Useful or Useless: A Panel Discussion on Diagnostics, Monitoring, and Treatment in Antimicrobial Stewardship

Moderator: Ryan Dare, MD; UAMS, CAVHS, Baptist Health
Panelist: Cole Wood, MD; Washington Regional Medical Center
Panelist: Erin McCreary, PharmD; University of Pittsburgh Medical Center


USE
FUL
LESS

Scenario 1

- 65yo M presented to the ED with 3-day history of increased shortness of breath, non-productive cough, and low-grade fever (max 100.2F at home)
- PMH: COPD and mild CHF
- Social Hx: Wife recently had influenza
- Physical Exam:
  - Temp 100.0F, HR 90, BP 135/85, O2 sat 92% on room air (baseline 94%)
  - Bilat wheezes
- Workup:
  - Chest Xray: interstitial infiltrates bilat
  - WBC 9K (40% PMNs, 50% Lymph, 8% Monocytes)
  - SCr 2.0 (baseline 1.3)
  - RPP pending
  - BNP pending
- Course:
  - ED initiated ceftriaxone and azithromycin

Would you request procalcitonin level in this patient

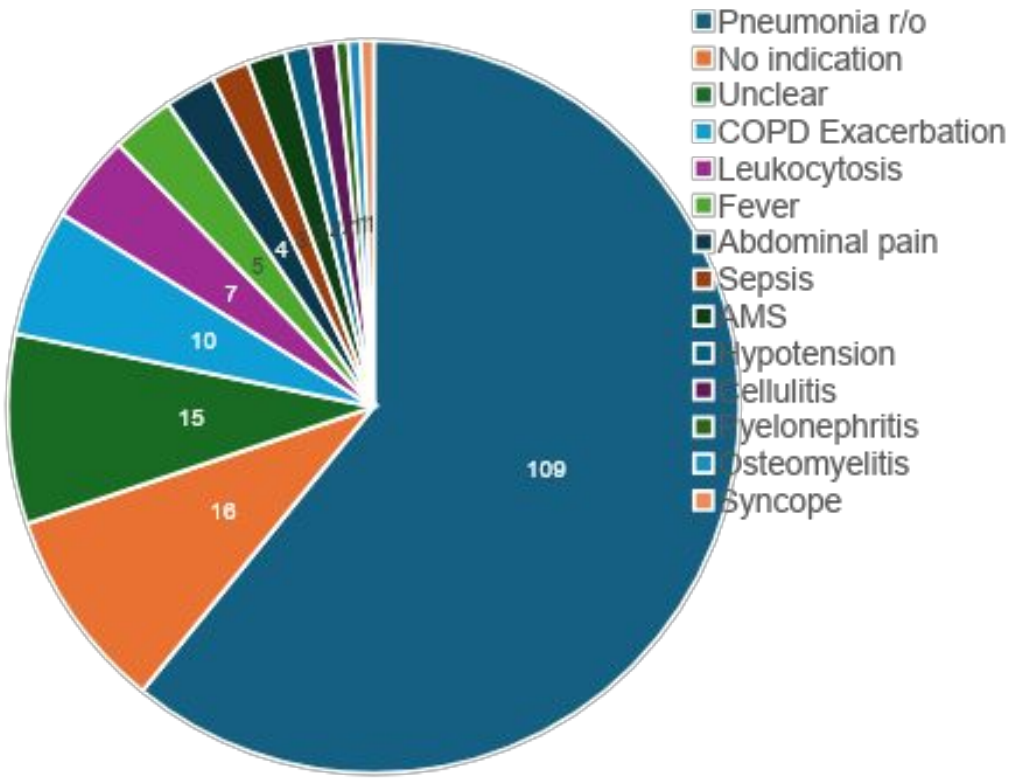
Procalcitonin

- Multiple, recent large RCTs suggest no benefit to procalcitonin testing outside of workup of febrile infant
- From March 2024-Feb 2025: over 1M in consumable costs for PCT
- Stewardship – perform systematic review by disease state, adult and peds
- Lab – pulled data, assessed equipment

Chart review of 1 month of orders from four high volume hospitals

N=755		Antibiotics After PCT Result	
		NO n=252	YES n=503
PCT result	Negative n=453	179 (24%)	274 (36%) *[average **4 days duration** inpatient abx after result; 23 (8%) discontinued abx within 24 hours]*
	Positive n=302	69 (9%)	233 (31%)

PCT indication and informativeness



*Did a **negative** PCT result impact the decision to stop or withhold antibiotics?* (N=179)

Yes = 3% (6)

Maybe = 26% (47)

No = 70% (126)

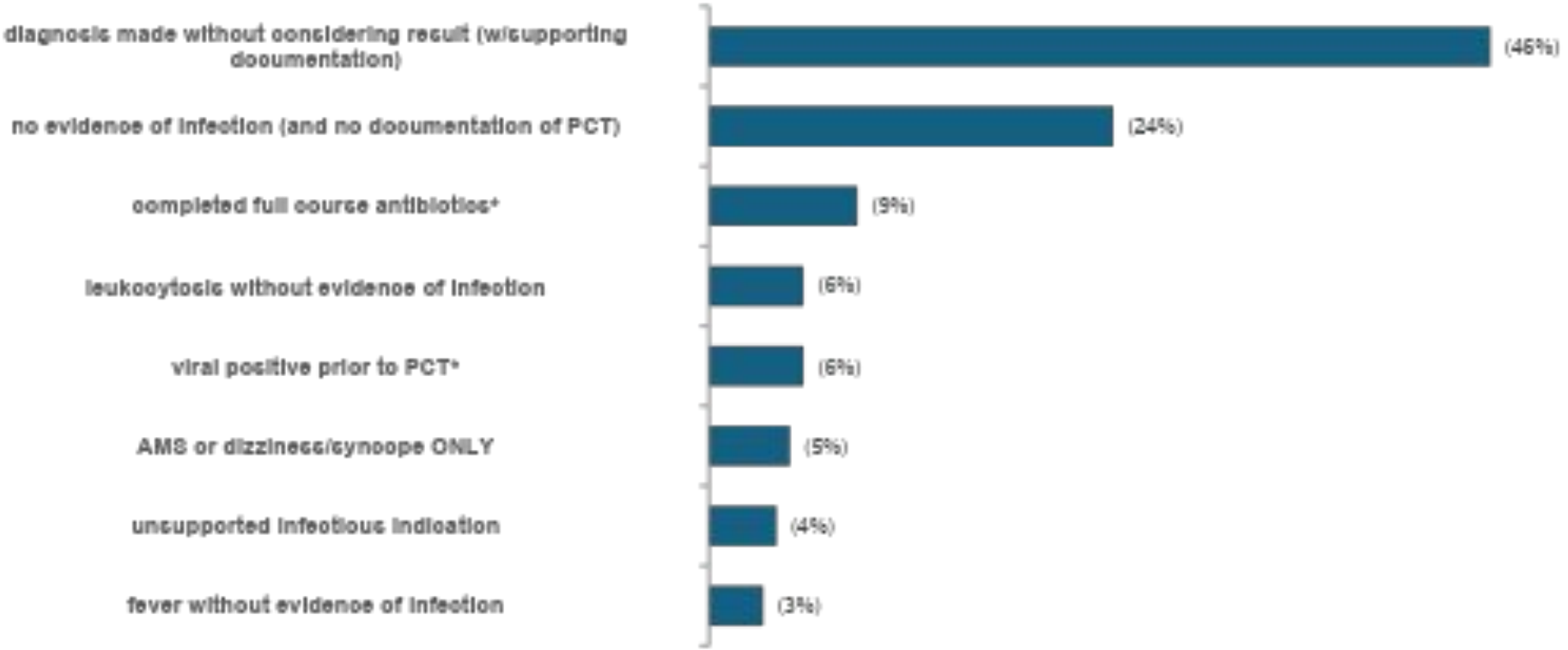
Details of the 6 instances when a negative PCT informed antibiotic decision ("Yes")

Providers specifically documented negative result as reason for withholding abx

5 out of 6 already decided to withhold antibiotics before PCT result

	Radiology	Clinical
Pneumonia (n=5)	No	Pleuritic chest pain (only)
	No	Lung malignancy/collapsed lung, worsening productive cough, acute respiratory failure requiring intubation
	Yes	New/worsening productive cough, acute symptoms & duration > 5 days, viral neg
	Yes	CHF, leukocytosis
	Yes	New/worsening productive cough, bronchiectasis
Cellulitis (n=1)	Discuss role in r/o cellulitis infectious mimics?	

Reasons the negative PCT result did not impact antibiotic decision making ("No")



**Not mutually exclusive. Two patients completed a full course of antibiotics and had a positive viral result prior to PCT*

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Biomarker-Guided Antibiotic Duration for Hospitalized Patients With Suspected Sepsis•

The ADAPT-Sepsis Randomized Clinical Trial

Paul Dark, MD, PhD; Anower Hossain, PhD; Daniel F. McAuley, MD; David Brealey, MD; Gordon Carlson, MD; Jonathan C. Clayton, MPhil, MSc; Timothy W. Felton, PhD, MD; Belinder K. Ghuman, BSc; Anthony C. Gordon, MBBS, MD; Thomas P. Hellyer, MD; Nazir I. Lone, MD; Uzma Manazar, MSc; Gillian Richards; Iain J. McCullagh, MD; Ronan McMullan, MD; James J. McNamee, MD; Hannah C. McNeil, BSc; Paul R. Mouncey, MSc; Micheal J. Naisbitt, MD; Robert J. Parker, MD; Ruth L. Poole, MPhil;

