Syndrome Specific Interventions: SSTI and Pneumonia

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Shifting Focus in Medicine

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"Antimicrobial stewardship interventions have been proven to improve individual patient outcomes, reduce the overall burden of antibiotic resistance, and save healthcare dollars." CDC Website

www.cdc.gov/getsmart/healthcare/evidence

Syndromic Stewardship

- Stewardship activities focusing on improving care for a specific infectious syndrome
  - SSTI, UTI, pneumonia, asymptomatic bacteriuria, etc.
- Addresses multiple aspects of care (bundled)
- Allows to address key decision points where choices can go wrong
  - Is this an infection?
  - What infectious syndrome is it?
  - How should I evaluate this infection using lab and imaging?
  - How should I choose empiric therapy?
  - How should I adjust therapy based on subsequent data?
  - How long should I continue therapy?
  - What can be done to prevent the infection?

Advantages of Syndromic Focus

- Multidisciplinary
- Improve diagnostic activities
- Improve therapeutic activity (empiric, definitive, duration)
- Targeted education and improved messaging
- Prevention

Reasons that Antimicrobial Courses Were Not Appropriate According to Accuracy of Provider Initial Diagnosis

		Reason antimicrobial course not appropriate, No. (%, row)				
Accuracy of Provider Initial Diagnosis	Antimicrobial Course Appropriate	Incorrect Drug	Incorrect Dose	Incorrect Duration	Other	Antimicrobial Not Indicated
Correct (n = 291)	181 (62)	81 (28)	5 (2)	43 (15)	1 (0)	10 (3)
Correct, but sign or symptom rather than a syndrome or disease (n = 31)	2 (7)	6 (19)	1 (3)	1 (3)	1 (3)	25 (81)
Incorrect (n = 156)	6 (4)	21 (14)	1 (1)	5 (3)	0 (0)	131 (84)
Indeterminate (n = 22)	2 (9)	4 (18)	0 (0)	7 (32)	0 (0)	11 (50)

NOTE. Percentages sum to >100% because some courses involved multiple errors.

Filice GA, et al. *Infect Control Hosp Epidemiol*. 2015;36:949-56.

Skin and Soft-Tissue Infections Requiring Hospitalization at an Academic Medical Center: Opportunities for Antimicrobial Stewardship

Clin Infect Dis. 2010;51:895-903.

Timothy C. Jenkins,[1,4] Allison L. Sabel,[2,5] Ellen E. Sarcone,[2,4] Connie S. Price,[1,4] Philip S. Mehler,[2,3,4] and William J. Burman[1,4]

Retrospective analysis of 322 SSTI

***S. aureus* or Streptococci isolated from 97% cultures**

(only pathogens in >70%)

Antimicrobial	Cellulitis (N=66)	Cutaneous Abscess (N=103)	SSTI with Complicating Factors (N=153)
Vancomycin	79%	73%	73%
Cefazolin	20%	20%	17%
Beta-lactam/Beta-lactamase inhibitor	53%	65%	66%
Clindamycin	26%	18%	33%
Levofloxacin	11%	5%	14%
Gram-positive therapy only	38%	33%	17%
Broad-spectrum Gram-negative therapy	**61%**	**67%**	**80%**
Anaerobic therapy	**74%**	**73%**	**83%**
Three or more antibiotics	**52%**	**40%**	**48%**
Median Duration Therapy (days)	**11**	**14**	**14**

Opportunities for Improvement

Utilization of Imaging in SSTI

Imaging	Cellulitis (N=66)	Cutaneous Abscess (N=103)	SSTI with Complicating Factors (N=153)	Yield of Image for Deep Infection
Any imaging	**94%**	**69%**	**86%**	4%
Plain film	94%	69%	86%	1%
Ultrasound	42%	14%	26%	0.3%
CT image	9%	15%	17%	2%
MRI	8%	3%	9%	1%
CT or MRI	17%	17%	24%	NR

Jenkins TC, et al. *Clin Infect Dis*. 2010;51:895-903.

