The Use of Therapeutic Drug Monitoring in Complex Oral Outpatient Antimicrobial Therapy for Serious Bacterial Infections

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Disclosures

- None

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Learning Objectives

- Discuss the outpatient management of serious bacterial infections requiring extended duration

- Recall the current literature evidence concerning the use of therapeutic drug monitoring for oral antimicrobial agents in mitigating adverse side effects

Management of Serious Bacterial Infections

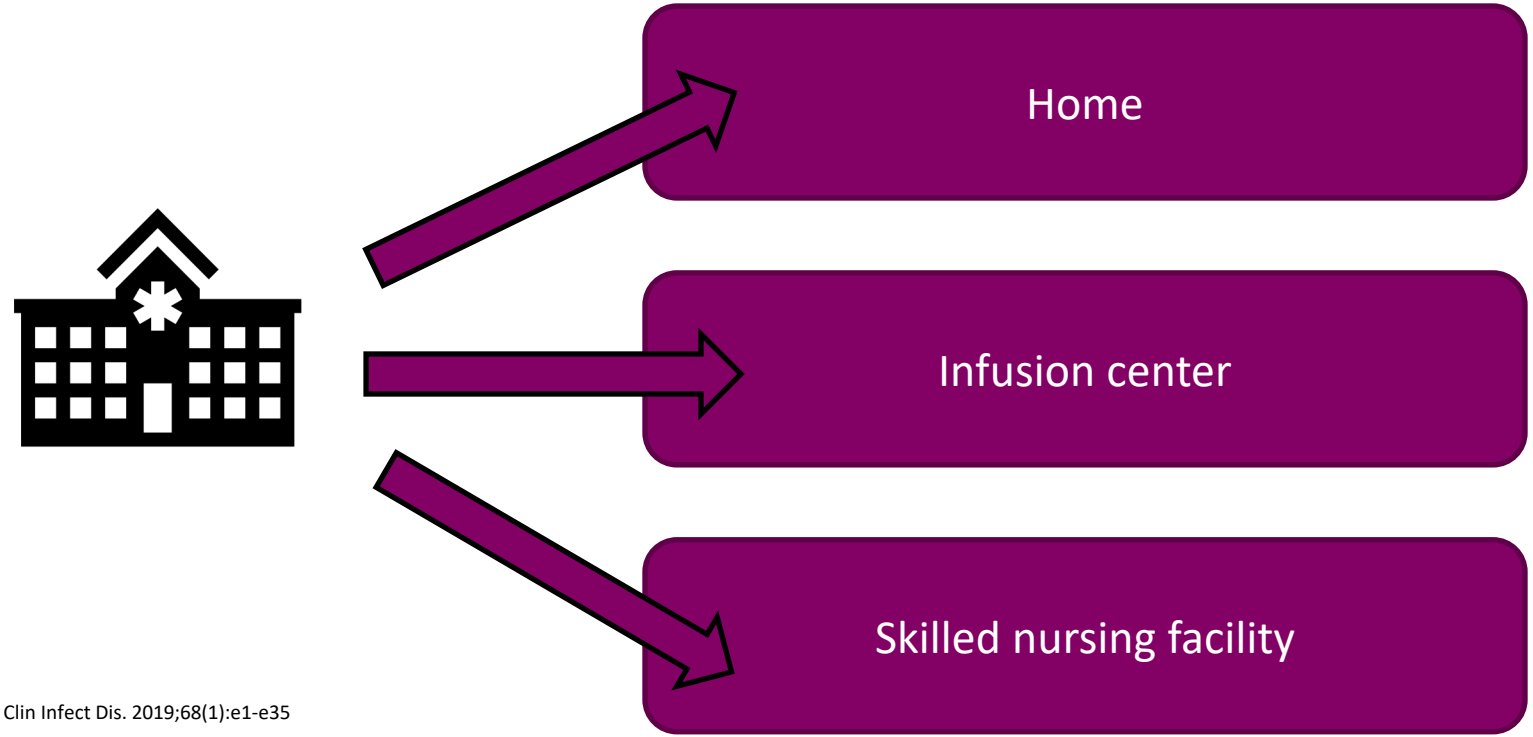
Serious bacterial infections: endocarditis, bone/joint infections, etc.

Surgical intervention + antimicrobial therapy

Typically 4-6 weeks of IV therapy

Lowy FD. N Engl J Med. 1998;339(8):520
Liu C et al. Clin Infect Dis 2011;52(3):e18

Outpatient Parenteral Antimicrobial Therapy (OPAT)



Norris AH, et al. Clin Infect Dis. 2019;68(1):e1-e35

Oral Therapy is Non-Inferior to IV Therapy

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 31, 2019 VOL. 380 NO. 5

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

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ABSTRACT

BACKGROUND

Patients with infective endocarditis on the left side of the heart are typically treated with intravenous antibiotic agents for up to 6 weeks. Whether a shift from intravenous to oral antibiotics once the patient is in stable condition would result in efficacy and safety similar to those with continued intravenous treatment is unknown.

