UTAH SOCIETY OF HEALTH-SYSTEM PHARMACISTS

Addressing the Misconceptions: IV vs Oral Antibiotics in Invasive Infections

Julie Gray, PharmD
PGY1 Pharmacy Resident
University of Utah Health
Julie.Gray@hsc.Utah.edu
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Disclosure

- **Relevant Financial Conflicts of Interest**
  - **CE Presenter, Julie Gray, PharmD**
    - None
  - **CE mentor, Sage Greenlee, PharmD, BCIDP**
    - None
  - **CE mentor, Ali Earl, PharmD, BCIDP**
    - None
- **Off-Label Uses of Medications**
  - All antibiotics discussed in this presentation are considered off-label indications

Abbreviations

- IV: Intravenous
- PO: Oral
- IDSA: Infectious Diseases Society of America
- PJI: Prosthetic joint infection
- NVO: Native Vertebral Osteomyelitis
- MDRO: Multi-drug resistant organism
- DFI: Diabetic foot infection
- DFO: Diabetic foot osteomyelitis
- TMP-SMX: Trimethoprim-sulfamethoxazole
- AHA: American Heart Association
- IE: Infective endocarditis
- NVE: Native valve endocarditis
- PVE: Prosthetic valve endocarditis
- BJI: Bone and Joint Infections
- CoNS: Coagulase-negative staphylococci
- AE: Adverse events
- AKI: Acute kidney injury
- GNO: Gram negative organisms

Learning Objectives – Pharmacists

1. Analyze literature surrounding the use of oral agents in the treatment of invasive infections
2. Describe the bioavailability, penetration, and adverse effects of preferred oral antibiotics
3. Evaluate a treatment and monitoring regimen for patients with invasive infections

Learning Objectives – Technicians

1. Identify oral antibiotics appropriate for treating invasive infections
2. Recognize common adverse effects associated with preferred oral antibiotics for invasive infections
3. Differentiate between infectious indications for which oral antibiotics may be appropriate

Background

Intravenous (IV) antibiotics were preferred due to few well-absorbed oral antibiotics with broad spectrums of activity

Newer antibiotics were not subject to more rigorous testing until the 1980's

Few well designed studies on oral treatment until more recently

Clinical and professional society guidelines endorsed IV-only therapy for invasive infections

Wald-Dickler, N., *et al.*, Oral Is the New IV: Challenging Decades of Blood and Bone Infection Dogma: A Systematic Review. Am J of Med 2022.

Risks of IV Therapy

- Line-related infections
- Thrombophlebitis
- Extravasation
- Longer hospital length of stay (LOS)
- Increased drug cost

McCarthy, K., *et al.*, Oral or intravenous antibiotics? Aust Prescr 2020
Li, H.K., *et al.*, An Unsupported Preference for Intravenous Antibiotics. PLoS Med 2015

Benefits of Oral Therapy

- Absence of line-related complications
- More affordable for patients
- Potentially shorter LOS
- Convenient to patients and healthcare system

McCarthy, K., *et al.*, Oral or intravenous antibiotics? Aust Prescr 2020
Li, H.K., *et al.*, An Unsupported Preference for Intravenous Antibiotics. PLoS Med 2015

Considerations for Preferred Oral Antibiotics

Preferred Oral Antibiotics

Antibiotic	Bioavailability	Dosing*	Data	Drug Interactions	Adverse Effects
Amoxicillin	80%	1000 mg Q6-8H	Good in IE, but limited in BJI	No significant	GI upset
Amoxicillin-clavulanate	60%	500 mg Q8H	Good in DFI	No significant	GI upset
Ciprofloxacin	80%	750 mg Q12H	Strong in BJI	Polyvalent cations in supplements and foods	QT prolongation Aortic aneurysm Tendonitis *C. diff* infection CNS effects

Abbreviations: BJI, bone and joint infection; C diff., Clostridioides difficile; CNS, central nervous system; DFI, diabetic foot infection; GI, gastrointestinal; H, hours; IE, infective endocarditis
**In normal renal function*

Preferred Oral Antibiotics

Antibiotic	Bioavailability	Dosing*	Data	Drug Interactions	Adverse Effects
Levofloxacin	99%	750mg Q24H	Good in BJIs	Polyvalent cations in supplements and foods	QT prolongation Aortic aneurysm Tendonitis *C. diff* infection CNS effects
Clindamycin	90%	600 mg Q8H	Some in BJIs	No significant	GI upset *C. diff* infection
Linezolid	100%	600 mg Q12H	Strong in BJI and IE	Many interactions	Thrombocytopenia Anemia Myelosuppression Neuropathies

