



Till the Bugs Give Out We Can't Shut Our Mouths

Opportunities for Increased Pharmacy Involvement in Complex Outpatient Antimicrobial Therapy

Ashley Logan, PharmD, BCIDP

Ryan Mynatt, PharmD, BCPS

Infectious Diseases / Outpatient Parenteral Antimicrobial Therapy (OPAT) Clinical Pharmacists

University of Kentucky HealthCare



Faculty Disclosure

- Neither Ashley Logan nor Ryan Mynatt have any relevant financial relationships to disclose.



Objectives (Pharmacist)

- Identify common, clinically relevant disease states in which complex outpatient antimicrobial therapy (COpAT) is prescribed.
- Choose an appropriate monitoring strategy for a patient being treated with COpAT for an invasive infectious disease.
- Describe and discuss pragmatic strategies to design, implement, and evaluate potential monitoring strategies for COpAT in the outpatient setting.



Objectives (Technicians)

- Recognize common antimicrobials employed in complex outpatient antimicrobial therapy (COpAT) and describe typical durations where monitoring may be considered.
- Identify typical barriers to the implementation of COpAT monitoring while assessing the impact of team-based interventions to improve adherence.
- Describe and discuss the role pharmacy technicians can play in the expansion of oral antimicrobial therapy programs.



Audience Questions

- How many of you work in the inpatient space, ambulatory space, or a mix of both?
- Who here has an OPAT or COpAT program at their institution?



Let's First Define OPAT versus COpAT

- OPAT – Outpatient Parenteral Antimicrobial Therapy
 - Administration of parenteral antimicrobial therapy in at least 2 doses on different days without intervening hospitalization
- COpAT – Complex Outpatient Antimicrobial Therapy
 - Oral antimicrobial agents used for an extended period or require monitoring while on therapy
 - Anticipated duration is GREATER than 30 days OR the administration of oral antimicrobials that can cause significant adverse drug events (ADEs)



A (Brief) History of Time... aka "the Lore"

- Current treatment dogmas pre-date the incorporation of the randomized controlled trial (RCT).
 - Long-standing recommendations espousing the superiority of intravenous (IV) over oral (PO) regimens
 - Similarly, improved efficacy of longer treatment durations versus short-course therapies
- Earliest evidence and/or advocacy for IV-only describes treatment of endocarditis (mostly Streptococcal) in the 1940s and 1950s with penicillin-based therapy compared with oral sulfonamides, tetracyclines, and macrolides.
- Similarly, uncontrolled case series describing treatment of osteomyelitis in 1950s and 1960s (which included no oral comparators) served as long-standing seminal works in medical training programs.

Lichtman SS. *New Eng J Med* 1943.
Smith C, et al. *JAMA* 1942.
Kelson SR. *Ann Int Med* 1945.
Finland M. *New Eng J Med* 1954.
Davar K et al. *Open Forum Inf Dis* 2022.

"the Lore" Continued...

- Historical dogma prevailed despite a lack of evidence to the contrary and further supported by eminent opinion within healthcare or academic settings.
- In 2007, linezolid prescribing information was updated to reflect a mortality imbalance when used to treat patients with catheter associated bloodstream infections (CRBSI).
 - Study subsequently published in 2009.
 - Mortality driven primarily in Gram-negative and/or no identifiable pathogen groups.
- Contributed significantly in prolonging notion of superiority of IV therapies

Linezolid for CRBSI...

- Included patients ≥ 13 years with central venous access device > 3 days with suspected infection.

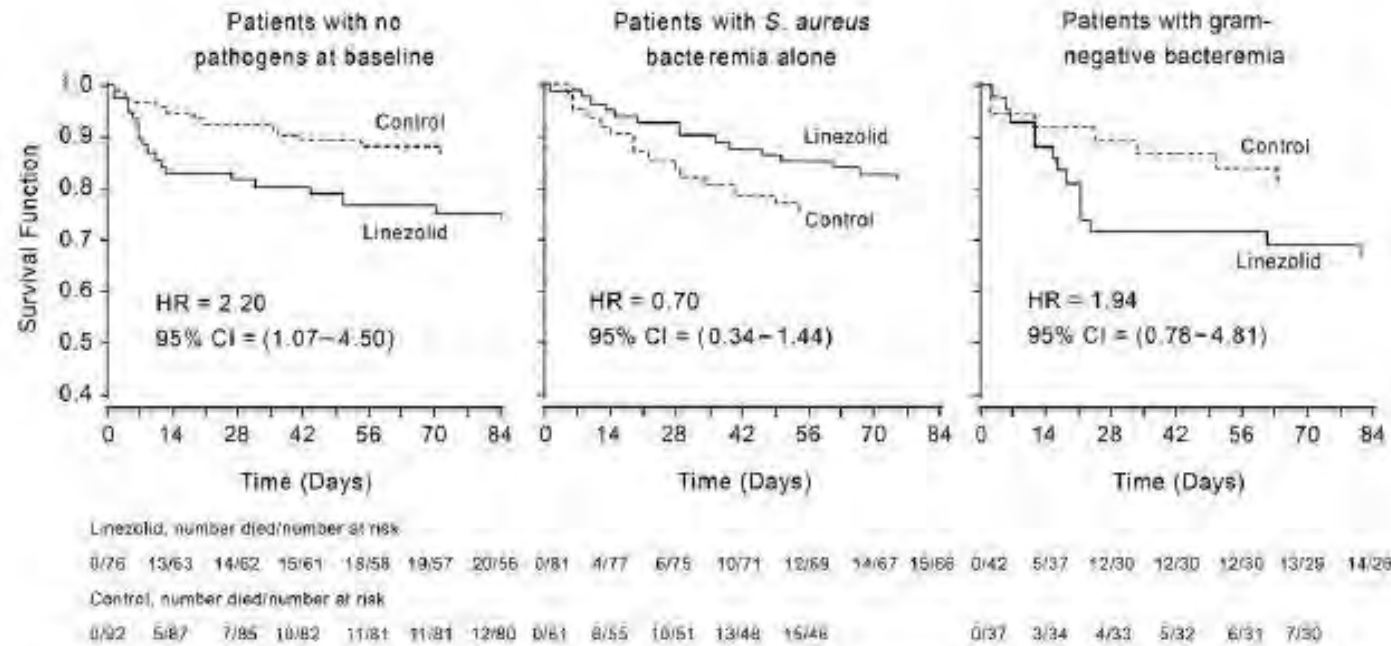


Figure 3. Kaplan-Meier survival curves in subsets of the intent-to-treat population. Post hoc comparisons were assessed using point estimates and 95% CIs for the hazard ratio (HR).