METHODS

In a randomized, noninferiority, multicenter trial, we assigned 400 adults in stable condition who had endocarditis on the left side of the heart caused by streptococcus, *Enterococcus faecalis*, *Staphylococcus aureus*, or coagulase-negative staphylococci and who were being treated with intravenous antibiotics to continue intravenous treatment (199 patients) or to switch to oral antibiotic treatment (201 patients). In all patients, antibiotic treatment was administered intravenously for at least 10 days. If feasible, patients in the orally treated group were discharged to outpatient treatment. The primary outcome was a composite of all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteremia with the primary pathogen, from the time of randomization until 6 months after antibiotic treatment was completed.

RESULTS

After randomization, antibiotic treatment was completed after a median of 19 days (interquartile range, 14 to 25) in the intravenously treated group and 17 days (interquartile range, 14 to 25) in the orally treated group (P=0.48). The primary composite outcome occurred in 24 patients (12.1%) in the intravenously treated group and in 18 (9.0%) in the orally treated group (between-group difference, 3.1 percentage points; 95% confidence interval, −3.4 to 9.6; P=0.40), which met noninferiority criteria.

CONCLUSIONS

In patients with endocarditis on the left side of the heart who were in stable condition, changing to oral antibiotic treatment was noninferior to continued intravenous antibiotic treatment. (Funded by the Danish Heart Foundation and others; POET ClinicalTrials.gov number, NCT01375257.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Bundgaard at the Department of Cardiology B 2141, the Heart Center, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen, Denmark, or at henning.bundgaard@regionh.dk.

Drs. Iversen, Ihlemann, Høfsten, Fosbøll, Køber, and Bundgaard are members of Copenhagen Health Science Partners.

This article was published on August 28, 2018, at NEJM.org.

N Engl J Med 2019;380:415-24.
DOI: 10.1056/NEJMoa1808312

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral versus Intravenous Antibiotics for Bone and Joint Infection

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ABSTRACT

BACKGROUND

The management of complex orthopedic infections usually includes a prolonged course of intravenous antibiotic agents. We investigated whether oral antibiotic therapy is noninferior to intravenous antibiotic therapy for this indication.

METHODS

We enrolled adults who were being treated for bone or joint infection at 26 U.K. centers. Within 7 days after surgery (or, if the infection was being managed without surgery, within 7 days after the start of antibiotic treatment), participants were randomly assigned to receive either intravenous or oral antibiotics to complete the first 6 weeks of therapy. Follow-on oral antibiotics were permitted in both groups. The primary end point was definitive treatment failure within 1 year after randomization. In the analysis of the risk of the primary end point, the noninferiority margin was 7.5 percentage points.

RESULTS

Among the 1054 participants (527 in each group), end-point data were available for 1015 (96.3%). Treatment failure occurred in 74 of 506 participants (14.6%) in the intravenous group and 67 of 509 participants (13.2%) in the oral group. Missing end-point data (39 participants, 3.7%) were imputed. The intention-to-treat analysis showed a difference in the risk of definitive treatment failure (oral group vs. intravenous group) of −1.4 percentage points (90% confidence interval [CI], −4.9 to 2.2; 95% CI, −5.6 to 2.9), indicating noninferiority. Complete-case, per-protocol, and sensitivity analyses supported this result. The between-group difference in the incidence of serious adverse events was not significant (146 of 527 participants [27.7%] in the intravenous group and 138 of 527 [26.2%] in the oral group; P=0.58). Catheter complications, analyzed as a secondary end point, were more common in the intravenous group (9.4% vs. 1.0%).

CONCLUSIONS

Oral antibiotic therapy was noninferior to intravenous antibiotic therapy when used during the first 6 weeks for complex orthopedic infection, as assessed by treatment failure at 1 year. (Funded by the National Institute for Health Research; OVIVA Current Controlled Trials number, ISRCTN91566927.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. M. Scarborough at Microbiology Level 6, John Radcliffe Hospital, Oxford OX3 9DL, United Kingdom.

*A complete list of the OVIVA trial collaborators is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Bejon and M. Scarborough contributed equally to this article.

This article was updated on January 31, 2019, at NEJM.org.