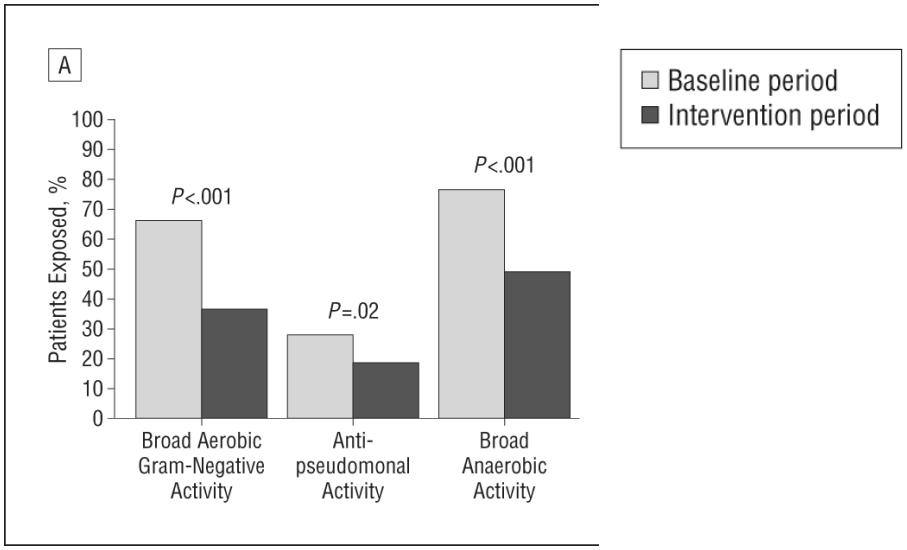
SSTI Intervention

- Multidisciplinary guideline
- Diagnosis
  - When and what labs to order
  - Discouraged use of swab cultures and imaging
- Treatment
  - Discouraged gram negative and anti-anaerobic agents
  - Empiric vancomycin only
  - Transition to oral therapy at 48-72 hours
  - Duration of therapy 7 days
- Implementation
  - Created order set
  - Educated using peer champions
  - Audit-feedback to departments by champions

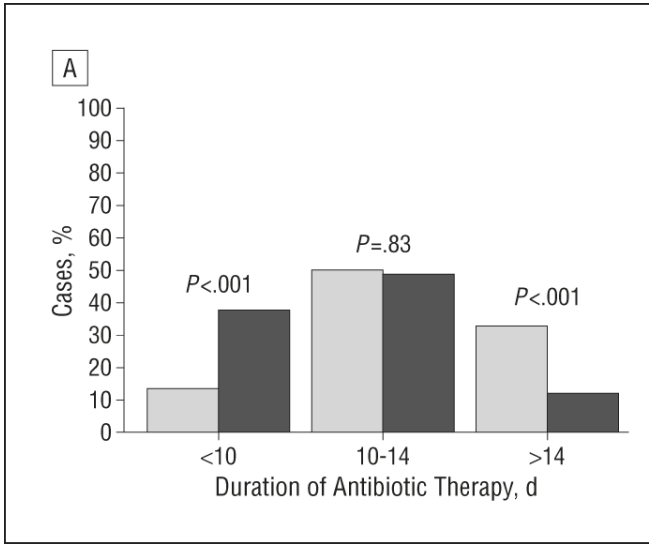
Jenkins TC, et al. *JAMA Int Med*. 2011;171:1072-9.