Linezolid for CRBSI...

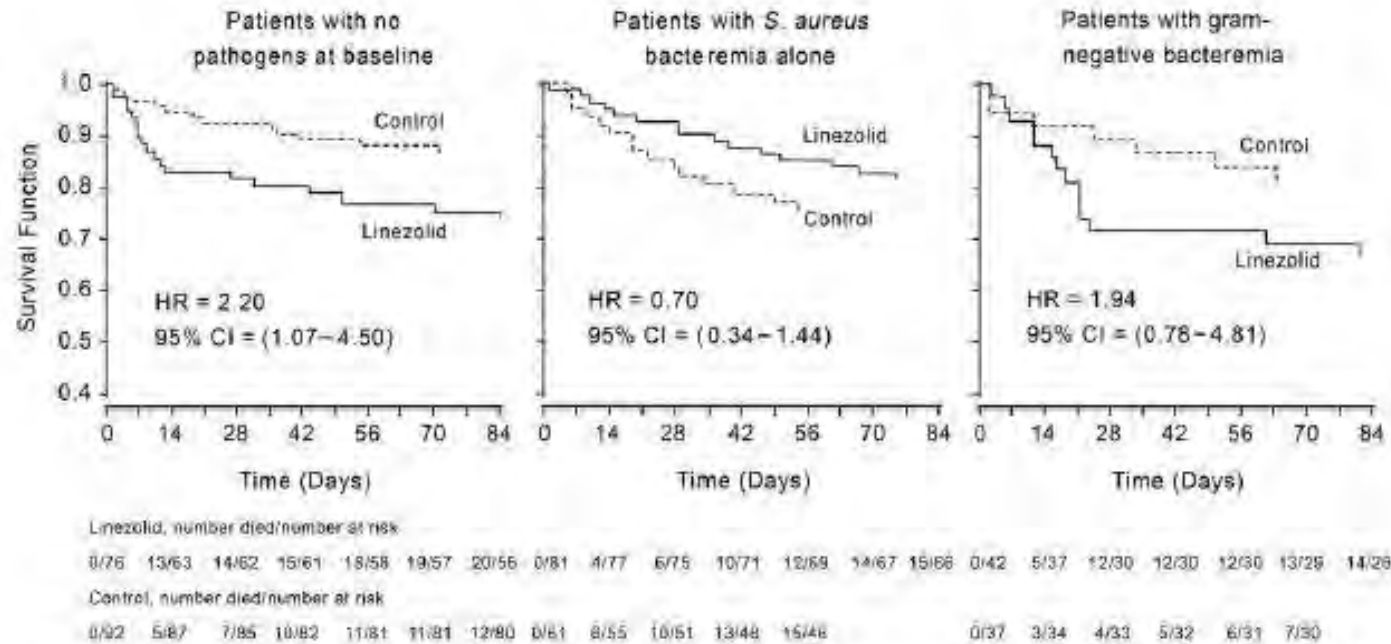


Figure 3. Kaplan-Meier survival curves in subsets of the intent-to-treat population. Post hoc comparisons were assessed using point estimates and 95% CIs for the hazard ratio (HR).

What is happening here specifically?

(1) Linezolid doesn't cover GNR, so study allowed for empiric aztreonam or amikacin.

(2) How are we to interpret given data demonstrating attenuated activity of aztreonam and ceftazidime in *in vitro* models of *E. coli* infection?

Benefits of COpAT

Avoidance of PICC line placement and associated complications

Avoidance of need for home health, home infusions or skilled nursing facilities

Potential decrease in lab monitoring

Potential cost savings

Positive impact on patient quality of life



What Data are There For or Against COpAT?

Summary of Randomized Controlled Trial (RCT) of Oral (PO) versus IV-Only Treatment

Diagnosis	# of RCTs IV > PO	# of RCTs PO ≥ IV	Ref #
Osteomyelitis	0	9 (all equivalent)	1 - 9
Bacteremia	0	10 (8 equivalent; 2 PO superior)	7, 10 - 18
Infective Endocarditis	0	3 (2 equivalent; 1 PO superior*)	19 - 21

* superior relative to mortality

Table adapted from Davar K et al. *Open Forum Inf Dis* 2022.

Interpretation: There is ample, high-quality evidence demonstrating equivalence between IV and PO therapies

1. Manning L et al. *Int J Antimicrob Agent* 2022.
2. Greenberg RN, et al. *Am J Med* 1987.
3. Mader JT et al. *J Bone Joint Surg Am* 1990.
4. Gentry LO, et al. *Antimicrob Agents Chemother* 1990.
5. Gentry LO, et al. *Antimicrob Agents Chemother* 1991.