N Engl J Med 2019;380:425-36.
DOI: 10.1056/NEJMoa1710926

Li H-K et al. N Negl J Med 2019;380(5):425
Iversen K et al. N Engl J Med 2019;380(5):415

Complex Oral Antimicrobial Therapy (COpAT)

Defined as oral antimicrobials that are used for extended periods of time or require outpatient monitoring

Possible advantages of COpAT vs. OPAT

Concerns with Prolonged Outpatient Antimicrobial Therapy

Risk of vascular device complications and infections

Antimicrobial-associated adverse side effects

Rivera CG, et al. JACCP. 2021;4(9):1161

Precision Medicine with Therapeutic Drug Monitoring (TDM)

Underlying principle of TDM

- Concentration of a drug in blood is correlated to the pharmacological activity.

Definition of TDM

- The clinical practice of measuring drug concentration in blood/plasma, or in other biological fluids that can be linked to blood drug concentrations.

Impact of TDM

- Optimization of drug dosing regimen by targeting a predefined therapeutic range that has correlation to efficacy and toxicity thresholds.

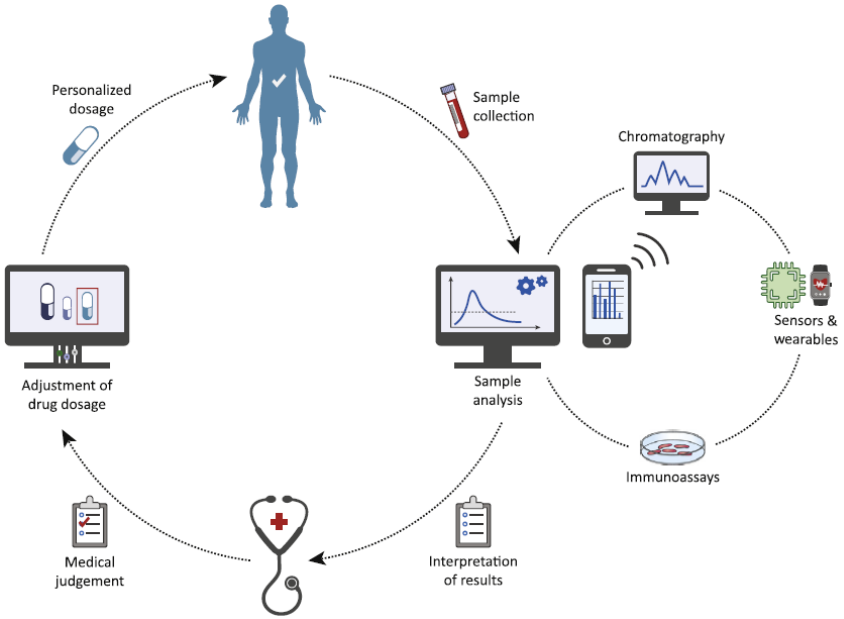


Figure. Overview of TDM Process

Ates HC et al. Trends Biotechnol 2020;38(11):1262

TDM in Antibiotics

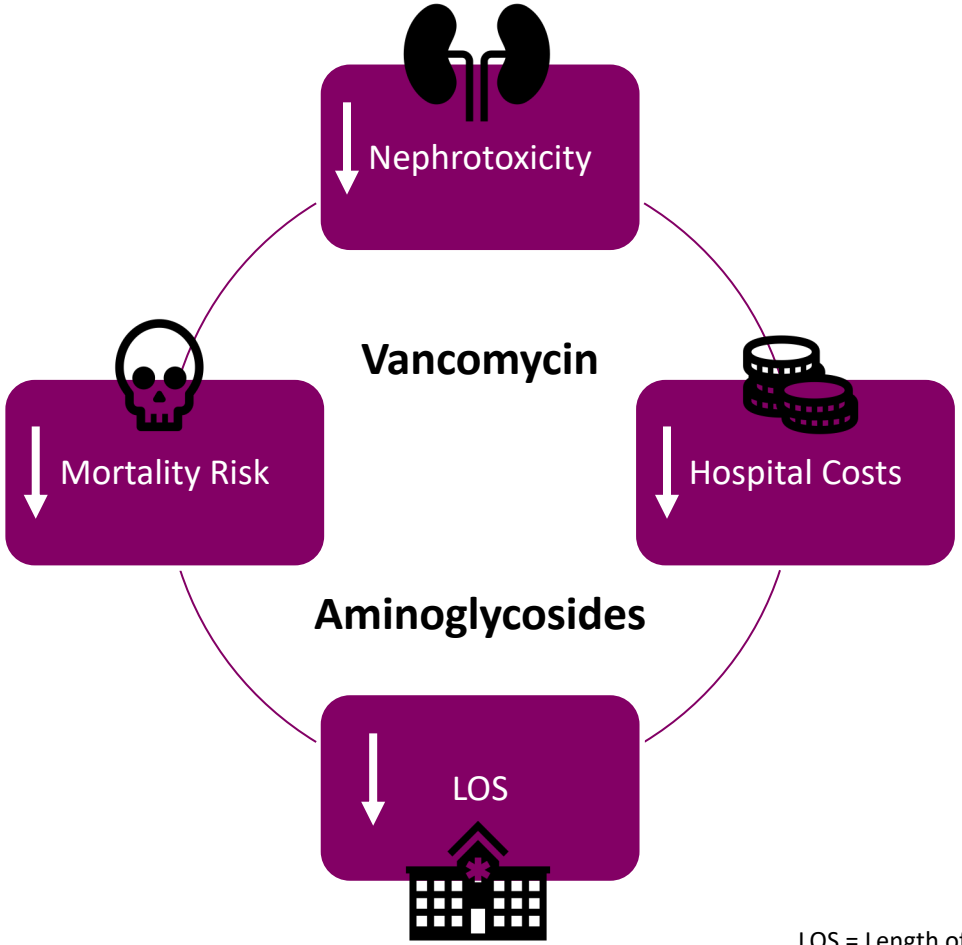
Clinical Infectious Diseases

IDSA GUIDELINE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America

Tamar F. Barlam,[1,a] Sara E. Cosgrove,[2,a] Lilian M. Abbo,[3] Conan MacDougall,[4] Audrey N. Schuetz,[5] Edward J. Septimus,[6] Arjun Srinivasan,[7] Timothy H. Dellit,[8] Yngve T. Falck-Ytter,[9] Neil O. Fishman,[10] Cindy W. Hamilton,[11] Timothy C. Jenkins,[12] Pamela A. Lipsett,[13] Preeti N. Malani,[14] Larissa S. May,[15] Gregory J. Moran,[16] Melinda M. Neuhauser,[17] Jason G. Newland,[18] Christopher A. Ohl,[19] Matthew H. Samore,[20] Susan K. Seo,[21] and Kavita K. Trivedi[22]