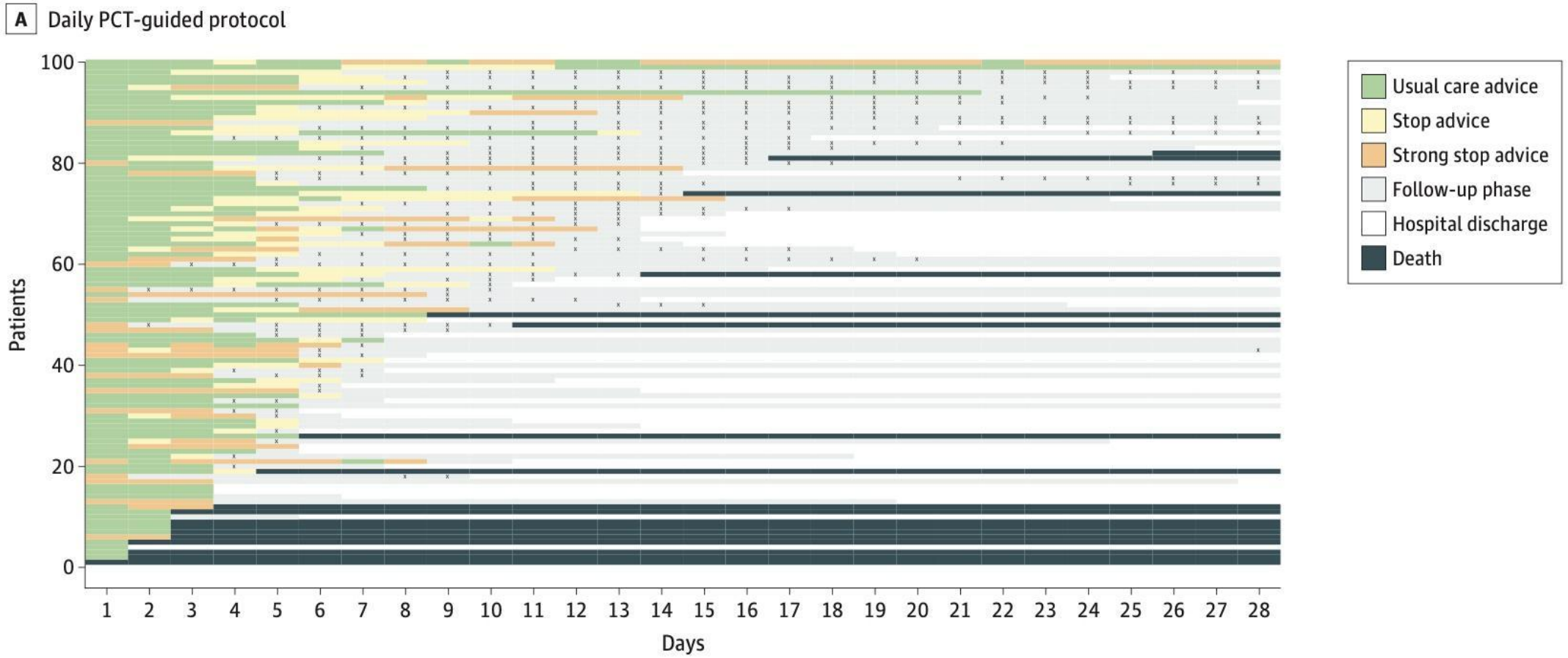
"There was a significant reduction in antibiotic duration from randomization to 28 days for those in the daily PCT-guided protocol compared with standard care (mean duration, **10.7** [SD, 7.6] days for standard care and **9.8** [SD, 7.2] days for PCT; mean difference, 0.88 days; 95% CI, 0.19 to 1.58, P = .01)."

eTable 29: DURATION IN DAYS BETWEEN RANDOMIZATION AND FIRST STOP/STRONG STOP ADVICE

		Daily PCT-guided protocol	Daily CRP-guided protocol
Duration (days) between randomisation and first stop advice production - mean (SD) [N]	SUGGEST stop	3.7 (1.9) [502]	3.7 (2.3) [519]
	STRONG stop	3.5 (3.8) [248]	5.1 (4.0) [139]
Total antibiotic duration (days) for the sepsis period- mean (SD) [N]		7.0 (5.7) [893]	7.4 (6.0) [889]

SD: Standard Deviation

Interventions and outcomes on day to day bases



A closer look

ABX stopped day after STOP advice given (i.e., PCT 'worked') in 8% (4/45).

STOP advice ignored for 2+ days 18/45 (40%).

PCT irrelevant to management in 20/45 (44%).

For 2 pts Abx were stopped 2 days after STOP signal

1	Died Day 1
2	Died Day 2
3	Died Day 2
4	Usual care advice x 1 day, discharged day 2
5	Died Day 2
6	Strong stop advice x 2 days, died day 3
7	Usual care advice x 2 days, then died day 3
8	Usual care advice x 2 days, then died day 3
9	Usual care advice x 2 days, then died day 3
10	Usual care advice x 2 days, off abx day 3-5, discharge day 6
11	Usual care advice x 2 days, then died day 3
12	Usual care advice x 1 day, strong stop x 2 days, died day 4
13	Strong stop x 3 days, off abx day 4
14	Usual care x 3 days, off abx day 4-6, discharge day 7
15	Usual care x 3 days, discharge day 4
16	Usual care x 3 days, discharge day 4
17	Strong stop x 3 days, off abx day 4
18	Strong stop x 1 day, off abx day 2, received abx day 8 and 9
19	Usual care day 1-3, stop advice day 4, died day 5
20	Usual care day 1-3, abx day 4, off abx day 5-7, discharge day 8
21	Strong stop day 1, usual care day 2, strong stop day 3-6, usual care day 7, strong stop day 8, off abx 9-10, discharge day 11
22	Usual care day 1-2, stop day 3, abx day 4, off abx day 5-18, discharge day 19
23	Usual care day 1-4, off abx day 5, discharged day 6
24	Usual care day 1, strong stop day 2-5, discharged day 6
25	Usual care day 1, stop day 2, strong stop day 3-4, abx day 5, off abx day 6-24, discharge day 25
26	Usual care day 1-5, died day 6
27	Usual care day 1-3, stop day 4, abx day 5, discharge day 6
28	Usual care day 1-4, stop day 5, off abx day 6-13, discharge day 14
29	Usual care day 1-4, stop day 5, off abx day 6-10, discharge day 11
30	Usual care day 1, stop day 2, strong stop day 3-4, abx day 5, off abx day 6, discharge day 7
31	Strong stop day 1-3, abx day 4-5, discharge day 6
32	Usual care day 1-5, off abx day 6-28
33	Usual care day 1-3, abx day 4-5, off abx day 6-7, discharge day 8
34	Usual care day 1-5, stop day 6, off abx day 7-28
35	Strong stop day 1-5, abx day 6, off abx day 7-13, discharge day 14
36	Usual care day 1-3, stop day 4-5, abx day 6, discharge day 7
37	Usual care day 1-4, stop day 5-6, off abx day 7-11, discharge day 12
38	Strong stop day 1-3, off abx day 4, abx day 5-7, off abx day 8-28
39	Usual care day 1-2, stop day 3, abx day 4, off abx day 5, abx day 6-7, discharge day 8
40	Usual care day 1-3, stop day 4-5, strong stop day 6, off abx day 7-28
41	Usual care day 1-5, stop day 6-7, discharge day 8
42	Strong stop day 1-5, abx day 6-7, off abx day 8, discharge day 9
43	Strong stop day 1, stop day 2, strong stop day 3-5, abx day 6, off abx day 7-27, abx day 28
44	Strong stop day 1, usual care day 2, strong stop day 3, usual care day 4, strong stop day 5-6, abx day 7, off abx day 8-28

Procalcitonin Removal

- Official as of 9/27/25
- Key stakeholder groups – critical care, peds, pulmonology
- Removed from all EMRs; provided paper flier for non-UPMC providers ordering from UPMC sites; removed from send-out
- Published systemwide guidance

UPMC System Procalcitonin Guidelines

Use of procalcitonin at UPMC

- **Procalcitonin is only available to order at UPMC in patients 90 days of age or younger for the workup of the febrile infant.**
  - A threshold of >0.5 ng/mL considered abnormal.[1]
- Procalcitonin should not be utilized to initiate antibiotics or guide the duration of antibiotics in any other condition.
- Procalcitonin is not available as a send-out lab at UPMC. All UPMC hospitals that care for infants 90 days of age or younger have procalcitonin available, with the test restricted to patients in this age range.

Monday, October 27, 2025

10/27/2025 2:24 PM

> McCreary, Erin 10/9/2025 11:53 AM
> Everyone sharing a huge win - since 9/27, based on historic volumes, our system expected PCT usage was 1259 tests. We sent SEVEN (7)...

update - at this point we would have sent 3439 procalcitonin tests and we have only sent 15!!

❤️ 9 😮 2 🎉 😎

Scenario 2 (Progression of Scenario 1)

- Reminder:
  - 65yo M with COPD/CHF has 3d Hx SOB/Dry-Cough/temp ~100F
  - WBC 9K (40% PMNs, 50% Lymph, 8% Monocytes)
  - SCr 2.0 (baseline 1.3)
  - Interstitial infiltrates bilat lung fields on CXR

- Clinical Update:
  - O2 saturation 88-92%
  - RPP positive for influenza A+ (Ct value: 18)
  - BNP <100pg/mL (within normal range)
  - Procalcitonin 0.19
  - CRP 25 mg/L (normal <10mg/L)

- Hospital Course:
  - Admitted to Hospitalist service with diagnosis of pneumonia
  - Updraft inhalers ordered
  - Oseltamivir initiated
  - Ceftriaxone and Azithromycin continued by hospitalist

Would you recommend continuing antibiotics in this patient

Antibiotics in confirmed viral infections

Cole Wood, MD
Washington Regional Infectious Disease

Washington Regional

Recommendation	Strength and Evidence Quality	Factors that Strengthen the Recommendation	Factors that Weaken the Recommendation
2. Empiric antibacterial therapy for CAP with positive respiratory virus testing			
For adult outpatients without comorbidities who have clinical and imaging evidence of CAP and who have positive test result for a respiratory virus, we suggest not prescribing empiric antibiotics.	Conditional Very low-quality evidence 93% consensus	Low suspicion for bacterial coinfection (clinical history, low/normal inflammatory markers, clinical history, radiologic findings suggestive of viral etiology, viral pathogen with low prevalence of bacterial codetection) Higher risk of harm from antibiotic exposure (history of *Clostridioides difficile*, severe antibiotic allergy or adverse event) Patient preference to avoid antibiotic exposure	Suspicion of bacterial coinfection (long symptom onset, "double sickening," purulent sputum, elevated inflammatory markers, radiologic findings such as consolidative infiltrate, viral pathogen with high prevalence of bacterial codetection, exposure to *Mycoplasma pneumoniae*) High risk of harm if missed bacterial infection (elderly, pregnant, signs/symptoms suggestive of more severe illness) Barriers to follow-up or communication
For adult outpatients with comorbidities who have clinical and imaging evidence of CAP and who have positive test result for a respiratory virus, we suggest prescribing empiric antibiotics because of concern for bacterial-viral coinfection.	Conditional Very low-quality evidence 73% consensus	Suspicion of bacterial coinfection (long symptom onset, "double sickening," purulent sputum, elevated or increasing inflammatory markers, radiologic findings such as consolidative infiltrate) Low likelihood that virus identified explains etiology and severity of pneumonia (i.e., virus with low virulence or high risk of coinfection) High risk of harm if missed bacterial infection High illness severity, severe symptoms Higher number, severe, or poorly controlled comorbidities	Low suspicion of bacterial infection (clinical history, normal inflammatory markers, radiologic findings suggestive of viral etiology) High likelihood that virus identified explains etiology and severity of pneumonia (virus with high virulence, low risk of coinfection) Lower risk of harm if missed bacterial infection Lower illness severity Single, mild, or well-controlled comorbidities Higher risk of harm from antibiotic exposure (History of *C. difficile,* antibiotic allergy/adverse event) Patient preference to avoid antibiotic exposure
For adult inpatients with clinical and imaging evidence of nonsevere CAP who have positive test result for a respiratory virus, we suggest prescribing empiric antibiotics because of concern for bacterial-viral coinfection.	Conditional Very low-quality evidence 80% consensus	Same as above	Same as above
For adult inpatients with clinical and imaging evidence of severe CAP who have positive test result for a respiratory virus, we suggest prescribing antibiotics because of concern for bacterial-viral coinfection	Conditional Very low-quality evidence 100% consensus	Sepsis, severe respiratory failure, elevated or increasing inflammatory markers Chest radiograph showing consolidation infiltrates	Higher risk of harm from antibiotic exposure (history of *C. difficile*, antibiotic allergy, or antibiotic adverse event)