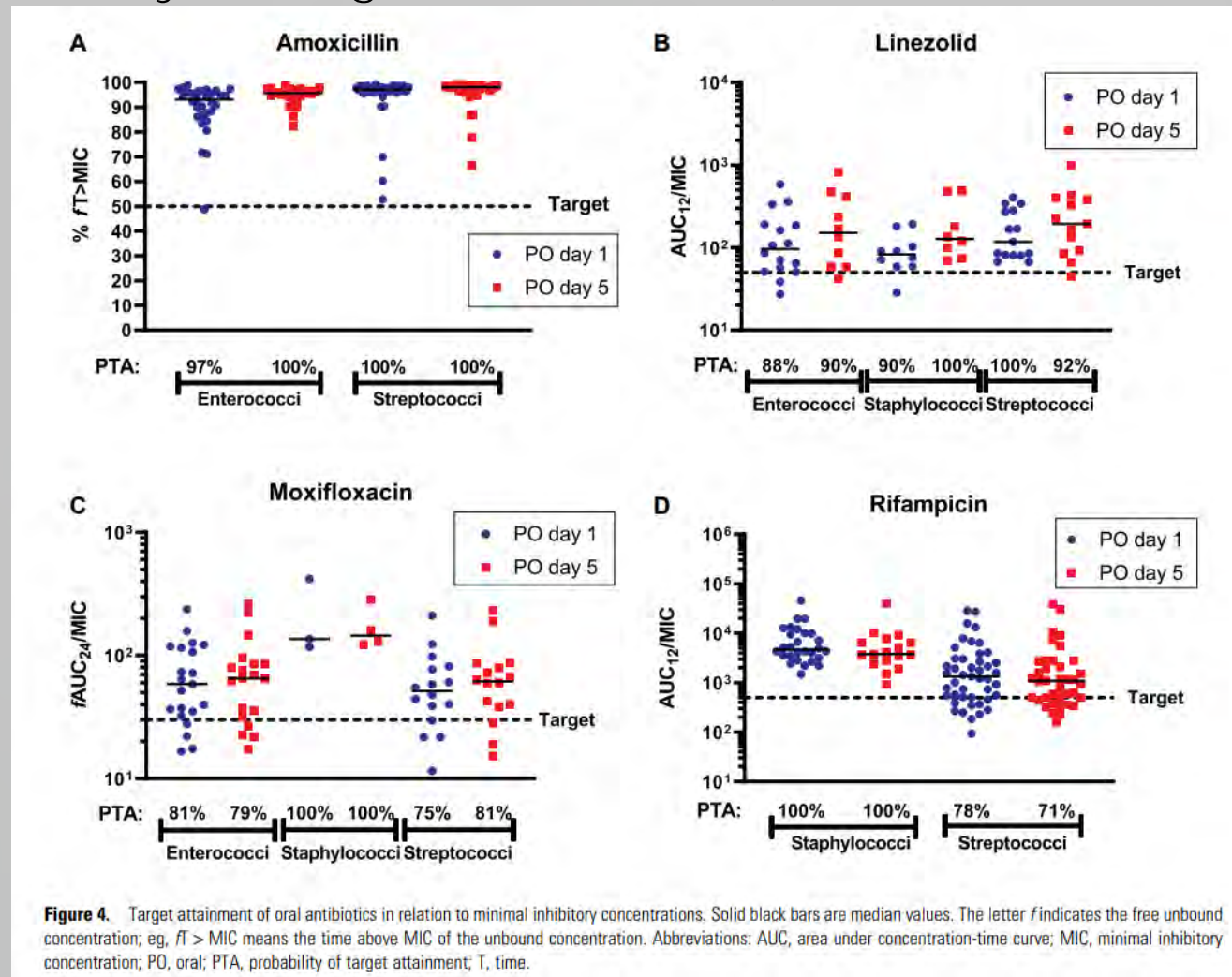
6. Gomis M, et al. *Rev Esp Quimioter* 1999.
7. Schrenzel J. et al. *Clin Inf Dis* 2004.
8. Euba G. et al. *Antimicrob Agents Chemother* 2009.
9. Li HK, et al. *New Eng J Med* 2019.
10. Pedro GSS, et al. *Scan J Infect Dis* 2002.
11. Deville JG, et al. *Pediatr Infect Dis* 2003.
12. Janatausch BA, et al. *Pediatr Infect Dis J.* 2003.

13. Kaplan SL, et al. *Pediatr J Infect Dis* 2003.
14. Wilcox M, et al. *J Antimicrob Chemother* 2009.
15. Wilcox MH, et al. *Clin Inf Dis* 2009.
16. Amodio-Groton M, et al. *Ann Pharmacother* 1996.
17. Monmaturapoj T, et al. *Int J Infect Dis* 2012.
18. Park TY, et al. *Dig Dis Sci* 2014.
19. Stamboulian D et al. *Rev Infect Dis* 1991.

20. Heldman AW, et al. *Am J Med* 1996.
21. Bundgaard H, et al. *New Eng J Med* 2019.

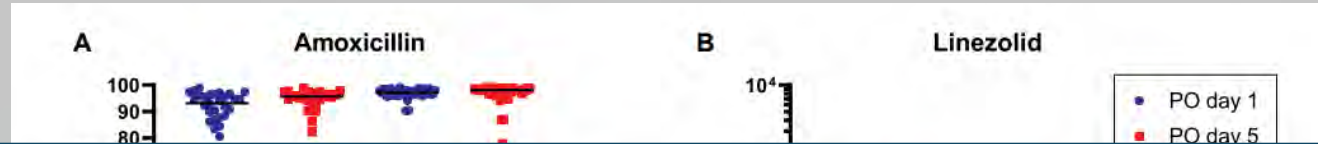
Target Attainment with Oral Therapy

- A POET substudy analyzed the PK / PD of oral therapies used to assess probability of target attainment (PTA).



Target Attainment with Oral Therapy

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PTA was achieved in the majority of patients with the individual antibiotic therapy. In patients with sub-target levels, there was compensation from the use of combination therapy with two different agents of different antimicrobial classes.