Barlam TF et al. Clin Infect Dis 2016;62(10):e51

LOS = Length of stay

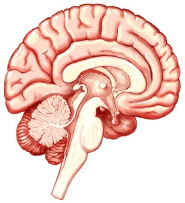
Oral Antimicrobial Candidates for TDM

Linezolid

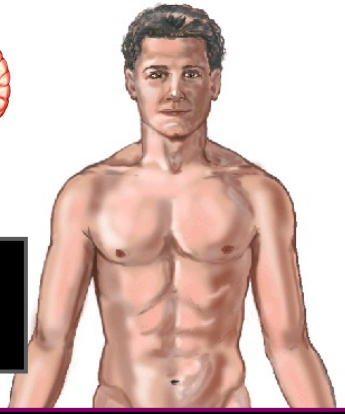
Amoxicillin

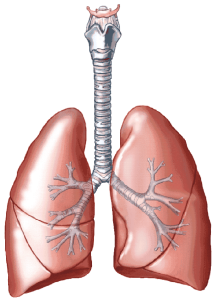
Linezolid Penetration

CNS[1]: 70%*



Saliva[2]: 120%

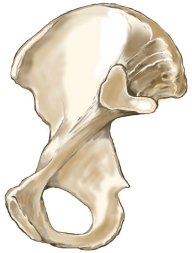


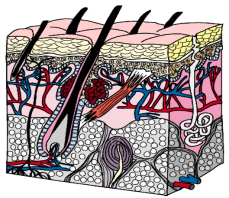


Epithelial lining fluids[4]: 120%

Alveolar cell[4]: 15%

Bone[3]: 40-60%*





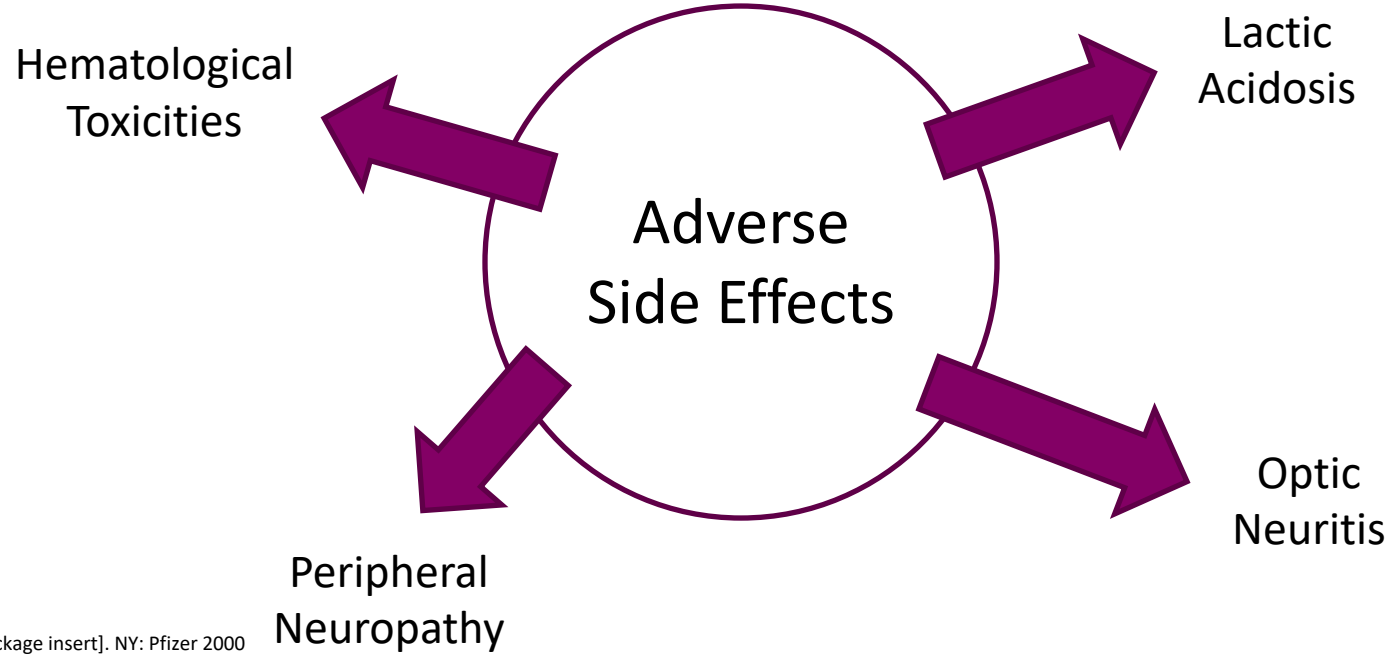
Sweat[2]: 55%

Skin Blister Fluid[5]: 100%

1. Cottagnound et al. *J Antimicrob Chemother.* 2000;46:981-985
2. ZYVOX® (linezolid injection, tablets, and oral suspension) [package insert]. Kalamazoo, Mich: Pharmacia & Upjohn, a Pfizer Company; revised 2003
3. Lovering AM et al. *J Antimicrob Chemother*. 2002, 50:73-77
4. Conte JE et al. *Antimicrob Agents Chemother*. 2002;46:1475-1480
5. Gee T. *Antimicrob Agents Chemother*. 2001;45:1843-1846

Slide courtesy of Dr. Brandon Bookstaver

Hesitancy of Prolonged Linezolid Therapy



Linezolid (ZYVOX®) [package insert]. NY: Pfizer 2000