Table 5. Comorbidities that May Warrant Antibiotic Therapy for Outpatients with Community-acquired Pneumonia Who Have a Positive Test Result for a Respiratory Virus

Comorbidity (See Footnotes for Further Definitions and Examples)	Percentage of Committee Members Who Voted This Condition that May Warrant Antibiotics
Greater than 50% agreement	
Chronic pulmonary disease other than asthma	82
End-stage liver disease	71
End-stage renal disease	65
Cardiovascular disease	53
Alcoholism	53
Neoplastic disease	53
Less than 50% agreement	
Neurological disease	47
Chronic liver disease	35
Malnutrition	35
Current smoker	35
Corticosteroid therapy* (<20 mg daily or <4 wk)	30
Diabetes mellitus	29
Chronic kidney disease	24
HIV* (CD4, >200)	24
Asthma	21
Rheumatological diseases* (not receiving immunosuppressants)	18
Obesity (BMI, >30 kg/m^2)	12

AMERICAN THORACIC SOCIETY DOCUMENTS

Diagnosis and Treatment of Adults with Community-acquired Pneumonia

An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America

Joshua P. Metlay*, Grant W. Waterer*, Ann C. Long, Antonio Anzueto, Jan Brozek, Kristina Crothers, Laura A. Cooley, Nathan C. Dean, Michael J. Fine, Scott A. Flanders, Marie R. Griffin, Mark L. Metersky, Daniel M. Musher, Marcos I. Restrepo, and Cynthia G. Whitney; on behalf of the American Thoracic Society and Infectious Diseases Society of America

This official clinical practice guideline was approved by the American Thoracic Society May 2019 and the Infectious Diseases Society of America August 2019

Question 14: In Adults with CAP Who Test Positive for Influenza, Should the Treatment Regimen Include Antibacterial Therapy?

Recommendation. We recommend that standard antibacterial treatment be initially prescribed for adults with clinical and radiographic evidence of CAP who test positive for influenza in the inpatient and outpatient settings (strong recommendation, low quality of evidence).

Clinical Infectious Diseases
VIEWPOINTS
IDSA OXFORD

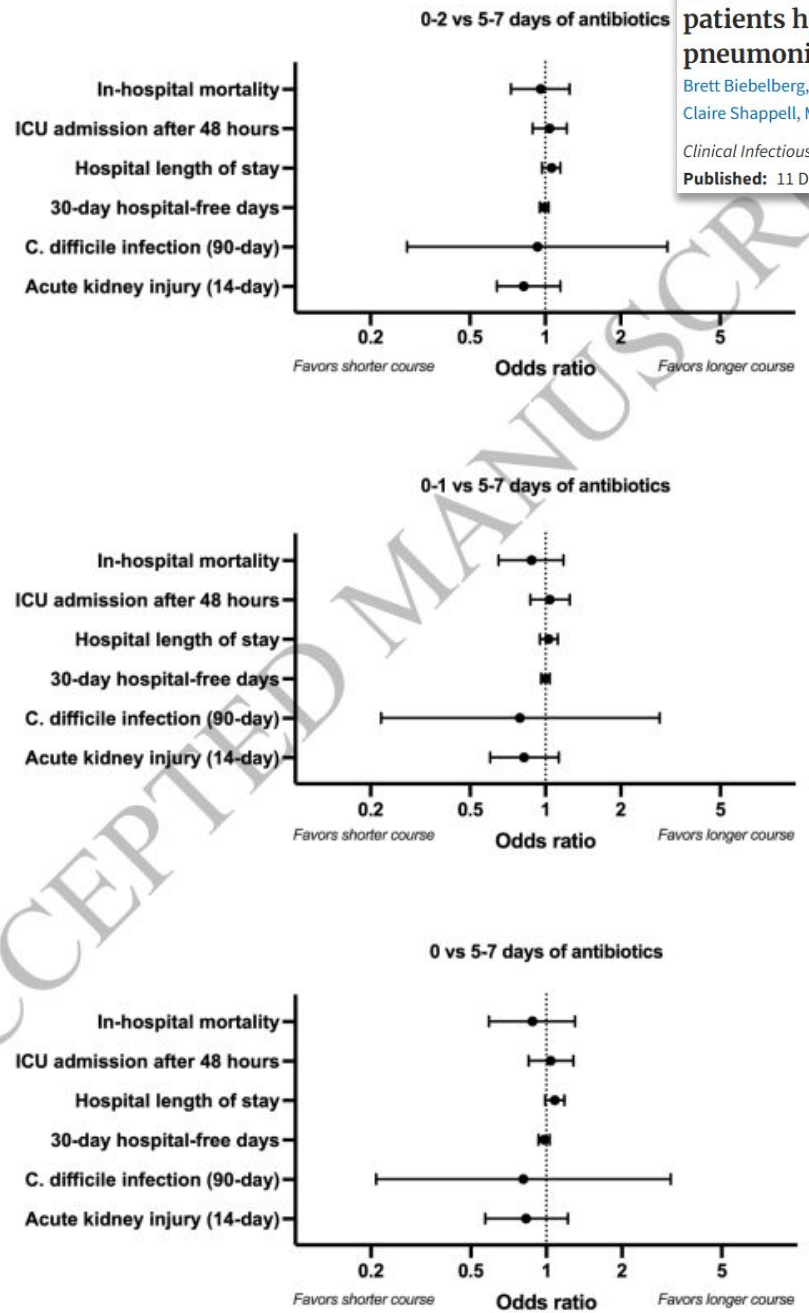
We Dissent: Lessons From the 2025 Community-Acquired Pneumonia (CAP) Guidelines

Leila S. Hojat,[1] Maryrose R. Laguio-Vila,[2] Liam R. Sullivan,[3] and Valerie M. Vaughn[4]

[1]Department of Internal Medicine, Division of Infectious Disease, Emory University, Atlanta, Georgia, USA; [2]Department of Internal Medicine, Division of Infectious Disease, Rochester Regional Health System, Rochester, New York, USA; [3]Infectious Disease, Corewell Health West Medical Group, Grand Rapids, Michigan, USA; and [4]Department of Internal Medicine, Division of General Internal Medicine, University of Utah, Salt Lake City, Utah, USA

- "no studies demonstrating benefit of antibacterial therapy for viral pneumonia"
- "no studies have found delayed antibacterial prescribing induces harm in mild-to-moderate severity pneumonia.
- "individualized, risk-based treatment decisions are critical"

Figure 2: Propensity-weighted outcomes in patients with suspected pneumonia and a positive respiratory viral assay treated with shorter vs longer antibacterial course



JOURNAL ARTICLE ACCEPTED MANUSCRIPT

Associations between antibiotic use and outcomes in patients hospitalized with community-acquired pneumonia and positive respiratory viral assays FREE

Brett Biebelberg, MD, Tom Chen, PhD, Cara McKenna, MPH, Sanjat Kanjilal, MD, MPH, Claire Shappell, MD, MPH, Chanu Rhee, MD, MPH, Michael Klompas, MD, MPH

Clinical Infectious Diseases, ciaf687, https://doi.org/10.1093/cid/ciaf687

Published: 11 December 2025 **Article history**

Scenario 3 (Progression of current case)

- Reminder:
  - 65yo M with COPD/CHF has 3d Hx SOB/Dry-Cough/temp ~100F
  - Admitted with Influenza A pneumonia, on Tamiflu +/- abx

- Clinical Update:
  - HD #5: He developed hallucinations/confusion thus foley was placed
  - Completed oseltamivir (and antibiotic course). Pneumonia clinically resolved.
  - Confusion resolved
  - Current meds: Metoprolol
  - Remained inpatient awaiting rehab

- Ongoing Course:
  - HD # 7 spiked fever 102F with suprapubic pain. HR 80s bpm. BP 130/80
  - UA with 100+ WBC, +Nitrites
  - UCx: *Pseudomonas aeruginosa*
    - [Resistant to cefepime, pip/tazo, mero, ceftazidime, aztreonam]
    - [Susceptible only to ciprofloxacin and levofloxacin]
  - BCx Negative at 48h
  - EKG: QTc 440ms
  - Sodium 140 mE/L, Potassium 4.0 mE/L, SCr 1.3 mg/dL (baseline GFR 80)
  - **Foley removed and started on Ciprofloxacin 500mg PO BID with plan for 7-day course**

Would you request a repeat EKG 48h after starting Ciprofloxacin in this patient

Risk factors for long QT syndrome

(not a complete list)

Non-modifiable

- Female sex
- Increased age
- Bradycardia
- Hypothyroidism
- CNS infection or tumor
- Obesity
- History of myocardial infarction
- Heart failure
- Pheochromocytoma
- Stroke
- Renal failure

Modifiable

- Electrolytes – replace K+, Mg++, Ca++
- **Medications**
- Sleep
- Diarrhea
- Eating licorice
- Alcohol intake

https://www.crediblemeds.org/ndfa_list

Slide modified from Dr. Meghan Jeffres, PharmD and Erin McCreary, PharmD

Antimicrobials Associated with High Risk of QTc prolongation and *torsade's de points*