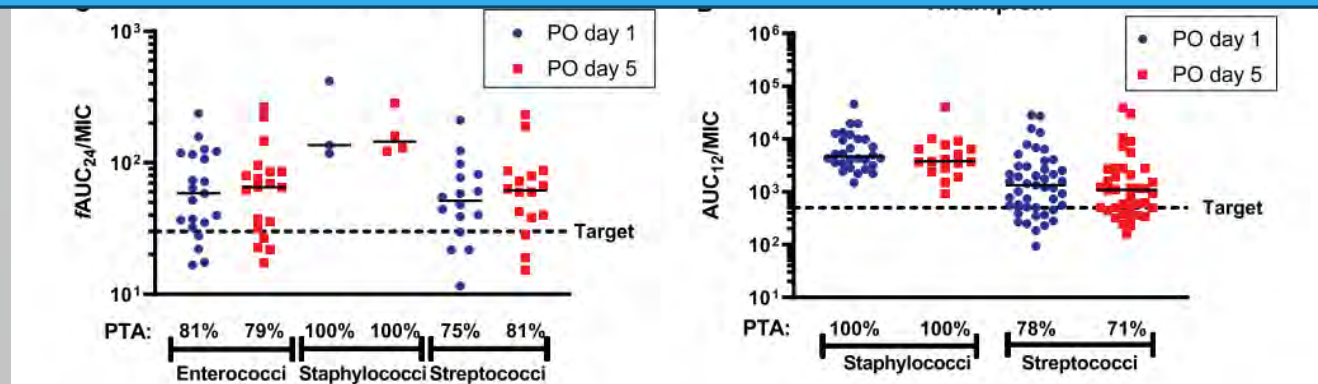


Figure 4. Target attainment of oral antibiotics in relation to minimal inhibitory concentrations. Solid black bars are median values. The letter *f* indicates the free unbound concentration; eg, *f*_T > MIC means the time above MIC of the unbound concentration. Abbreviations: AUC, area under concentration-time curve; MIC, minimal inhibitory concentration; PO, oral; PTA, probability of target attainment; T, time.

What About Bone and Joint Infections?

Li HK, et al. Oral versus Intravenous Antibiotics for Bone and Joint Infections (OVIVA Trial)

Methods	Multicenter, open-label, parallel-group randomized controlled non-inferiority trial <ul style="list-style-type: none">- Adult patients normally requiring 6 weeks of IV therapy for acute or chronic bone and joint infections
Outcomes	<ul style="list-style-type: none">- Primary: definite treatment failure within 1-year after randomization- Secondary: probable or possible treatment failure, early discontinuation of assigned treatment strategy, IV catheter complications, <i>C. difficile</i> diarrhea, serious adverse events, resource use, health status and adherence to treatment



OVIVA Trial

Organism Identified	Total [%] (n = 1003)
<i>Staphylococcus aureus</i>	378 [37.7]
Coagulase-negative staphylococcus	272 [27.1]
<i>Streptococcus</i> species	145 [14.5]
<i>Pseudomonas</i> species	51 [5.1]
Other Gram-negative organisms	168 [16.7]
Culture negative	155 [15.5]

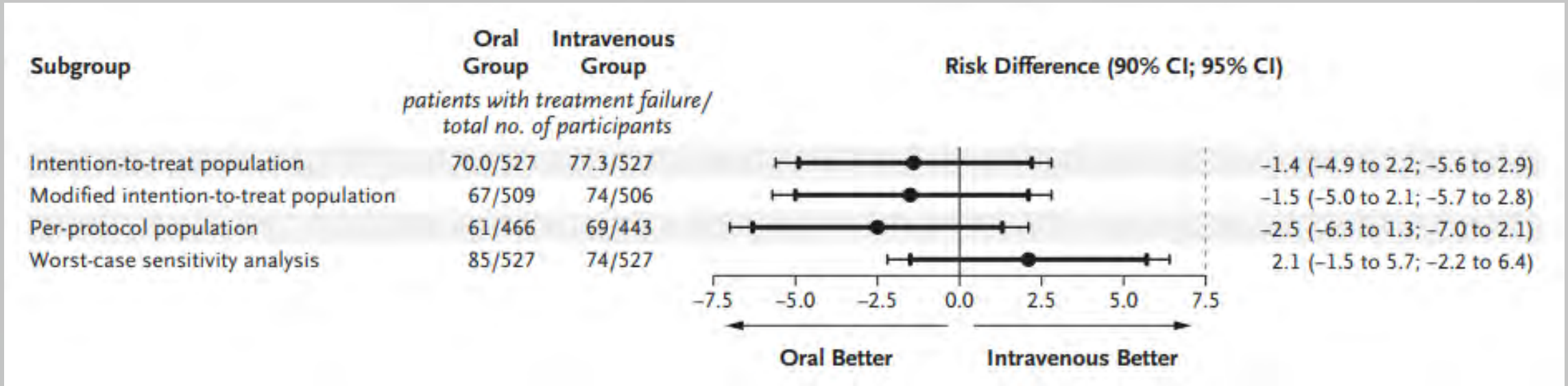
Oral Therapies Utilized

- Penicillins (15.9%)
- Quinolones (36.5%)
- Tetracyclines (10.9%)
- Macrolides / Lincosamide (13.0%)
- Other single PO antibiotics (10.3%)
- Combination PO antibiotics (16.6%)

Patients on Rifampin

- 48.2% of total population received rifampin for any period of time

OVIVA Results



- Early discontinuation of therapy occurred in 99/523 (18.9%) in the IV group versus 67/523 (12.8%) in the PO group ($p = 0.0006$)
- Notably, serious adverse events occurred in 27.7% of patients in the IV group versus 26.2% patients in the PO group

Oral Antibiotics



Benign

High Rate of Unplanned Drug Discontinuation

- An evaluation of the safety and tolerability of fluoroquinolones (FQ) in patients with staphylococcal periprosthetic joint infections found a significantly higher rate of unplanned drug discontinuation when compared to non-FQs.

FQ / Non-FQ Cause for Early Discontinuation			
Procedure (total number of patients included)	FQ (%)	Non-FQ (%)	P value
TJA (n = 156)	32/90 (35.6)	2/66 (3.0)	< 0.001
THA (n = 64)	11/40 (27.5)	1/24 (4.2)	0.021
TKA (n = 92)	21/50 (42.0)	1/42 (2.4)	< 0.001

TJA: total joint arthroplasty; THA: total hip arthroplasty; TKA: total knee arthroplasty

Adverse Events with COpAT

- Review of oral linezolid, trimethoprim sulfamethoxazole, voriconazole, and itraconazole and association of adverse drug events when used for prolonged durations.
- 70/124 (56.5%) of patients experienced an adverse reaction, with 44/70 having ≥ 2 events in the treatment course.
- Patients frequently required regimen modifications or changes in duration of therapy.