Measure the Impact

Exposure to Antimicrobial Classes by Time Period



Duration of Therapy by Time Period

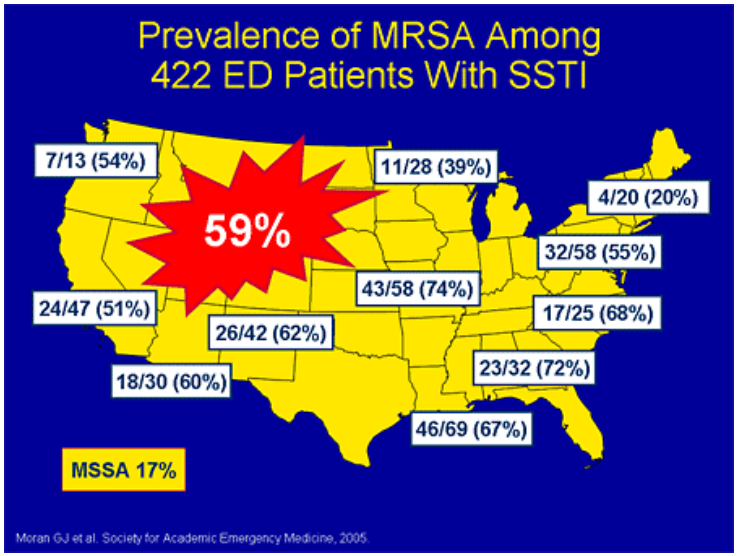


- Clinical outcomes no difference pre- and post-intervention
  - Clinical failure → 7.7% vs. 7.4% (P=0.93)
  - Rehospitalization → 7.7% vs. 5.1% (P=0.33)
  - Median length of hospital stay → 4 vs. 4 (P=0.43)

Jenkins TC, et al. *JAMA Int Med*. 2011;171:1072-9.

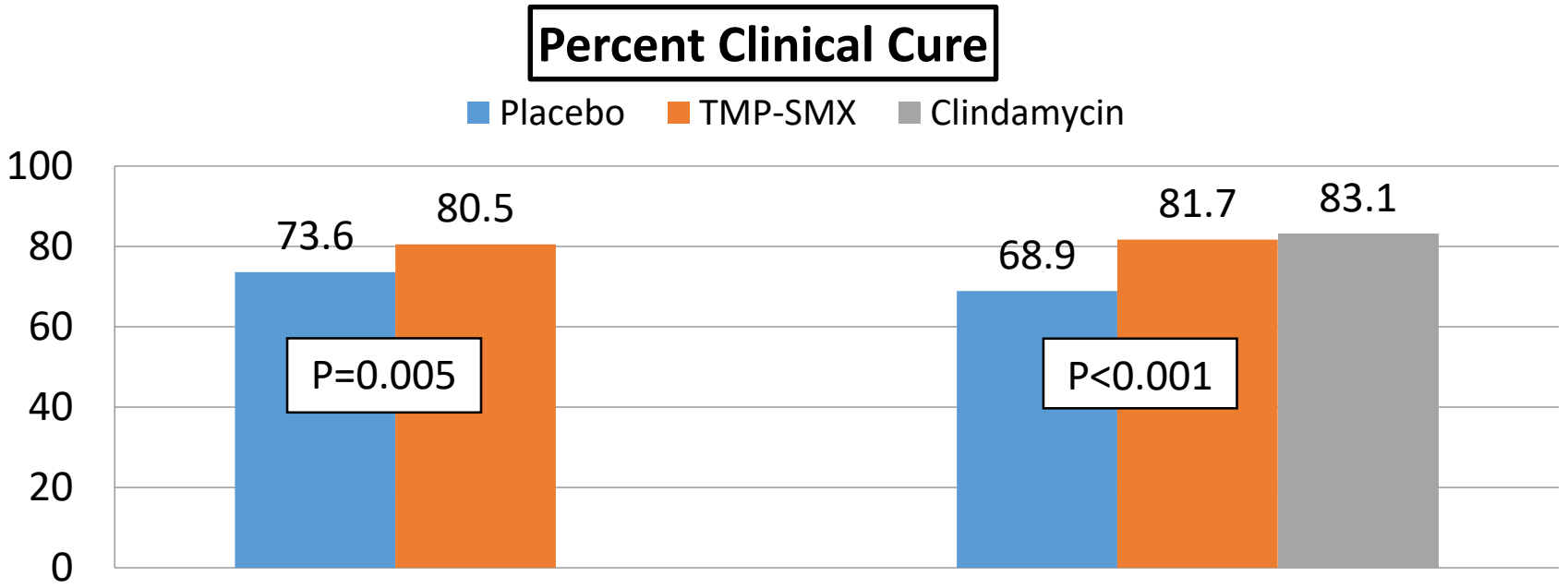
SSTI Issues to Consider

- Specific Infection Being Treated – Cellulitis vs. Abscess



- **I&D primary therapy**
  - Multiple, immune suppressed, can't drain, systemic symptoms, rapid spread or severe, lesions size?? = antibiotics
- Targeting MRSA unless you know different
  - Mild-Moderate = TMP/SMX, doxycycline, clindamycin
  - Severe = Vancomycin, linezolid, daptomycin
- Duration therapy 5-7 days

Should we give antibiotics after incision and drainage?