- Fluoroquinolones:
  - Ciprofloxacin
  - Moxifloxacin
  - Levofloxacin

- Azoles:
  - Fluconazole
  - Voriconazole

- Macrolides:
  - Azithromycin

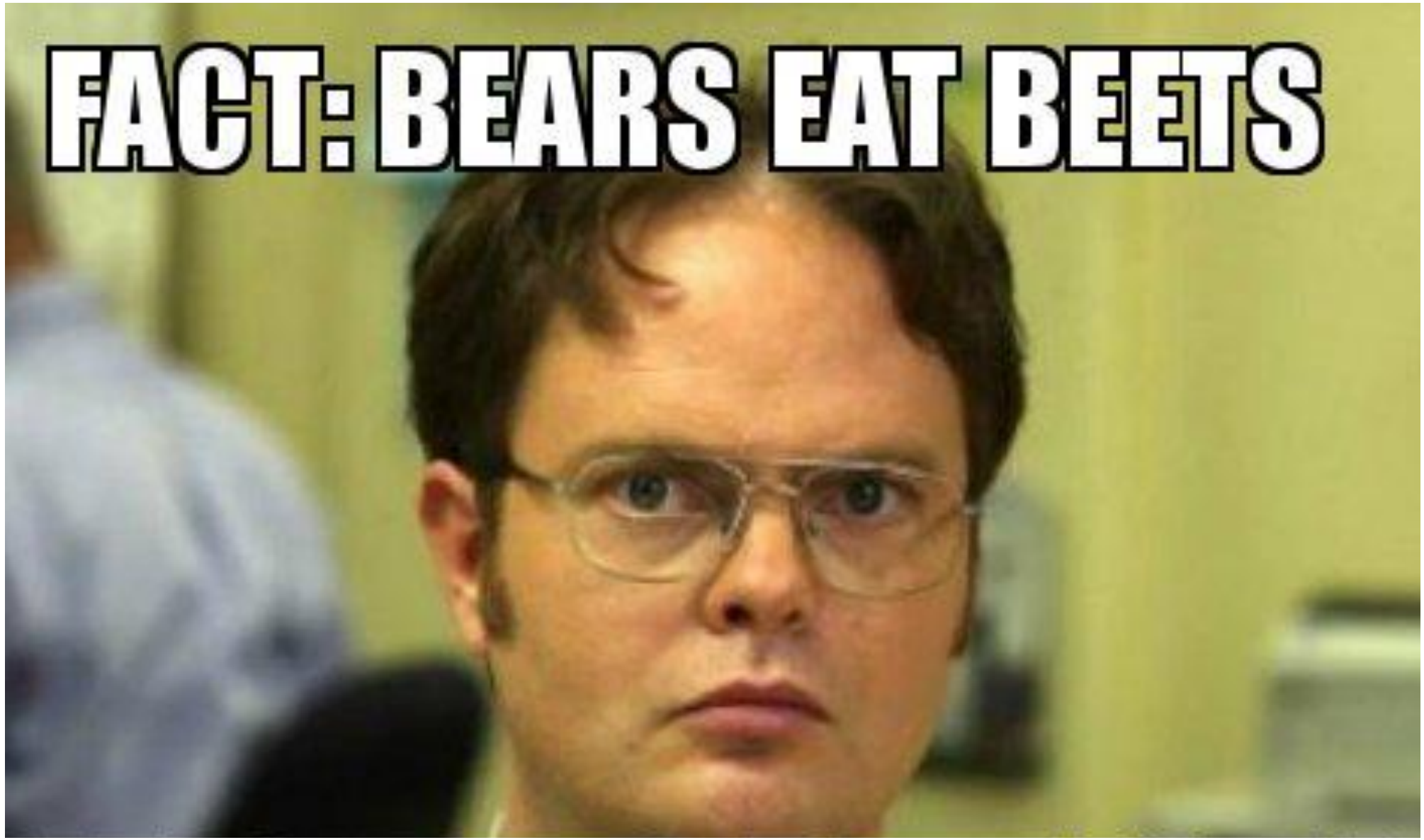
- Hydroxychloroquine

Drug	Details	Mean change in QTc
Ciprofloxacin[3]	1500mg once	2.27-4.93 ms
Levofloxacin[3]	1000mg once	3.53-4.88 ms
Fluconazole[4]	1200mg/day	3.1 ms
Azithromycin[2]	500mg once	5 ms
Moxifloxacin[3]	800mg once	16.34-17.83 ms
Clarithromycin[1]	500mg once	20 ms

QTc prolongation is generally dose and concentration-dependent

Slide shared/modified from Dr. Erin McCreary, PharmD

1. Biaxin FDA Drug Label
2. Zithromax FDA Drug Label
3. doi:10.1016/s0009-9236(03)00009-2
4. doi:10.1097/QAD.0000000000001961


FACT: BEARS EAT BEETS

FACTS

- FQ block cardiac potassium channels prolonging QTc when concentration >8x therapeutic dosing[1]
- Estimated incidence of TdP is very low[2]:
  - 0.3 per 10 million Ciprofloxacin Rx
  - 5.4 per 10 million Levofloxacin Rx
- Ciprofloxacin/Fluconazole Combination increases QTc[3]:
  - Study of 170 pts (88% heme malignancies; 92% on other QTc prolonging drugs)
  - 4.4% increased above normal [general population 5-11%]
  - QTc increased: 10.7ms
- Case reports exist

1. Kang et al. Mol Pharm 2001
2. Frothingham et al. Pharmacother 2001
3. Berger et al. B J Clin Pharm 2018

J Antimicrob Chemother 2025; 81: dkaq020
https://doi.org/10.1093/jac/dkaq020

Journal of Antimicrobial Chemotherapy 50 years

The effect of oral ciprofloxacin at conventional doses on the QT interval in a tertiary outpatient setting

Weber Liu[1,2,3,4], Hugh G. Dickson[2,4,5], Hany Dimitri[2,4], Yashodha Shankar Pani[2,4,5], Jayanathi Ramanathan[2,4,5,7], Dana West[5], Sarah Tima[5] and Winston Thai[2,4,5]

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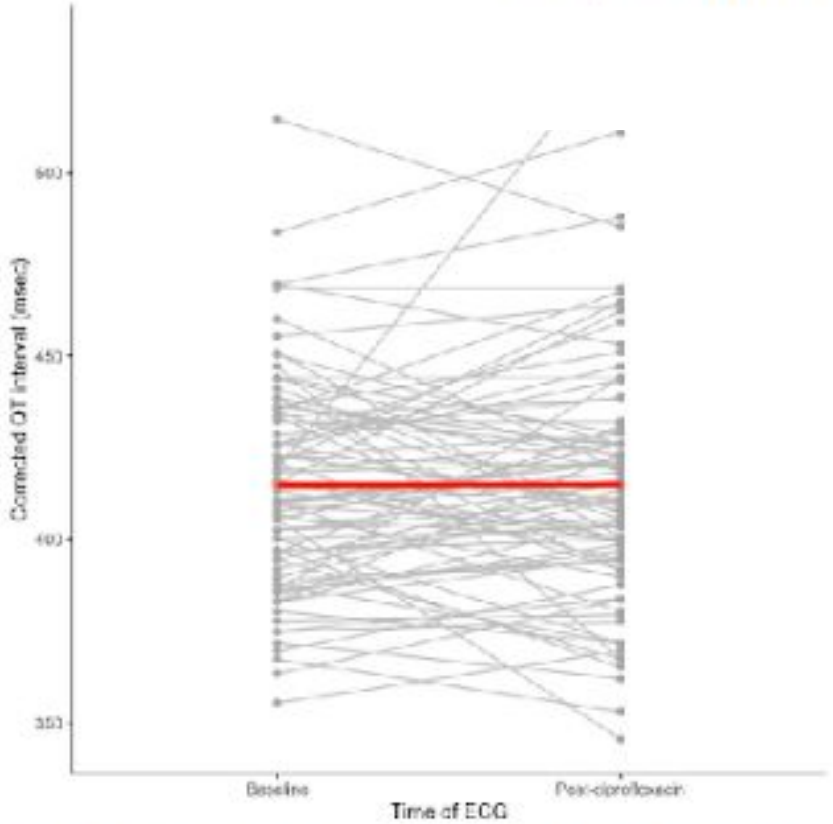


N=88	Baseline EKG	Follow up EKG
QTc	416ms	416ms

N=88	Without concomitant QTc-prolonging agents	With concomitant QTc-prolonging agents
QTc >500	0/51 (0%)	2/37 (5.4%)

Observational Study > Circ Cardiovasc Qual Outcomes. 2013 Jul;6(4):479-87.
doi: 10.1161/CIRCOUTCOMES.113.000152. Epub 2013 May 28.

Development and validation of a risk score to predict QT interval prolongation in hospitalized patients

James E Tisdale [1], Heather A Jaynes, Joanna R Kingery, Noha A Mourad, Tate N Trujillo, Brian R Overholser, Richard J Kovacs

Risk Factor	Points
Age ≥ 68 years	1
Female sex	1
Loop diuretic	1
Serum K^+ ≤ 3.5 mEq/L	2
Admission QTc ≥ 450 msec	2
Acute myocardial infarction	2
Sepsis	3
Heart failure	3
1 QTc-prolonging drug	3
≥2 QTc-prolonging drug	3
Maximum Risk Score	**21**

Risk Category	Risk Score
Low	<7
Moderate	7-10
High	≥11

ECG Monitoring suggested for: Tisdale risk ≥ 11 or baseline QTc > 500 msec

High risk score
Sensitivity = 0.74
Specificity = 0.77
PPV = 0.79
NPV = 0.76

Tisdale J , et al. Circ Cardiovasc Qual Outcomes. 2013

Slide shared/modified from Dr. Erin McCreary, PharmD

Worth tackling systematically?

- Implemented CDS alert to prevent drug-induced QT prolongation
- 178,097 hospitalizations ; 102,847 patients
- Alert fired in 8.4% of encounters
  - 60.13% provider compliance
- Alert successfully identified high risk patients (OR 2.28) but had no impact on risk of QT prolongation or risk of mortality
- No evidence of an effect of provider action on risk of QT prolongation; no relationship with any specific medication

Observational Study > J Med Internet Res. 2025 Apr 14:27:e68256. doi: 10.2196/68256.