C_{trough} is Correlated with Risk of Thrombocytopenia

	Pea F et al. 2012	Dong H.-Y et al. 2014	2020
Thrombocytopenia Definition	• ≥30% reduction from baseline	•	00K: me 0K:
Inciden			
			penia
Key Resu	mg/L	>50%: C_{trough} ≥6.3 mg/L	50%: C_{trough} 7.9 mg/L
	>95%: C_{trough} 9.96 mg/L		>95%: C_{trough} 11.9 mg/L

Current proposed toxicity threshold 7-8 mg/L

Dong H.-Y et al. Eur J Clin Microbiol Infect Dis 2014;33:1029
Pea F et al. J Antimicrob Chemother 2012;67:2034
Fang J et al. Ann Transl Med 2020;8(7):493

Plt: platelet

C_{trough} Does NOT Predict the Risk of Linezolid-Induced Neuropathy

	Sotgiu G et al. 2012	Zhang X et al. 2014	. 2016
Study Design		Systematic a	
Key Baseline Characteri	• N = 121		00
Treatm Duratio			ays
Incidenc			• 30%
C_{trough} as Predictor		• Incidence was higher in those with ≤600 mg/day (13.7%, p = 0.018)	• No

Treatment duration is associated with the risk of linezolid-induced neuropathy

Sotgiu G et al. Eur Respir J 2012;40:1430
Zhang X et al. J Thorac Dis 2015;4:603
Agyeman AA et al. Ann Clin Microbiol Antimicrob 2016;15:41