Talan, et al (N=1265)	Daum, et al (N=786)
ED patients >12 yrs. old	ED/clinic/urgent care patients >6 mo. old
Lesion >2cm induration/fluctuance	Abscess/lesion < 5cm
Placebo vs. TMP-SMX 2 DS tabs BID	Placebo vs. TMP-SMX 1 DS tab BID vs. Clindamycin 300mg TID
TMP-SMX decreased subsequent surgical intervention, new skin infection, and infection in a household member	**Decreased subsequent infections (8% vs. 12-13%) with clindamycin only but more adverse events with clindamycin (21.9% vs. 11-12%)**

Talan DA, et al. *NEJM*. 2016;374:823-32.

Daum RS, et al. *NEJM*. 2017;376:2545-55

Do we need to worry about MRSA in Cellulitis?

- Two multicenter RCT evaluating addition of TMP-SMX to beta-lactam in uncomplicated cellulitis
  - No abscess, immunosuppression, PVD, device present
- All treated with cephalexin and randomized TMP-SMX OR placebo
  - Various dosing regimens
    - Weight-based high dose cephalexin and TMP-SMX for 7-14 days
    - Traditional cephalexin and high dose TMP-SMX for 7 days

Outcomes (TMP-SMX vs. Placebo)	Pallin, et al. (N=146)	Moran, et al. (N=496)
Clinical Cure Rate	85% vs. 82% (95%CI, -9.3%-15%, *P*=.66)	83.5% vs. 85.5% (95%CI, -9.7%-5.7%, *P*=.5)
Adverse Events	49% vs. 53% (*P*=.62)	41.1% vs. 36.3%, P=NS)

Pallin DJ, et al. *Clin Infect Dis*. 2013;56:1754-62.
Moran GJ. *JAMA*. 2017;317:2088-96

Abscess and Cellulitis Summary

- Treat based on infectious syndrome
- Non-purulent cellulitis → treat for strep using beta-lactam
  - Use high doses in obese or severe edema
- Abscess → drainage alone may be adequate but increasing evidence benefit from treatment
- Purulence present → treat for MRSA
  - Mild-Moderate = TMP/SMX or Doxy (or Clinda??)
    - Recent trials suggested no difference between TMP-SMX and Clindamycin in outcomes
  - Severe = Vancomycin or others
- Complicated infections = same as purulent infections
- Don't routinely cover gram-negatives/anaerobes
  - Use with necrotizing fasciitis and severe DFI

Liu C, et al. *Clin Infect Dis*. 2011;52:1-38

Pneumonia (CAP, ~~HCAP?~~, HAP, VAP)

Ventilator-Associated Pneumonia: Overdiagnosis and Treatment Are Common in Medical and Surgical Intensive Care Units

- Only 41.6% of 231 possible VAP cases determined to be VAP
- Antibiotics continued beyond day 3 in 76% without VAP (1183 DOT)

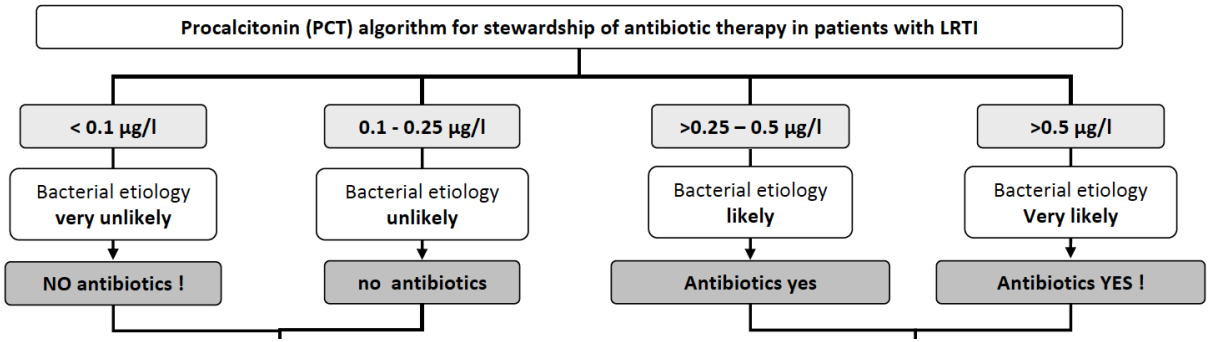
Pneumonia Opportunities

- Diagnostics
  - Procalcitonin
  - Blood and sputum culture
  - Viral and MRSA PCR
  - Urine antigens
- Treatment
  - When to treat for MDROs and use combination therapy
  - De-escalation
  - Duration of therapy
- Prevention including vaccines