Impact of an Alert-Based Inpatient Clinical Decision Support Tool to Prevent Drug-Induced Long QT Syndrome: Large-Scale, System-Wide Observational Study

Katy E Trinkley [1], Steven T Simon [2], Michael A Rosenberg [2]

Slide shared/modified from Dr. Erin McCreary, PharmD

Thoughts

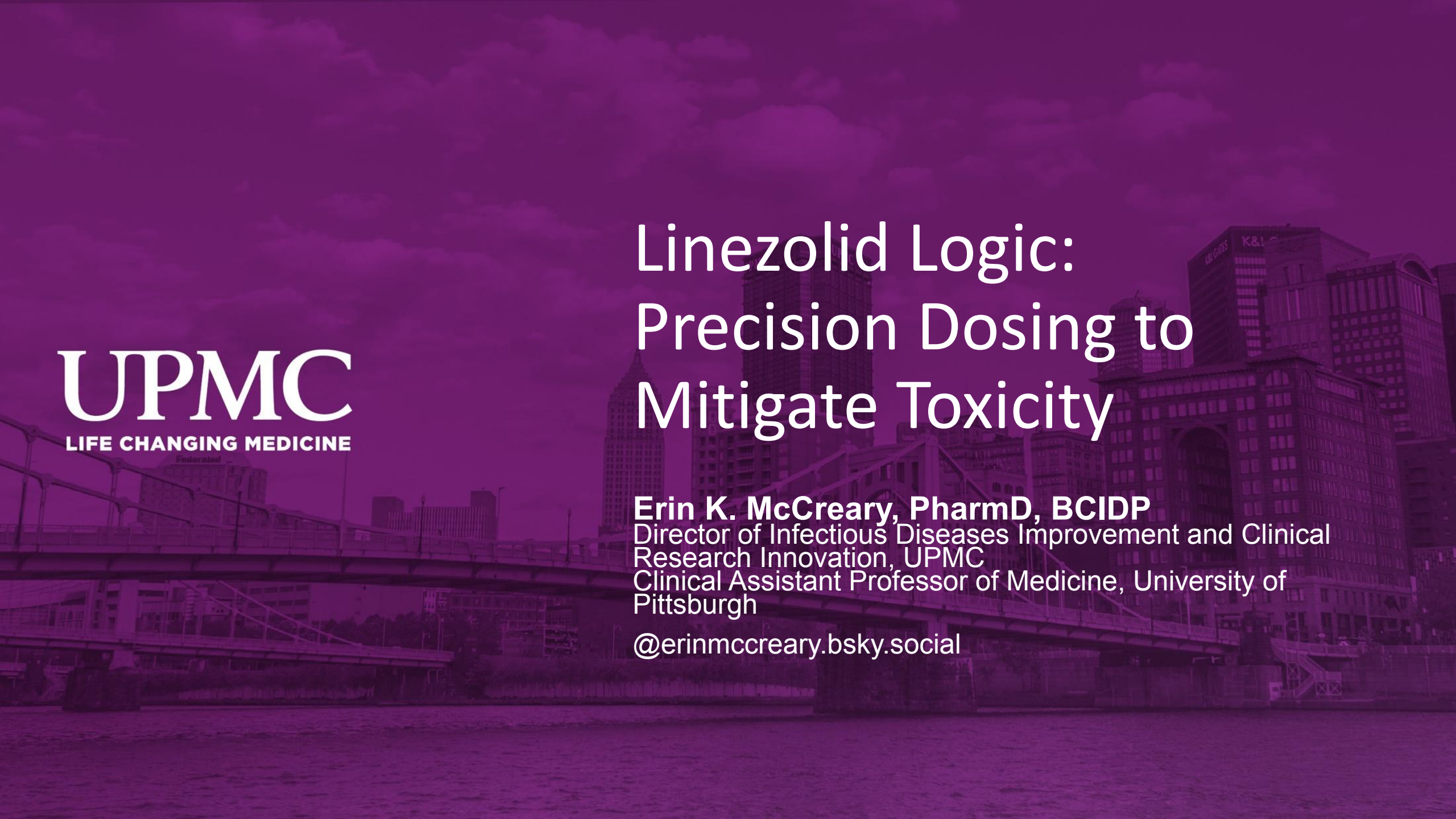
- Clinically significant prolonged QTc leading to TdP is rare
- Medication interactions is not unique and should always be considered when treating complicated infections
- High risk patients should be monitored:
  - Anti-arrhythmic meds, cardiac history, electrolyte dysfunction….
- Balance other medication modification vs patient risk

Scenario 4 (New Case)

- 44yo F with Cirrhosis on liver transplant list admitted with hemoptysis:
  - WBC 20K, Platelets 54K
  - AKI (SCr 4.1; GFR 13), baseline ~2.0
  - Hypoalbuminemia (2.3 g/dL; normal 3.4-5.4 g/dL)
  - Pleural effusion

- Hospital Course:
  - Started on ceftriaxone
  - Chest tube placed
  - Enterococcus faecium (linezolid MIC=1) isolated from chest tube
  - BCx negative
  - Started on linezolid 600mg PO BID

Would you obtain linezolid levels during treatment for VRE-empyema in this patient



Linezolid Logic: Precision Dosing to Mitigate Toxicity

Erin K. McCreary, PharmD, BCIDP
Director of Infectious Diseases Improvement and Clinical Research Innovation, UPMC
Clinical Assistant Professor of Medicine, University of Pittsburgh

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It was right there the whole time

"Renal Insufficiency: The pharmacokinetics of the parent drug, linezolid, are not altered in patients with any degree of renal insufficiency; however, the two primary metabolites of linezolid may accumulate in patients with renal insufficiency, with the amount of accumulation increasing with the severity of renal dysfunction. The clinical significance of accumulation of these two metabolites has not been determined in patients with severe renal insufficiency. Because similar plasma concentrations of linezolid are achieved regardless of renal function, no dose adjustment is recommended for patients with renal insufficiency. **However, given the absence of information on the clinical significance of accumulation of the primary metabolites, use of linezolid in patients with renal insufficiency should be weighed against the potential risks of accumulation of these metabolites.**"

Zyvox FDA Approval 2002
Package Insert last updated 2011: Zyvox (linezolid) injection label (fda.gov)

Accumulation in renal impairment is seen clinically

TABLE 1 Concentrations of linezolid and its major metabolites stratified by renal impairment

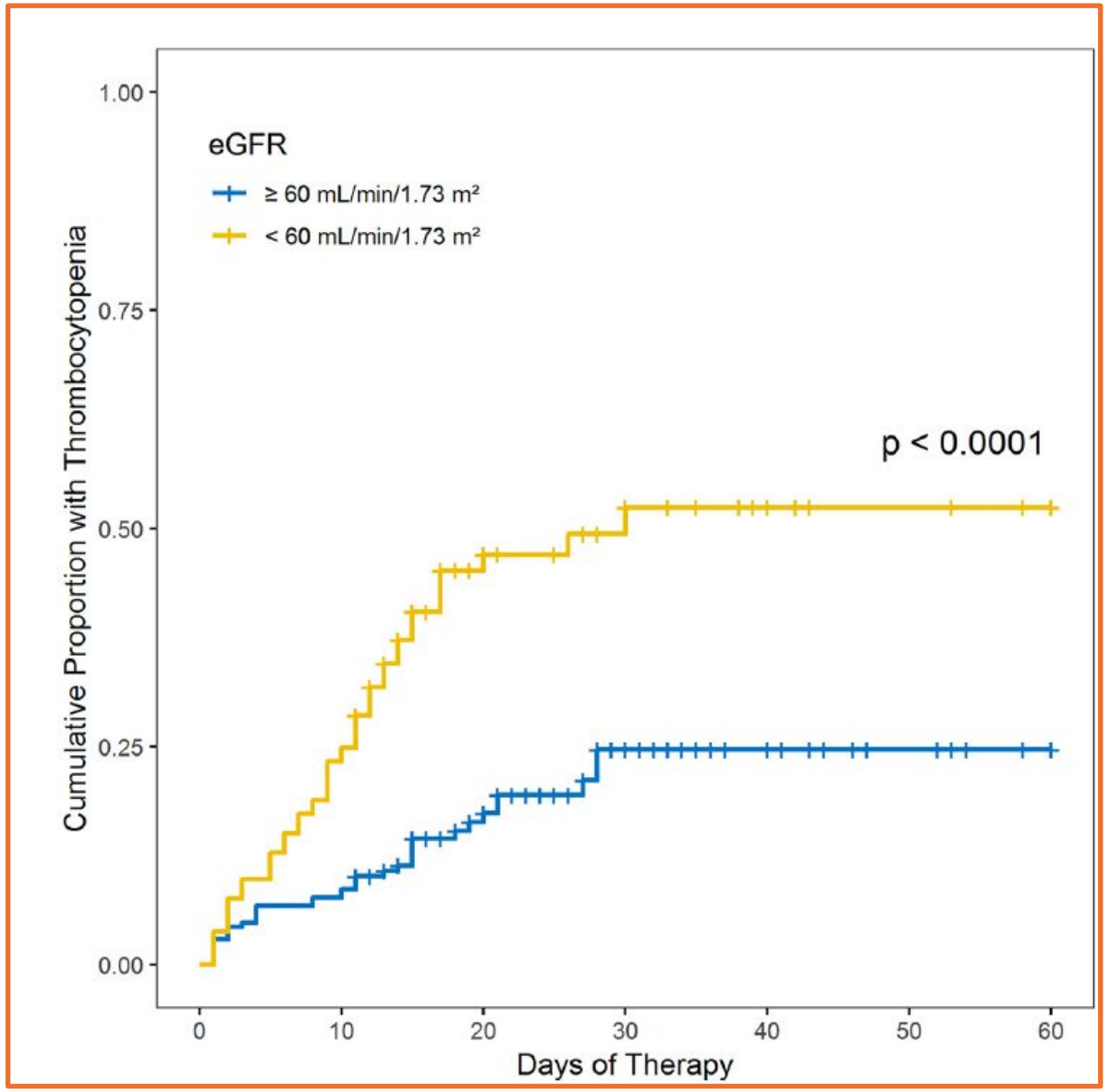
Variable	Total (n = 39)	Study group	
		No renal impairment (n =17)	Renal impairment[b] (n = 22)
No. of serum samples	138	41	97
No. of samples/patient	3 (2–4)	2 (2–3)	4 (2–6)
Concentration (mg/liter)[a]			
Linezolid	10.8 (6.3–17.4)	7.6 (4.4–14.3)	12.3 (8.0–18.1)
PNU-142300	4.4 (2.5–6.6)	1.6 (0.8–3.1)	5.2 (3.8–10.9)
PNU-142586	11.4 (6.2–19.4)	4.9 (2.7–7.0)	13.8 (9.7–24.6)
Time since last dose (h)	7.5 (3.6–9.7)	7.6 (3.6–9.8)	7.5 (3.5–9.6)

[a]Data are presented as medians (IQR).
[b]Renal impairment defined as eGFR of <60 ml/min/1.73 m².