MDR-TB: multidrug resistant-tuberculosis

C_{trough} Does NOT Predict the Risk of Linezolid-Induced Lactic Acidosis

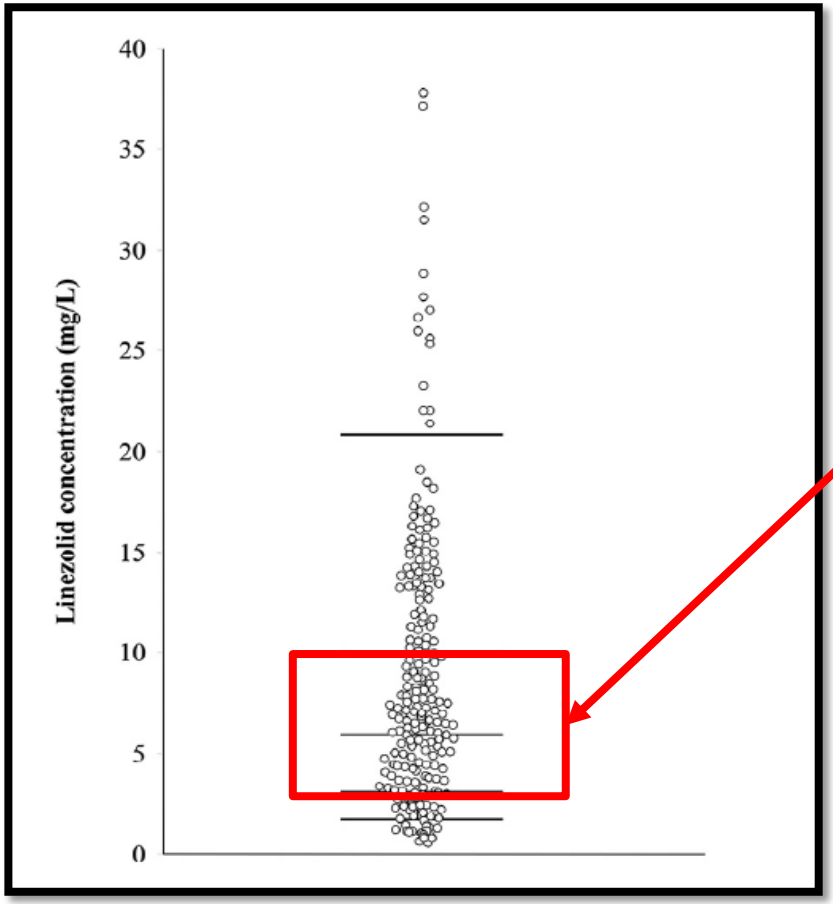
	Im JH et al. 2015	Mori N et al. 2018	[illegible]21
Study Design	Retrospective, Sin[illegible]		
Key Baseline Characteri[illegible]	• N = 72 • Mea[illegible]		[illegible]QR: [illegible]43.9%
Treatme[illegible] Duration		[illegible]s (IQR: 6-14)	• Median 9 days (IQR: 6-11.3)
Incidence		• 10%	• 36%
C_{trough} as a Risk Predictor?	• No	• No	• No

Treatment duration is associated with the risk of linezolid-induced lactic acidosis

Im JH et al. Int J Infect Dis 2015. 47
Mori N et al. Eur J Clin Pharmacol 2018;74:405
Liu T et al. Front Med 2021;8:604680

CKD: chronic kidney disease, DM: diabetes mellitus, NR: Not reported

Traditional Linezolid Dosage is Associated with Variable Exposure



Linezolid 600 mg BID IV/PO

383 linezolid C_{trough}

Median C_{trough} 5.9 mg/L (IQR: 3-10.2)