Highlights the importance of evidence-based protocols for guiding monitoring and clinical management in patients receiving COpAT.

Audience Assessment Question

- You are the ID pharmacist rounding with a team who wants to discharge a 57 YOM with osteomyelitis of the LLE with cultures growing *E. coli* (susceptible to ceftriaxone and fluoroquinolones). It's decided to send the patient home on levofloxacin 750 mg PO daily for 6 weeks for treatment. How would you respond on rounds to the team?
 - A. The patient should be transitioned to IV ceftriaxone based on available data for treatment of bone and joint infections.
 - B. The patient should be set up for appropriate outpatient monitoring while on PO therapy given potential for adverse drug events.
 - C. No further recommendations are needed.



So How Would We Monitor
Patients on CO₂pAT?



Monitoring in COpAT – Developing a Protocol

Who gets monitored?

What agents need monitoring?

- How long will the patient be on therapy?
- Are there risks for serious adverse reactions?

Where will patients get their labs done?

- **Local lab? Physician's office?**

When / how often should labs be done?

- IDSA Guidelines for OPAT recommends once weekly monitoring. Would this translate to COpAT? Is once weekly needed for most agents?

How will we obtain those labs?

- Will they auto-enter into the EHR or do they need manually entered?
- Does someone need to call to get the labs or will they be sent upon completion?



Table 1	Frequency of Laboratory Assessments per Week					
	CBC w/ differential	BUN & Serum Creatinine	Electrolytes	Liver Function	Drug Concentrations	Other, Miscellaneous
Antimicrobials						
Beta-lactams (see appendix for drug list) <ul style="list-style-type: none"> • Penicillins • Cephalosporins • Carbapenems • Aztreonam • Beta-lactam / Beta-lactamase inhibitors 	Once	Once	(Potassium once weekly if on aqueous PCN G potassium salt)	Once w/ aqueous penicillin G, ceftriaxone, nafcillin, piperacillin-tazobactam, aztreonam and carbapenems		
Glycopeptides / Lipoglycopeptides <ul style="list-style-type: none"> • Vancomycin • Telavancin • Dalbavancin • Oritavancin 	Once	Once**		Once** (only for dalbavancin / oritavancin)	Vancomycin concentration(s)* should be monitored weekly, or more frequently, as clinically indicated	
Daptomycin	Once	Once		Once		Creatine Kinase (CK) Once
Linezolid	Once			Once		
Metronidazole	Once			Once		
Trimethoprim-Sulfamethoxazole (≥ 10 mg/kg/day)	Once	Once	Once (potassium IV/PO; Sodium and Potassium if on IV)	Once		
Aminoglycosides <ul style="list-style-type: none"> • Amikacin • Gentamicin • Tobramycin • Plazomicin 	Once	Twice**	Magnesium (with SrCr/BUN)		Concentration(s) should be performed at least once per week; more frequently if SrCr fluctuant	Assessment for ototoxicity (cochlear & vestibular) should be performed w/ each visit

University of Kentucky HealthCare Standard Operating Procedure: Monitoring Recommendations for patients receiving Outpatient Parenteral Antimicrobial Therapy (OPAT)



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Daptomycin	Once	Once		Once	
Linezolid	Once			Once	
Metronidazole	Once			Once	
Trimethoprim-Sulfamethoxazole (≥ 10 mg/kg/day)	Once	Once	Once (potassium IV/PO; Sodium and Potassium if on IV)	Once	
Aminoglycosides <ul style="list-style-type: none"> • Amikacin • Gentamicin • Tobramycin • Plazomicin 	Once	Twice**	Magnesium (with SrCr/BUN)		Concentration(s) should be performed at least weekly; more frequently if SrCr fluctuates

Individualization is often mentioned, but hard to operationalize



Strongly Advise Standardization

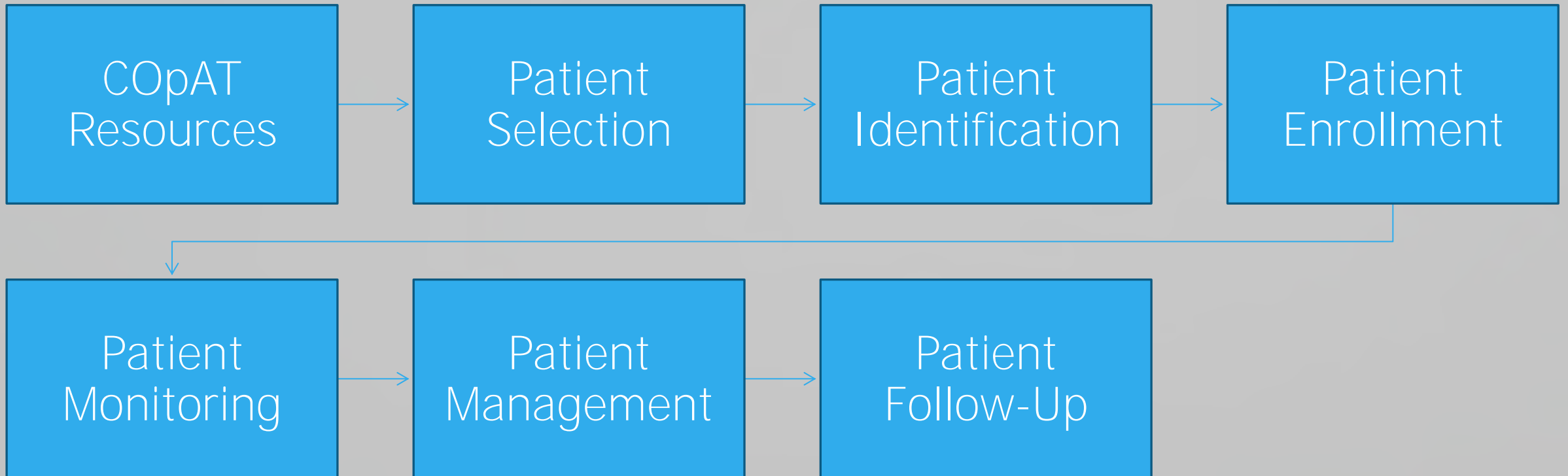
(1) Team members know what is expected / needed.