Souza E, et al. AAC. 2020.

Renal Impairment

- More likely to accumulate drug and metabolites with renal impairment
- 2-fold increase in risk of thrombocytopenia with eGFR < 60



Brier ME, AAC, 2003
Crass R, AAC, 2019

This is seen in cirrhosis, too

Cirrhosis = 11.4x higher to achieve supratherapeutic conc. compared to control

	Cases* (n = 26)	Controls† (n = 26)	*P*
PK/PD data			
Cmin, ss (mg/L), median (IQR)	20.6 (17.4)	2.7 (11.3)	**<0.001**
Cmax, ss (mg/L), median (IQR)	34.1 (22.7)	16.5 (11.6)	**0.001**
Cmin, ss < 2 mg/L, n (%)	0 (0)	10 (38.5)	**0.002**
Cmin, ss > 10 mg/L, n (%)	20 (76.9)	7 (26.9)	**<0.001**
100% time > MIC, n (%)	26 (100)	16 (61.5)	**0.002**
Toxicity data			
Anemia‡, n (%)	7/25 (28.0)	6/25 (24)	0.747
Thrombocytopenia§, n (%)	13/25 (52.0)	8/24 (33.3)	0.187
Final platelet count, median (IQR)§	81 (87)	203 (14)	**0.001**
Final platelet count <100.000/mm^3§, n (%)	17/25 (68.0)	4/24 (16.7)	**<0.001**

Luque S, et al. Therapeutic Drug Monitoring. 2019.

Defining the therapeutic window for linezolid

Pharmacokinetic Measurement	Lower Threshold (Efficacy)	Upper Threshold (Toxicity)
Time spent above the MIC (T>MIC)	>82–98%[40] or >85%[42]	N/A
Duration of therapy	N/A	Usually >14–28 days[42,83,91]
Area under the concentration versus time curve from 0 to 24 hours (AUC)	>160–400 mg × h/L depending on the MIC of the infecting pathogen[33,40,42]	>280–300 mg × h/L[33,42] or >400–800 mg × h/L[87] depending on the duration of therapy and severity of illness; the proposed higher end of this range may be tolerable for less than 2 weeks[87]
AUC:MIC	>100 (may vary with infection site)[23,40,42,43]	Depends on duration of therapy and pathogen MIC
Trough concentration (C_{min})	>2 mg/L (may be higher depending on the MIC of the infecting pathogen)[48]	>7–8 mg/L[46,48]

Rao GG, et al. Ther Drug Monit. 2020
Cattaneo D, Expert Opin Drug Metab Toxicol, 2016

The higher the MIC, the harder it is to safely achieve your goal

MIC	AUC_{0-24} (mg.h/L)	AUC:MIC	Cmin (mg/L)
1	100	100	0.22
2	200	100	4.8
4	400	100	13.8

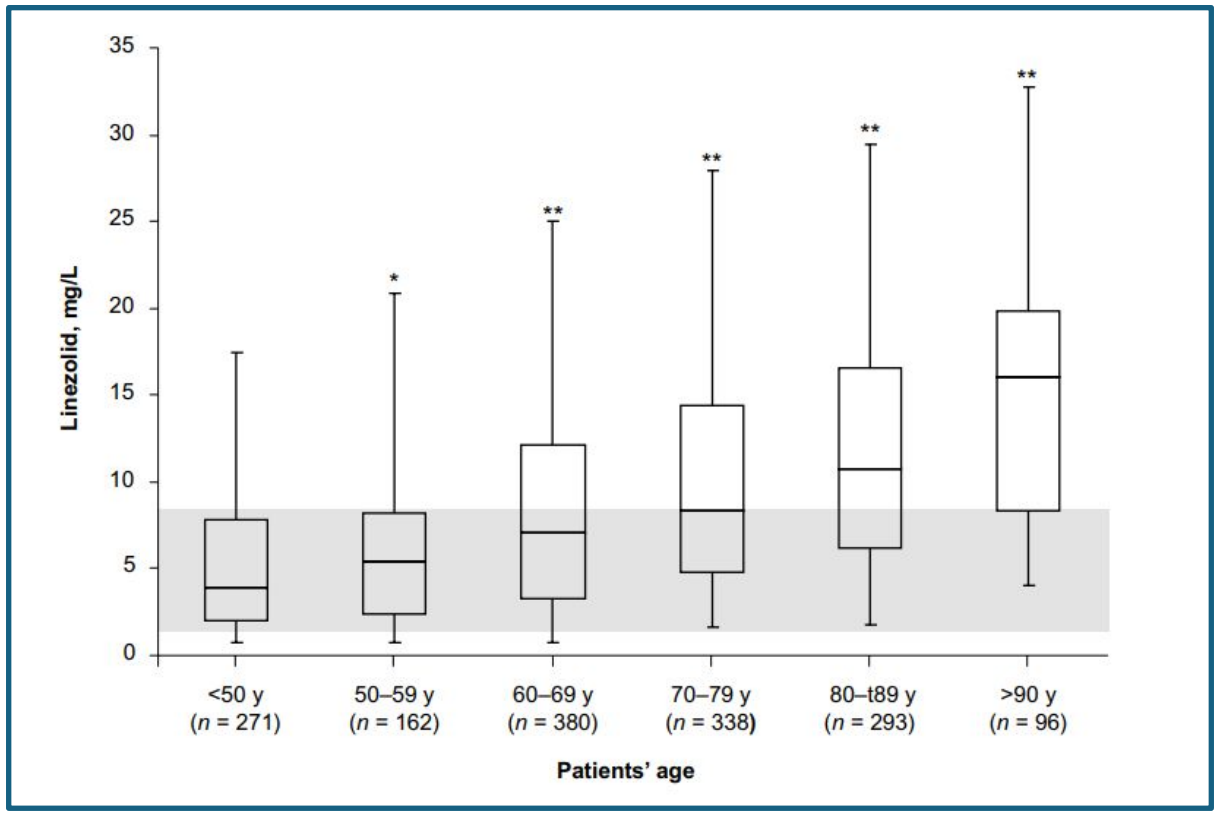
AUC:MIC > 100 associated with efficacy in Gram-positive infections

Correlates well with trough linezolid concentration (R^2 = 0.87)

Rao G, TDM, 2020
Adapted from Alsultan A, Saudi Pharm J, 2019
Slide modified from Dr Cindy Lau (Sydney, Australia)

Eldery

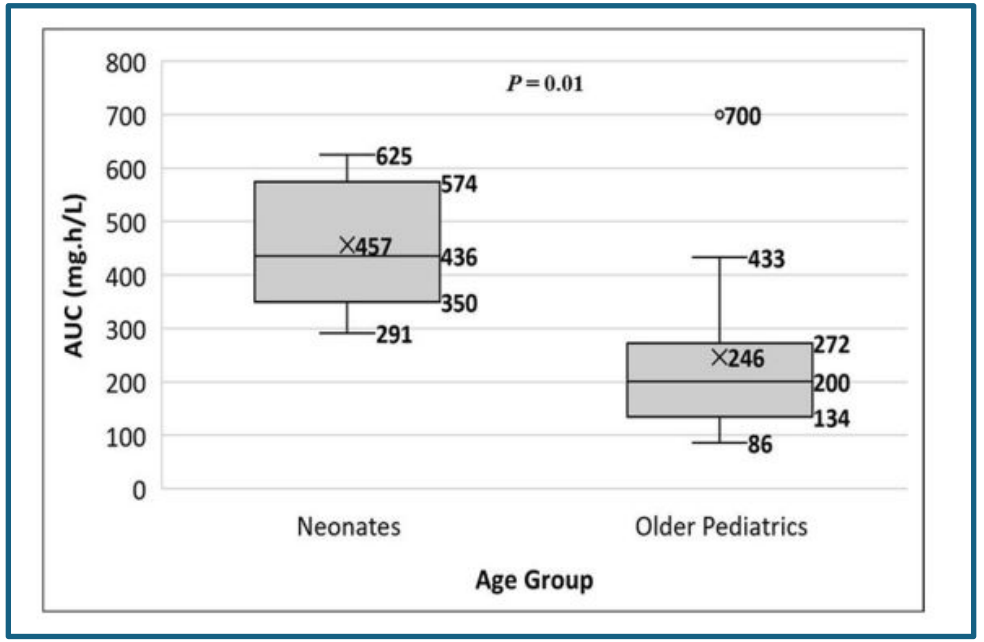
- Significant, progressive increment in linezolid troughs by decade (30% per decade of age)
- Supratherapeutic troughs
  - 30% of patients < 65
  - 50% of patients 65-80
  - 65% of patients >80
- Women had higher linezolid troughs than men
  - Difference remained when stratified by age

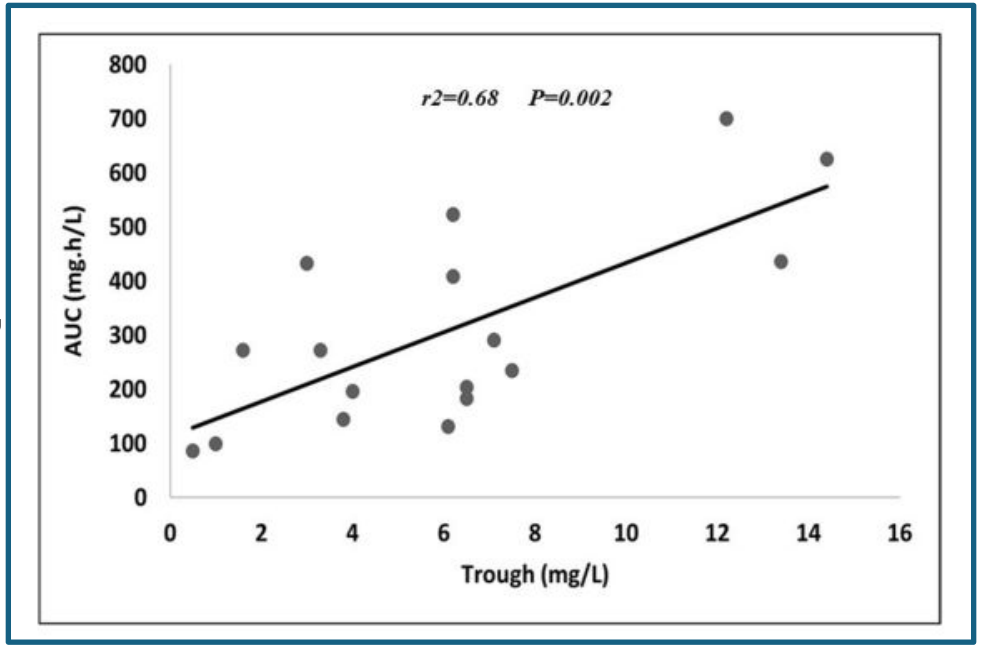


Cattaneo D, Clinical Pharmacokinetics, 2021
Cattaneo D, IJAA, 2016

Pediatrics

- 41% of pediatric patients achieve targets
  - 35% supratherapeutic
  - 24% subtherapeutic
- All patients with heme toxicity received linezolid > 7 days
- Age-related exposures
  - Newborn ~ adults
  - First week of life: ↑ clearance, then gradual decline
  - > 12 years ~ adults