Nussenblatt V, et al. *Infect Control Hosp Epidemiol.* 2014;35:278-84.

Procalcitonin

- Most specific biomarker for bacterial infection currently available
- Rapidly rises (~6 hr after insult) and has a half life of 24 hours
- Multicenter, non-inferiority, randomized trial of adults with LRTI presenting to ED
  - PCT levels at admission and if antibiotics started on day 3, 5, 7



- Decreased
  - Absolute abx starts -12.2%
  - Mean duration therapy -34.8% (-3 days)
  - Abx side effects 28.1% vs. 19.9%
  - 30-day adverse events 18.9% vs. 15.4%

Schuetz P, et al. *JAMA* 2009; 302:1059-66.

Diagnostic Testing Opportunities

- Blood cultures not needed in everyone
- Sputum cultures only obtained in half of patients
- Timing less than ideal
  - Gram-stain and culture can identify 80% Pneumococcal pneumonias if obtained within 12 hours of antibiotics[1]
  - Median time to sputum culture = 11 hours after antibiotics[2]
- Urine antigens can provide useful data
  - 474 CAP cases with 75 cases pneumococcal pneumonia diagnosed by antigen only and antibiotics adjusted in 41 based on this data[3]
- Nasal MRSA PCR testing
  - NPV ranging 84% to 99%[4,5]

1. Musher DM, et al. *Clin Infect Dis*. 2004;39:165-9.
2. Jenkins TC, et al. *Infection*. 2013;41:135-44.
3. Sorde R, et al. *Arch Intern Med.* 2011;171:166-72.
4. Dangerfield B, et al. *Antimicrob Agents Chemother.* 2014;58:859-64.
5. Sarikonda KV, et al. *Crit Care Med*. 2010;38:1991-5.

HCAP ☹

- Retrospective, observational, single-center analysis adult CAP/HCAP over 2 years (N=521)
  - MDRO = MRSA, Pseudomonas, ESBL GNR, CRE, Acinetobacter, Stenotrophamonas
  - 3.8% overall → **5.9% HCAP, 1.9% CAP**

"Once you start you can't stop"

- Patients with HCAP at VA hospitals over 4 years (N=9319)
  - >50% received both anti-MRSA and Pseudomonas abx
    - 6.7% had MRSA, 4.8% had Pseudomonas
  - Only 28.3% had any de-escalation by hospital day 4
- De-escalation safe and beneficial
  - Early antibiotics discontinuation in VAP with negative BAL safe with fewer superinfections and MDR pathogens
  - De-escalation was protective in multivariate analysis of hospital mortality in severe sepsis/septic shock (N=628) → OR 0.55 (0.32-0.98), P =0.022

Gross AE, et al. *Antimicrob Agent Chemother.* 2014;58:5262-8.
Madaras-Kelly K, et al. *J Antimicrob Chemother*. 2016;71:539-46.
Garnacho-Montero J, et al. *Intesive Care Med*. 2014;40:32-40.
Raman K, et al. *Crit Care Med*. 2013;41:1656-63.

Skin and Soft-Tissue Infection Cases

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Case #1

- 80yo female with LVAD
- Developed cellulitis around LVAD insertion site, fever, lethargy
- WBC remained normal throughout hospital stay
- Started empirically on daptomycin 4 mg/kg/day but had not failed PO ABX outpatient or received any IV ABX
- Prescriber rationale for ABX choice: want to be more aggressive due to risk of infection traveling to heart
- Blood culture prior antibiotic remained negative; wound culture grew MRSA sensitive to clindamycin, levofloxacin, TMP/SMX, vancomycin
- Patient discharged home on TMP/SMX

Questions

What would be the best way to approach the issue?