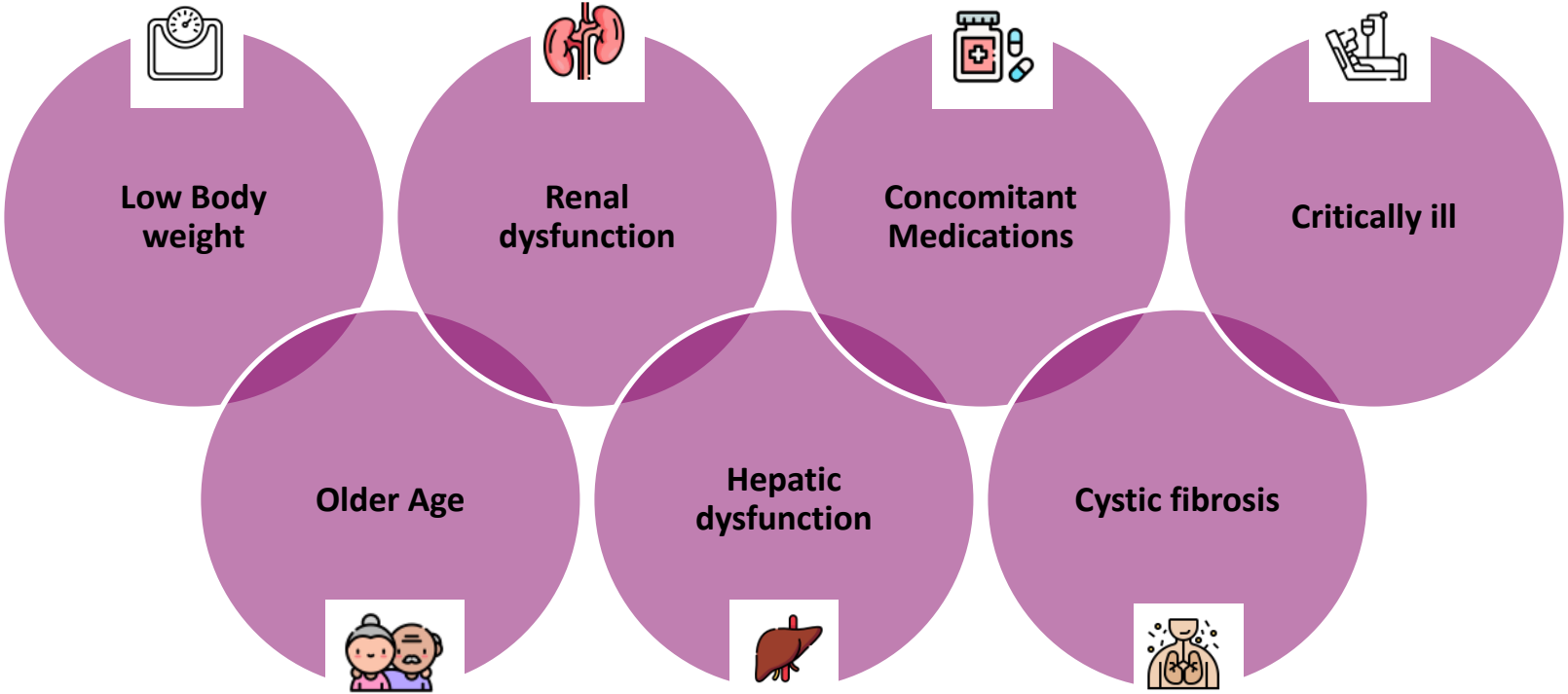
Interpatient coefficient 88.9%

Intrapatient coefficient 45.7%

Cattaneo D et al. Int J Antimicrob Agent 2016;728

Figure. Distribution of linezolid trough concentrations. Horizontal solid lines represent the 5th, 25th, 50th, 75th, and 95th percentiles

Risk Factors for Non-Therapeutic C_{trough}



Pea F et al. Basic Clin Pharmacol Toxicol 2017;121:303
Cattaneo D et al. Int J Antimicrob Agents 2016;48:728
Perry CM et al. Drugs 2001;61:525
Pea F et al. Antimicrob Agents Chemother 2010;54:4605

Is there An Impact of Proactive TDM-Guided Dosing? Evidence 1

STUDY DESIGN

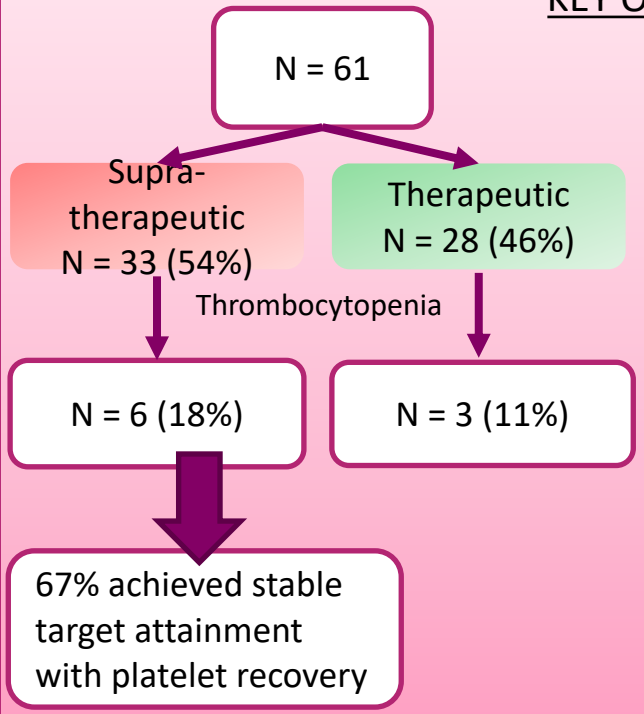
Prospective, Single-center, Italy, 6/2015-12/2017

Inclusion

- Adult
- MDR gram-positive infection
- Linezolid 600 mg IV/PO BID >10 days

Primary Aim

- Evaluate whether proactive TDM prevents/decreases risks for thrombocytopenia



KEY OUTCOMES

Median duration: 19-54 days

No difference observed in the incidence of thrombocytopenia due to duration (≤28 vs >28 days)

Predictors of Thrombocytopenia:
Baseline platelet count
Median linezolid C_{trough}