Abouelkheir M, et al. Eur J Clin Pharmacol. 2024
Jungbluth G, Paediatr Infect Dis 2003

Obesity

Weight-based vs fixed dosing

- Lower weight group = higher concentrations
- 10mg/kg: similar concentrations

Dose escalation up to 450mg Q8H recommended with $CrCL_{CKD\text{-}EPI}$ > 60mL.min/1.73m^2

- 600mg Q8H not recommended due to overexposure risk

Target attainment for standard dose not achieved in patients >140kg

Morbid obesity may require dose increase

Cojutti P, Clin Pharmacokinet, 2018
Blackman A, AAC, 2021
Ehmann L, CMI, 2020
Cai Y, Expert Opin Investig Drugs, 2013

National Jewish Health

Advanced Diagnostic Laboratories
1400 Jackson Street. Denver, CO 80206
Client Services (p): 800.550.6227 (f): 800.652.9556
ClinRefLabs@njhealth.org njlabs.org

Patient Nar [redacted]
DOB: 7/27/
Gender: M
Medical Record #: [redacted]

Client Nan [redacted]
Physicia
Submitter ID
Account

[redacted]

Order # [redacted]
Collected:
Received:
Verified:

Infectious Disease Pharmacokinetics Laboratory

(p): 303.398.1422 (f): 303.270.2124

Drug Level	Conc.	Unit	Flags
Linezolid Level by HPLC	25.48	mcg/mL	

Crass RL, et al. AAC. 2019.
Boak LM, et al. AAC. 2014.

Recent Case

44yo F presents to ED early January with melena, coughing blood

PMH: alcohol use disorder in remission, decompensated alcohol-related **cirrhosis**, grade 2 esophageal varices, recurrent ascites

Recently hospitalized for 27 days with **AKI** and **VRE bacteremia**

Listed for liver transplant

Admission: ceftriaxone, octreotide, IV PPI □ to ICU

Pertinent labs day of admission:

Plt 136
SCr 3.4
eGFR 16
Albumin 2.3
WBC 18.4

Pleural fluid from Pleurex sampled next morning

Last Update: [redacted]
Collected: [redacted]
Specimen Desc: Pleural fluid

BODY FLUID CULTURE

Accessio
Special R

Gram Stain: Few WBCs present; No organisms seen
Culture: Rare Enterococcus faecalis
Rare Enterococcus faecium

ENTEROCOCCUS FAECIUM

	MIC (mcg/mL)	MIC Interpretation
Ampicillin	>8	Resistant
Daptomycin	4	Sensitive
Linezolid	1	Sensitive
Penicillin	>8	Resistant
Vancomycin	1	Sensitive

ENTEROCOCCUS FAECALIS

	MIC (mcg/mL)	MIC Interpretation
Ampicillin	<=2	Sensitive
Daptomycin	1	Sensitive
Linezolid	2	Sensitive
Penicillin	2	Sensitive
Vancomycin	2	Sensitive

- Rare enterococcus x2 species from pleurex cath
- Expect to find organisms with indwelling chronic catheters which can lead to infection but today there is no other evidence of untreated infection including benign appearing cell counts from pleural fluid
- I would hold off on treatment purely in the setting of positive pleural fluid culture from indwelling pleural catheter as we will need to differentiate colonization from infection
- Will have to follow temp curve, clinical stability, WBC etc in case infection does arise. If so will need to target these Enterococci at a minimum.

Hospital Day 7

- Patient acutely worsens
  - Fever (Tmax 39ºC)
  - Leukocytosis persists
  - Chills, sweats
  - Increasing cell counts in pleural fluid
- ID re-consulted initiate linezolid
- Liver Transplant on hospital day 11

Pertinent labs:

Plt 54
SCr 4.1
eGFR 13
Albumin 4
(replacing)
WBC 19.7

Last Update: [redacted]
Collected: [redacted]
Specimen Desc: Pleural fluid

BODY FLUID CULTURE

Accession N
Special Requ

Gram Stain: Few WBCs present; No organisms seen
Culture: Rare Enterococcus faecium

ENTEROCOCCUS FAECIUM

	MIC (mcg/mL)	MIC Interpretation
Ampicillin	>8	Resistant
Daptomycin	4	Sensitive
Linezolid	1	Sensitive
Penicillin	>8	Resistant
Vancomycin	1	Sensitive

Day	Linezolid Dose	Linezolid Concentration	eGFR	Platelets
Day 7, PM	600mg PO		17	54
Day 8, AM	600mg PO		16	56
Day 8, PM	600mg PO		16	56
Day 9, AM	600mg PO		13	65
Day 9, PM	600mg PO		13	65
Day 10, AM	600mg PO		11	53

Patient initiated on linezolid 600mg PO BID

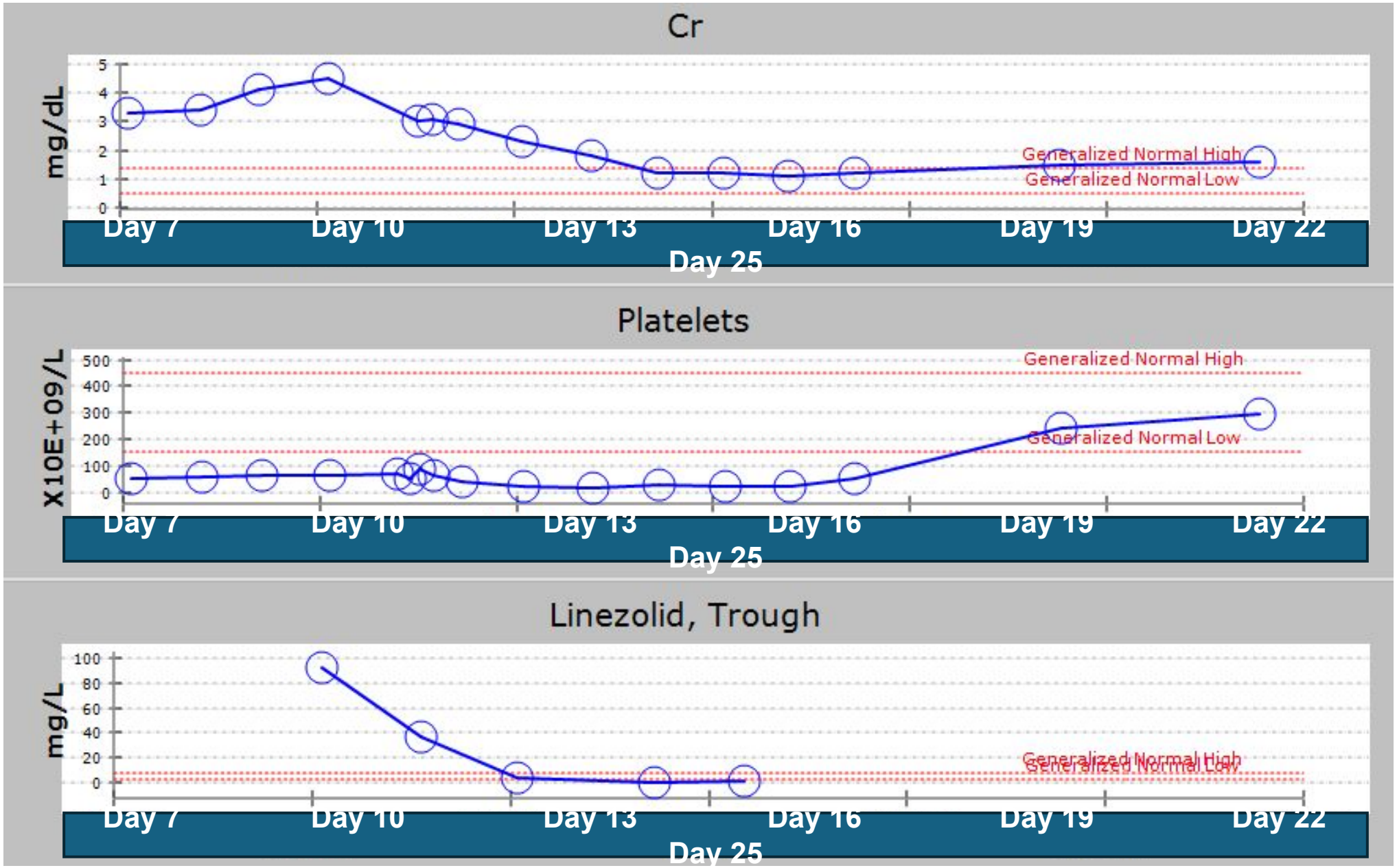
Day	Linezolid Dose	Linezolid Concentration	eGFR	Platelets
Day 7, PM	600mg PO		17	54
Day 8, AM	600mg PO		16	56
Day 8, PM	600mg PO		16	56
Day 9, AM	600mg PO		13	65
Day 9, PM	600mg PO		13	65
Day 10, AM	600mg PO	**92.4**	11	53

Received 5 doses, trough checked recommend HOLD further doses

Day	Linezolid Dose	Linezolid Concentration	eGFR	Platelets
Day 7, PM	600mg PO		17	54
Day 8, AM	600mg PO		16	56
Day 8, PM	600mg PO		16	56
Day 9, AM	600mg PO		13	65
Day 9, PM	600mg PO		13	65
Day 10, AM	600mg PO	92.4	11	53
Day 11, PM	HELD	36.5	18	38
Day 13, AM	HELD	3.9	26	16

Three days later, trough within goal range of 2-8 mg/L. Recommend single 300mg dose and repeat concentration in 24h