Would a formulary restriction be best in this scenario?

What is the best way to approach the physician who is overly aggressive treating this cellulitis?

Case #2

- 39yo male presented to ED with diagnosis of sepsis
- Weight = 91.1kg, BMI 31 kg/m^2
- PMHx: COPD, CAD, HTN, tobacco use
- Labs: Scr 0.7, CrCl >100 ml/min, WBC 12.6
- In ED, received pip/tazo 3.375g x 1, vancomycin 1.5g x 1
- Upon admission, continued pip/tazo 3.375g IV q8h, vancomycin 1.5g q8h for necrotizing fasciitis
- Vanco trough prior to 4^{th} dose 42.9 (8/17); dose held and re-dosed on 8/18
- Discharged 8/18, readmitted 8/19 with renal failure, likely due to vancomycin toxicity

Questions

Does your facility allow >4g/day of vancomycin doses for empiric therapy?

What incidence of renal toxicity have you seen with combination pip/tazo and vancomycin?

Does your facility have guidelines for vancomycin dosing in obese patients?

Incidence of Vancomycin Nephrotoxicity in Obese Patients

- Retrospective review compared vancomycin nephrotoxicity based on degree of obesity
- Dosing protocol
  - Loading dose: variable
  - Maintenance dose: 15 mg/kg actual body weight (2 g/dose max)
  - Frequency: q12h if CrCl 60-120 ml/min; q24h if CrCl 30-60 ml/min

	Non-Obese	Class I and II Obesity	Class III Obesity	p-value
Vancomycin therapy				
Duration of therapy, days	5 (4-8)	4 (3-7)	4 (3-6)	0.1213
Received loading dose	50 (33.33%)	46 (28.57%)	26 (26.80%)	0.2511
Mean (mg/kg)	23.31 ± 4.48	19.78 ± 5.40	14.50 ± 4.87	<0.0001
25-30 mg/kg	24 (48.0%)	3 (6.5%)	0 (0%)	<0.0001
Initial maintenance dose, mg/kg	18.41 ± 2.99	16.49 ± 2.95	13.82 ± 2.60	<0.0001
Initial maintenance dose, mg/kg/d	32.72 ± 9.16	30.20 ± 7.68	25.39 ± 7.28	<0.0001
Initial dosing frequency				0.0890
Every 8 hours	0 (0.00%)	1 (0.63%)	3 (3.03%)	
Every 12 hours	116 (77.33%)	132 (82.50%)	80 (80.81%)	
Every 24 hours	34 (22.67%)	27 (16.88%)	16 (16.16%)	

- Rate of nephrotoxicity: 8.7% non-obese; 14.3% Class I-II obesity; 26.3% Class III obesity
- ~35% in each group on pip/tazo
- Predictors: Obesity (OR 2.99), trough >20, concomitant pip/tazo therapy (OR 3.55), ICU stay, duration of therapy

Choi YC, et al. Ann Pharmacother 2017;51:937-44.

Nephrotoxicity from Vancomycin + Piperacillin/Tazobactam Therapy (VPT)

- Meta-analyses
  - 14 studies: VPT vs. vanco alone (aOR 3.11)
  - 15 studies: VPT vs vanco +/- other beta-lactam (OR 3.6)

- Individual studies
  - VPT vs. vanco + cefepime:
    - 29% vs. 11%
  - VPT vs. vanco + cefepime:
    - 2.18x more likely to cause AKI
  - VPT vs. vanco alone:
    - aOR 2.48
  - VPT as independent risk factors for AKI in 4 studies
    - OR ranged from 5.36 to 2.61

Watkins RR and Deresinski S. Clin Infect Dis 2017 Jul 29 [Epub ahead of print]

Risk Factors Associated Vancomycin Nephrotoxicity

Vancomycin Exposure Variables	**Loading dose** **Total daily dose** **AUC** **Trough level** **Duration**
Patient-Specific Factors	**Obesity** **Severity of illness** **ICU residence** **Chronic kidney disease** **Concurrent nephrotoxin exposure** **Concurrent aminoglycosides** **Concurrent piperacillin-tazobactam**

Filippone Ej, et al. Clin Pharmacol Ther 2017;102:459-69.

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Questions??

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