(2) Minimizes risk of errors.

University of Kentucky HealthCare Standard Operating Procedure: Monitoring Recommendations for patients receiving Outpatient Parenteral Antimicrobials



Establishing a COpAT Program



Optimal Team Members

Physicians

Advanced
Practice Providers
(APPs)

Pharmacists /
Pharmacy
Technicians or
Interns

Nurses

Case
Management

Information
Technology / E-
Health Assistant



Audience Question: How Much Time to Complete COpAT / OPAT Tasks?

Coordination of care for patients (inpatient versus outpatients)

Track and obtain outside lab results

Manual entry of lab results into electronic health record

Tracking drug levels and making dose adjustments



Assessing Staffing Needs

- Model for determining staffing needs for an OPAT program

OPAT RN Activity Summary	Activity Volume	RN Time per activity (weekly average)
Coordination of care for new inpatient enrollee	15–16/week	30 min/patient 7.5-8 hours per week
Coordination of care for new outpatient enrollee	2/week	2 hours/patient 4 hours a week
Weekly review of all patients	120–135 patients/week	2-3 hours/week
Track drug levels and coordinate adjustments	15–20 adjustments/week	20 min per dose change 5-6.5 hours a week
Track outside lab results	30-35 patients per week	10-15 min/patient 5-8 hours per week
Manual entry of outside labs into EHR	30-35 patients per week	5 min per lab/10-15 min per patient 5-8 hours per week
All other issues (e.g., access issues, adverse events, etc.)	Variable	12-18 hours per week
	Total:	Average: 47.5 hours/week Range: 40 – 55 hours/week

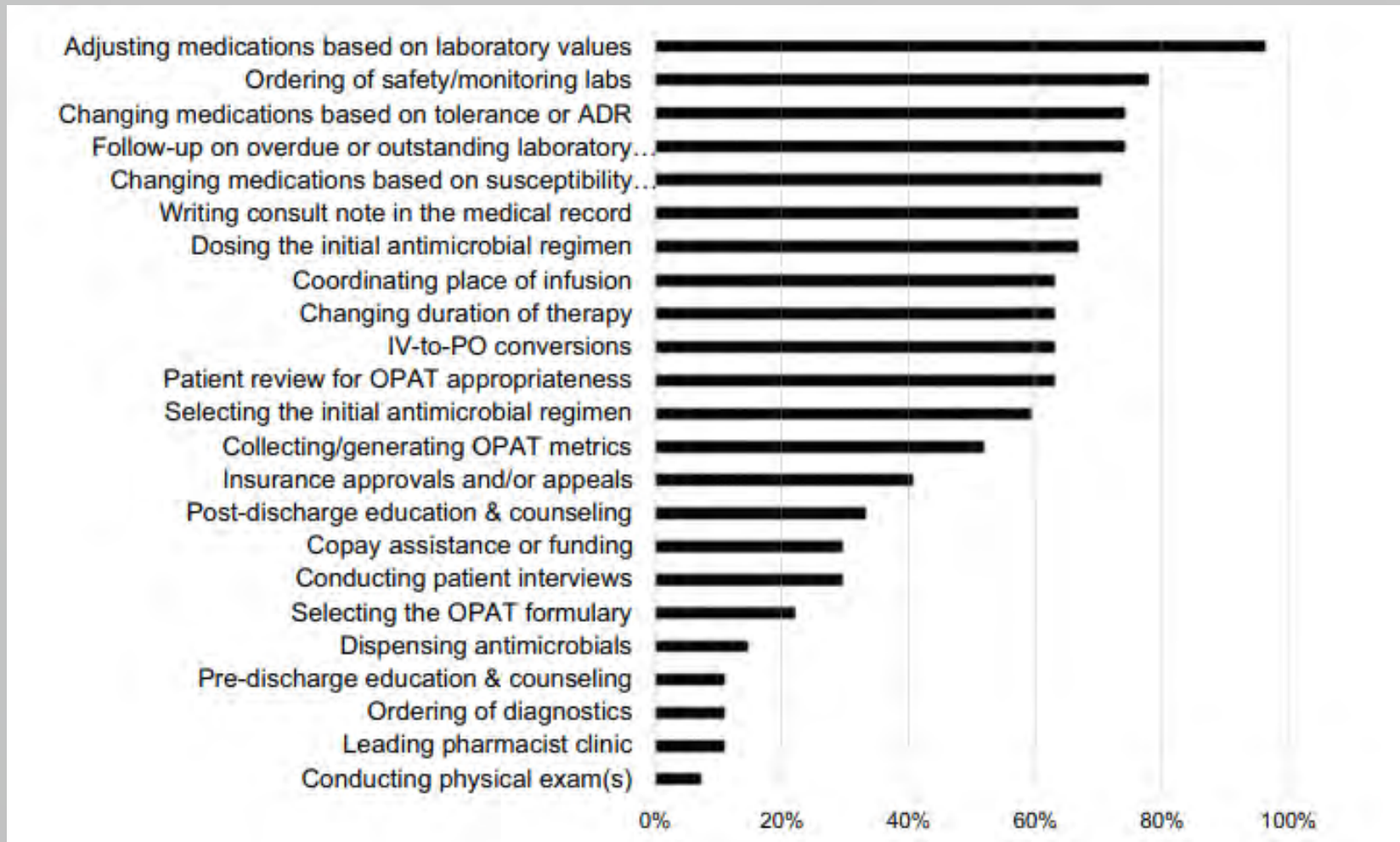
Assessing Staffing Needs

- Model for determining staffing needs for an OPAT program

OPAT RN Activity Summary	Activity Volume	RN Time per activity (weekly average)
Coordination of care for new inpatient enrollee	15–16/week	30 min/patient 7.5-8 hours per week
Coordination of care for existing enrollee		
Weekly care coordination		
Travel and adjustment		
Travel		
Manual entry of outside labs into EHR	30-35 patients per week	5 min per lab/10-15 min per patient 5-8 hours per week
All other issues (e.g., access issues, adverse events, etc.)	Variable	12-18 hours per week
	Total:	Average: 47.5 hours/week Range: 40 – 55 hours/week