Day	Linezolid Dose	Linezolid Concentration	eGFR	Platelets
Day 7, PM	600mg PO		17	54
Day 8, AM	600mg PO		16	56
Day 8, PM	600mg PO		16	56
Day 9, AM	600mg PO		13	65
Day 9, PM	600mg PO		13	65
Day 10, AM	600mg PO	92.4	11	53
Day 11, PM	HELD	36.5	18	38
Day 13, AM	HELD	3.9	26	16
Day 13, PM	600mg PO		26	16
Day 15, AM	[None]	0.0	57	26
Day 15, PM	600mg PO		57	26
Day 16, PM	600mg PO	1.7	57	19
Day 17, AM	600mg PO		63	21
Day 17, PM	600mg PO		63	21
Day 18, AM	600mg PO		57	54


Cr
mg/dL
5
4
3
2
1
0
Generalized Normal High
Generalized Normal Low
Day 7
Day 10
Day 13
Day 16
Day 19
Day 22
Day 25
Platelets
X10E+09/L
500
400
300
200
100
0
Generalized Normal High
Generalized Normal Low
Day 7
Day 10
Day 13
Day 16
Day 19
Day 22
Day 25
Linezolid, Trough
mg/L
100
80
60
40
20
0
Generalized Normal High
Generalized Normal Low
Day 7
Day 10
Day 13
Day 16
Day 19
Day 22
Day 25

Hospital Day 18

- Patient discharges on 600mg PO BID to complete 14 days total
- Stop date outpatient = day 21

Day	Linezolid Dose	Linezolid Concentration	eGFR	Platelets
Day 10, AM	600mg PO	92.4	11	53
Day 11, PM	HELD	36.5	18	38
Day 13, AM	HELD	3.9	26	16
Day 13, PM	600mg PO		26	16
Day 15, AM	[None]	0.0	57	26
Day 15, PM	600mg PO		57	26
Day 16, PM	600mg PO	1.7	57	19
Day 17, AM	600mg PO		63	21
Day 17, PM	600mg PO		63	21
Day 18, AM	600mg PO		57	54

Precision dosing saved this patient:

- Excess toxicity
- Unnecessary change in antibiotic
- Home on oral therapy (no PICC necessary)
- Hospital LOS (avoidance of toxicity; no need to coordinate OPAT)

The UPMC Approach

- Linezolid drug concentrations may only be ordered by providers associated with infectious diseases consult services or antimicrobial stewardship teams
- Patients should receive linezolid for at least 72 hours before TDM is performed
- Linezolid drug concentrations may only be ordered for patients meeting the following criteria:
  - Requiring long term linezolid (greater than 2 weeks of therapy) **OR**
  - Requiring greater than 1 week of therapy AND a risk factor for thrombocytopenia or deranged pharmacokinetics:
    - ≥75 years old
    - Critically ill on ECMO or RRT
    - Pediatric patients
    - Pregnancy
    - Previous or current thrombocytopenia
    - Cirrhosis
    - BMI ≥ 40
    - Receiving other myelosuppressive agents
    - eGFR < 60mL/min
    - Trauma or burn
  - Requiring repeat trough concentrations after dose adjustment or change in renal function to confirm therapeutic range achieved
  - Requiring a peak concentration to confirm oral absorption for treatment of Nocardiosis or mycobacterial infections
- **Do not perform linezolid TDM for patients requiring 7 days or less of linezolid therapy**

Apple Podcasts Preview

50 min PLAY

Dosing Consult: Linezolid Therapeutic Drug Monitoring

Breakpoints

Health & Fitness

Listen on Apple Podcasts ↗

In the second episode of Breakpoints' Dosing Consult series, Drs. Ryan Crass (@crasspofungin) and Amit Pai (@DosingMatters) join Dr. Jillian Hayes (@thejillianhayes) to break down the 5 Ws and 1 H of linezolid TDM.

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Bibliography

Scenario 5

- 75yo F with Hx of recurrent UTIs presents to Primary Care Clinic for routine annual visit
- Current concern is that her urine smells funny
- She requests Urine testing to make sure she doesn’t have a UTI

To expedite results, would you order Urine PCR to assess for infection?

CUAJ | JAUC
Canadian Urological Association Journal | Journal de l'Association des urologues du Canada

Can Urol Assoc J. 2022 Apr 11;16(9):E484–E489. doi: 10.5489/cuaj.7677

Accuracy of molecular diagnostic techniques in patients with a confirmed urine culture: A systematic review and meta-analysis

Ximena Guzmán Robledo [1,2], Karla Valeria Orejuela Arcila [1], Sergio Hernando Mina Riascos [1,2], Herney Andrés García-Perdomo [1,2,✉]

- Multiplex-PCR and RT-PCR included in meta-analysis
- Up to 1/3 of patients with symptoms have negative culture

Guidance from PALTmed

A Need for a Time-Out: A Consensus Statement From the Post-Acute and Long-Term Care Medical Association (PALTmed) on the Use of Urine Polymerase Chain Reaction Testing for Urinary Tract Infections

Jessica Zering PharmD [a,*], Ghinwa Dumyati MD [b], Nicole Osevala MD [c], Muhammad Salman Ashraf MBBS [d,e], on behalf of PALTmed

[a] Healthcare Associated Infections Program, Washington State Department of Health, Shoreline, WA, USA
[b] Department of Medicine, Infectious Diseases Division and Center for Community Health and Prevention, University of Rochester Medical Center, Rochester, NY, USA
[c] Division of Geriatric Medicine, Penn State University, Hershey, PA, USA
[d] Healthcare-Associated Infections and Antimicrobial Resistance Program, Nebraska Department of Health and Human Services, Omaha, NE, USA
[e] Division of Infectious Diseases, University of Nebraska Medical Center, Omaha, NE, USA

Table 2
Comparison of Urine Culture and Urine PCR for UTI Diagnosis and Decision Making

Factors Impacting Decision Making Between Using Urine Culture and Urine PCR	Urine Culture	Urine PCR
Sensitivity and specificity for UTI diagnosis	90% and 89%[19]	Unknown
Can independently diagnose a UTI	No[1,2]	No[1,2]
Scope	Live organisms only[5,6]	Live and dead organisms[5,6]
Organisms detected	Clinically significant organisms, with the option to order specialized testing[20]	Detects up to 42 different organism types regardless of clinical significance[5,24]
Turnaround time for final result	Up to 72 h[6,23]	24 h[3,5,6]
Detects antibiotic resistance genes	No	Yes
Phenotypic susceptibilities	Yes	No, but can be performed separately[5]
Standardized organism thresholds (eg, CFUs/mL) for UTI Diagnosis	Yes[1,2]	No[6]
Impact of contamination	Yes[5,6,38,41]	Yes, can lead to detection of clinically irrelevant organisms[5,6,38,41]
Available non–manufacturer-funded clinical outcomes data for older adults	Yes	No[5]

JAMA Network Open

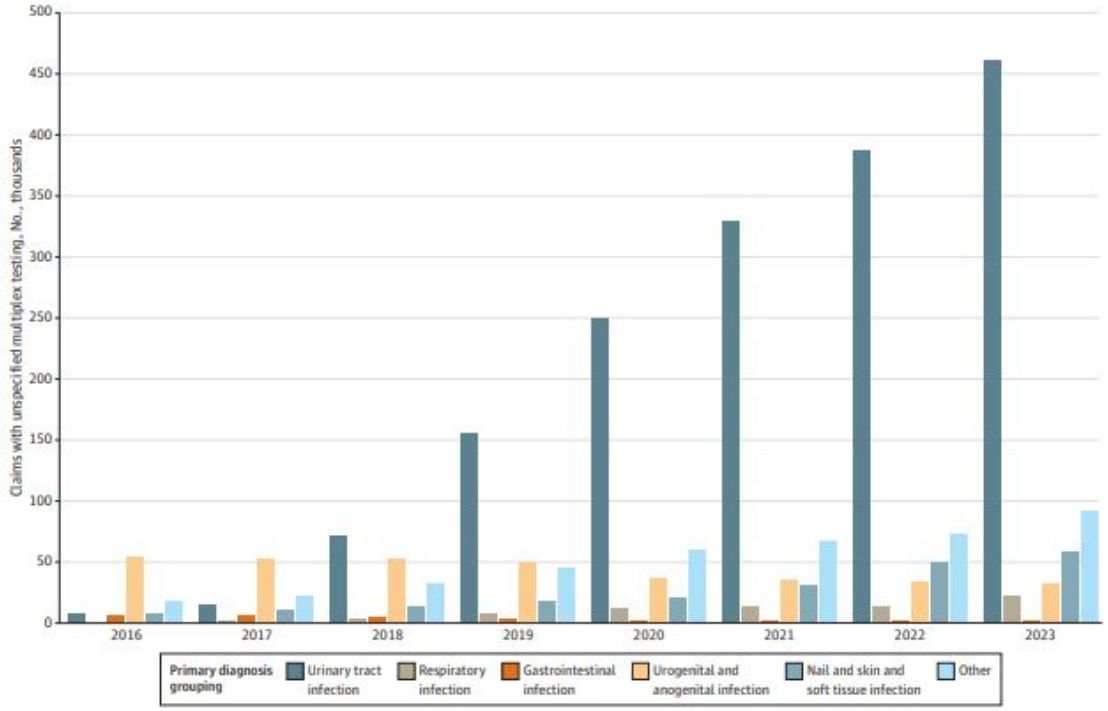
Original Investigation | Infectious Diseases

Use of Multiplex Molecular Panels to Diagnose Urinary Tract Infection in Older Adults

Kelly M. Hatfield, DrPH, MSPH; Sarah Kabbani, MD; Isaac See, MD; Dustin W. Currie, PhD; Christine Kim, PhD; Kara Jacobs Slifka, MD; Shelley S. Magill, MD, PhD; Lauri A. Hicks, DO; L. Clifford McDonald, MD; John Jernigan, MD, MS; Sujan C. Reddy, MD, MSc; Joseph D. Lutgring, MD

- Medicare beneficiaries, 2016 to 2023
- Rate of UTI multiplex testing from 2.4 to 148.1 claims per 10 000 beneficiaries
- Median cost of multiplex test $585
- Median cost of urine culture $8

Figure 1. Annual Number of Carrier Claims With Procedure Codes Indicating Unspecified Multiplex Tests Stratified by Primary Infection Diagnosis, 2016-2023



Current Procedural Terminology, Fourth Edition procedure codes were used. Data are from the Centers for Medicare & Medicaid Services Chronic Conditions Warehouse.