Is there An Impact of Proactive TDM-Guided Dosing? Evidence 2

STUDY DESIGN

Retrospective, Multicenter (11), Australia, 1/2015-12/2019

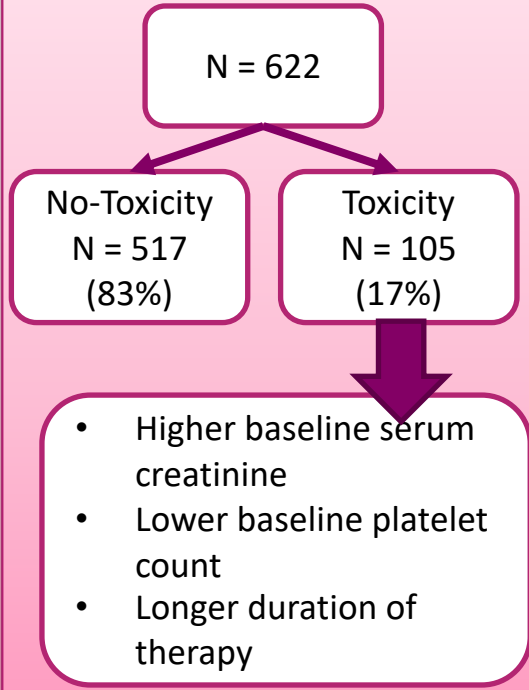
Inclusion

- Adults
- IV or oral linezolid therapy for >5 days

Primary Aim

- Evaluate linezolid toxicity and clinical management

KEY OUTCOMES



Median duration: 15 days (IQR 9-24)

Most common toxicities:
Thrombocytopenia (58%)
Anemia (33%)

Appropriate TDM is associated with reduced odds of linezolid toxicities (aOR 0.45, 95% CI 0.21-0.96, p=0.038)

Linezolid TDM Guidance

TDM of Amoxicillin

STUDY DESIGN

Observational, 2 centers (TDM vs. non-TDM), France, 2013-2018

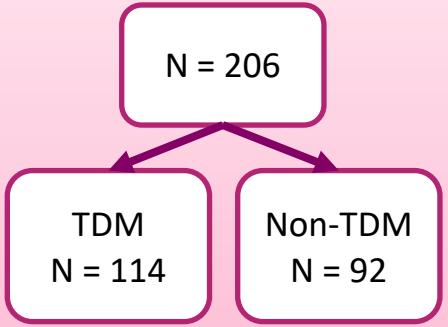
Inclusion

- Adults
- Streptococcal or enterococcal ID
- Treated with >7 days of IV amoxicillin

Primary Aim

- Evaluate the benefit of amoxicillin TDM during IE

KEY BASELINE CHARACTERISTICS



- Primarily males (75%), mean age of 70 y/o, mean CCI of 2.7
- 66% had aortic valve IE, 37% had prosthetic valve
- Predominately streptococcal species (68%)

KEY OUTCOMES

Lower total daily amoxicillin dose (10 g vs. 11.3g) p=0.003

Numerically lower incidence of AKI (23% vs. 30%) p=0.22

Numerically lower incidence of mortality (14% vs. 25%) p=0.046

CCI: Charlson Comorbidity Index

Doreal M, et al. Int J Antimicrob Agents. 2023;106821. doi:10.1016/j.ijantimicag.2023.106821

Key Takeaway

COpAT may be a favorable alternative to OPAT for the treatment of serious bacterial infections requiring prolonged duration

TDM of antimicrobials may mitigate the risk of antimicrobial-associated side effects that have demonstrated a concentration-dependent correlation

Recent evidence have emerged demonstrating the benefits of TDM in linezolid and amoxicillin, although more data is still needed to support their routine use in clinical practice

Learning Assessment Question 1

True or False:

Studies have demonstrated that oral step-down therapy is non-inferior to intravenous therapy for the treatment of serious bacterial infections such as endocarditis

Learning Assessment Question 1

True or False:

Studies have demonstrated that oral step-down therapy is non-inferior to intravenous therapy for the treatment of serious bacterial infections such as endocarditis

Learning Assessment Question 2

Which of the following statement is true based on the current literature evidence?

A. Linezolid-associated thrombocytopenia is correlated to its concentration
B. Linezolid-associated neuropathy is correlated to its concentration
C. Linezolid-associated lactic acidosis is correlated to its concentration
D. All of the above is true

Learning Assessment Question 2

Which of the following statement is true based on the current literature evidence?

A. **Linezolid-associated thrombocytopenia is correlated to its concentration**
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C. Linezolid-associated lactic acidosis is correlated to its concentration
D. All of the above is true

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Prisma Health Richland – University of South Carolina College of Pharmacy

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