Estimated one nurse can safely manage around 500 – 550 patients per year

Pharmacists Role in OPAT / COpAT



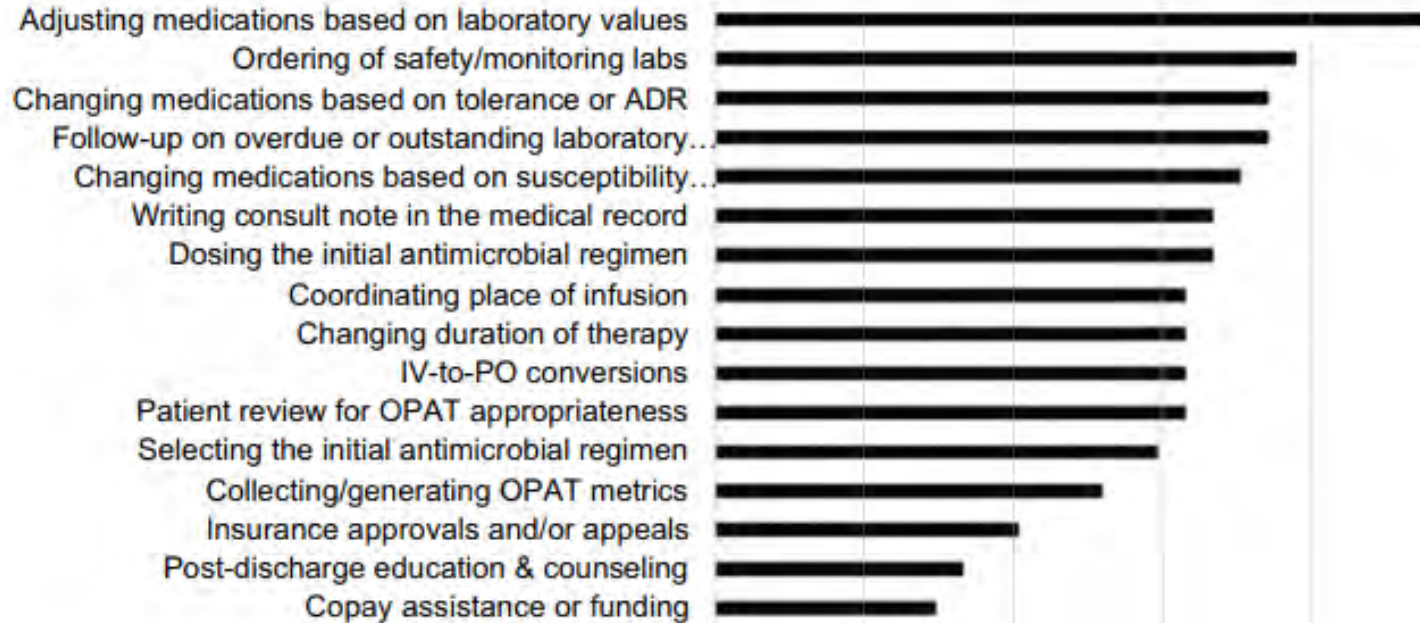
Survey results reported a median of 0.6 pharmacist FTE with a median of 43 OPAT patients



Authors suggest a pharmacist ratio of 1 to 45-70 patients



Pharmacists Role in OPAT / COpAT



Pharmacy Interns / Technicians can play a key role in assisting or championing antimicrobial prior authorizations, copay assistance / funding, as well as assisting with obtaining labs / communicating with patients.

Survey results reported a median of 0.6 pharmacist FTE with a median of 43 OPAT patients



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Show Me the Money

- Cost Considerations for OPAT versus COpAT
 - IV therapy versus PO antimicrobial therapy
 - Supply cost for IV administration (i.e. flushes, heparin locks, infusion devices)
 - Cost of IV catheter insertion / weekly maintenance (line care)
 - Lab frequency
 - Usually once weekly on OPAT, less frequently depending on recommended COpAT regimen
 - Therapeutic drug monitoring



Show Me the Money

- Cost Considerations for OPAT versus COpAT
 - IV therapy versus PO antimicrobial therapy

Studies have shown on average a cost savings of
~\$1730 – \$3800 per patient on COpAT versus
predicted OPAT costs

- Therapeutic drug monitoring

Identify and Select Patients for COpAT

- Infectious Diseases expert review prior to enrollment at most institutions
 - Recommended prior to initiation of OPAT per the IDSA guidelines
- Could stewardship services or transition of care programs help to identify patients?
- Patient selection:

Drug Based Criteria

- Duration of therapy (i.e. > 14 days)
- "High-risk" agents

Patient Criteria


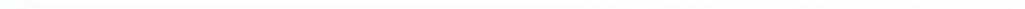
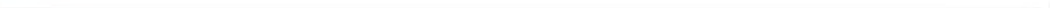
- Social determinants of health concerns (lack of insurance, etc.)
- PWID
- Oral therapy used in place of IV



PWID: persons who inject drugs

Enrollment Example

Home IV Antibiotics (OPAT)  Manage User Versions 

- ▼ OPAT Discharge Notification
 - ▼ Notify OPAT team patient is being discharged on IV antibiotic(s) 
 - Notification of home antibiotics
Routine, Hospital Performed
- ▶ Home Supplies
- ▼ Medications
 - ▶ Discharge Prescriptions for Antibiotics  Click for more
 - ▶ Discharge Prescriptions for Antifungals  Click for more
 - ▶ Discharge Prescriptions for Antivirals  Click for more
- ▼ Labs
 - ▶ Lab orders for Antibiotic Monitoring  Click for more
- ▼ Additional SmartSet Orders

 Search 



Enrollment Example

Outpatient Antimicrobials as of 5/12/2022

oxacillin IV (Outpatient Therapy) Infuse 12 g into the vein continuously over 24 hours for 10 days for Central Nervous System Infection, Infection of Bone and Bone Marrow

Patient

Patient Name
Address
Phone number

Recent Visits with You
None...

