Potential for software tools to assist in monitoring
  - T.D.M.S. 2000, BestDose
  - Based on single trough
- Useful as guidance

CONCLUSIONS



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QUESTIONS?

Thank you!

Carlina Grindeland, PharmD, BCPS

REFERENCES

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