Specialty Comments

05/02/22 0938
OPAT - Sign On Note
Start Date
ABX ID ABX-IV
Start Location SMH Inpatient
Diagnosis Osteomyelitis;Central nervous system infection
Organisms MSSA
Antibiotics Oxacillin
Infusion Pharmacy
Nursing Agencies
ID Fellows/APPc
ID Attending
IV Access PICC double
Labs CBC with diff;CMP;CRP;ESR
Anticipated therapy end date

Allergies

Medium: Nsaids; Pregabalin
Low: Capsaicin; Shellfish-derived Products

Preferred Pharmacy

OPAT & ID Notes (Last 90 days) 2/11/2022 to 5/12/2022

Date of Service: 05/02/22 0938

ID Imaging (Last 3 results in 90 days)

05/06/22 2052

Future Appointments

Provider	Department	Center

Lab results from last 90 days

	5/9/2022 8:13 PM	5/9/2022 4:41 AM	5/8/2022 8:06 AM	5/8/2022 4:15 AM	5/7/2022 4:12 AM
Vancomycin Trough	—	—	—	—	—
Sodium	138	139	—	142	141
Potassium	4.0	3.9	—	4.1	3.8
Magnesium	—	—	—	—	—
SCr	0.70	0.69	—	0.64	0.58
WBC	6.4	5.7	—	6.2	7.3
HCT	29 ▼	29 ▼	—	29 ▼	30 ▼
PLT	222	230	—	208	192
ANC	4.4	3.7	—	4.2	5.6
Eosinophil%	3.0	3.2	—	2.9	1.9
CRP	—	—	22 ▲	—	—
ESR	—	—	20	—	—

Microbiology Results

Go to now: 10/1/1977

Time:	11/02/17	04/12/18	04/02/19	05/29/19	05/31/20	06/01/20
	1550	1917 2110	1341 1403	2029	1722 1816	1419 1724
Micro Results						
ANAEROBIC CULTURE						
BLOOD CULTURE						
AEROBIC CULTURE						
AFB CULTURE						
AFB STAIN						
FUNGUS CULTURE						
LEGIONELLA CULTURE						
BETA-D GLUCAN						

Monitoring and Management of Patients

- Now that you have developed your COpAT Monitoring Protocol, who will oversee and manage these patients once they discharge?
- Dependent upon what resources are available within a program

Responsible
provider
(physician, APP)

Nursing-led
monitoring

Pharmacist
collaborative
practice
agreements

Patient Follow-Up

- Follow-up at end of therapy only versus mid-point evaluation
 - Patient and provider dependent
- Barriers to follow-up:
 - A review of COpAT patients discharged from a single center showed patients who were < 55 years old, unemployed or were experiencing substance use were more often lost to follow-up.
 - Patients < 55 years old or with a history of substance use had a longer time to initial lab monitoring.

Highlights again the need for a multi-disciplinary team and touch points with COpAT patients.

What if I Already Have a COpAT Program?

Tracking COpAT Metrics

- Utilizing the EHR or external software for tracking

Reallocate COpAT roles from physicians to other team members

- Utilization of collaborative practice agreements for pharmacists
- Guidelines for nursing for monitoring and escalation based on specific criteria

Quality Assurance Projects

COpAT Research and Publications

- Large gaps for data / knowledge within COpAT

Utilization of Artificial Intelligence within COpAT?

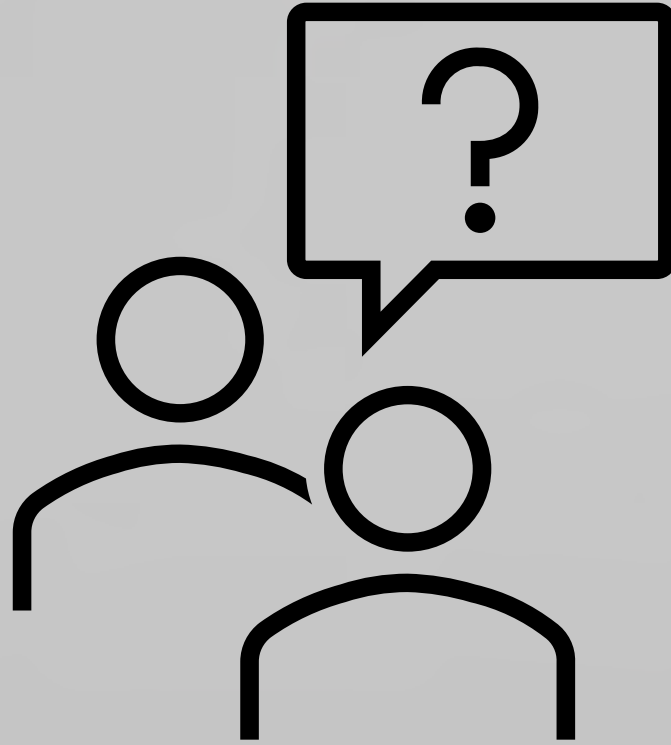


Summary

- Utilization of COpAT can be an effective treatment option for patients and avoid the complications associated with home intravenous antibiotics.
- Oral antimicrobials are not without adverse drug events and should be appropriately monitored when necessary.
- Establishing a COpAT program can assist with the coordination of care for these patients and promote enhanced patient care for patients discharged on oral antimicrobials.



Questions?





Till the Bugs Give Out We Can't Shut Our Mouths

Opportunities for Increased Pharmacy Involvement in Complex Outpatient Antimicrobial Therapy

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