Abbreviations: BJI, bone and joint infection; C diff., Clostridioides difficile; CNS, central nervous system; H, hours; IE, infective endocarditis
**In normal renal function*

Preferred Oral Antibiotics

Antibiotic	Bioavailability	Dosing*	Data	Drug Interactions	Adverse Effects
TMP-SMX	70-90%	7.5-10 mg/kg Q8H	Strong in BJI	Caution with nephrotoxic drugs and drugs that increase potassium	Hyperkalemia AKI Anemia Leukopenia Thrombocytopenia
Doxycycline	100%	100 mg Q12H	In vitro bone penetration	Polyvalent cations in supplements and foods	Photosensitivity Esophageal irritation Skin discoloration

Abbreviations: AKI, acute kidney injury; H, hours; kg, kilogram; mg, milligram; TMP-SMX, trimethoprim-sulfamethoxazole;
**In normal renal function*

Assessment of Bioavailability

High (>90%)	• Clindamycin, doxycycline, levofloxacin, linezolid
Moderate (60-90%)	• Aminopenicillins, TMP-SMX, ciprofloxacin
Low (<60%)	• Most cephalosporins

Considerations for Oral Therapy

- Clinically stable
- GI abnormalities that may limit absorption
  - Roux-N-Y gastric bypass, chronic diarrhea, inflammatory bowel disease
- Limited data in morbid obesity (BMI >40)
- Use a highly bioavailable antibiotic that is active against suspected/confirmed pathogens
- Assess compliance and affordability

Summary

- Oral antibiotics are more convenient, cost effective, and may decrease the hospital LOS
- Landmark trials provide insight into the use of oral therapy for invasive infections
- Patient and drug selection are the key to success

Bone and Joint Infections (BJIs)

Background

- **Management:**
  - Surgical source control when possible
  - Historically treated with a prolonged course of IV antibiotics (≥ 6 weeks)
- **IDSA guidelines are not updated frequently**
  - 2015 Native Vertebral Osteomyelitis IDSA guidelines
  - 2012 Diabetic Foot Infections IDSA guidelines
  - 2012 Prosthetic Joint Infections IDSA guidelines

Native Vertebral Osteomyelitis (NVO)

2015 IDSA Guidelines - NVO

- **Recommendation**
  - 6 weeks of IV or highly bioavailable oral antibiotics for most patients with NVO (*strong, low*)
  - Recommended oral antibiotics include fluoroquinolones, linezolid, and metronidazole
  - Oral beta-lactams not first line for initial treatment
- **NVO microbiology**
  - *Staphylococcus* spp. – oxacillin susceptible and resistant
  - *Enterococcus* spp. – penicillin susceptible and resistant
  - *Pseudomonas aeruginosa*
  - Enterobacterales

Berbari, E.F. *et al.*, 2015 Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for the Diagnosis and Treatment of Native Vertebral Osteomyelitis in Adults. Clin Infect Dis. 2015

Antibiotic Treatment for 6 Weeks Versus 12 Weeks in Patients with Pyogenic Vertebral Osteomyelitis

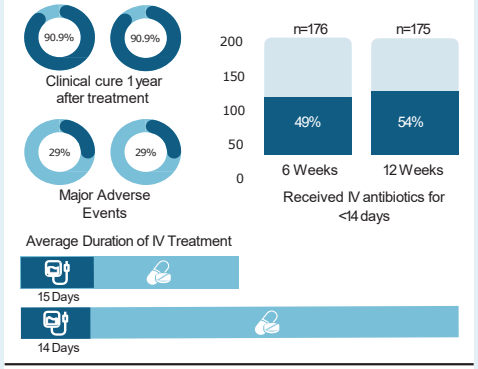
DESIGN
Multi-center (France), open-label, non-inferiority, randomized controlled trial from November 2006 through March 2011 (N=359)

ORAL ANTIBIOTICS
Fluoroquinolones +/- Rifampicin | Amino-penicillins

CLINICAL RELEVANCE
- Antibiotic regimens not pre-specified
- MRSA included in both groups
- Treatment failure: deaths at 1 year or treatment extension >6 days
- Most common: *S. aureus*, CoNS., *Strep* spp., *Enterococcus* spp., Enterobacteriaceae
- Follow up: 1 year

CONCLUSION
No difference in cure between groups with limited IV antibiotic duration

RESULTS (6 VS 12 WEEKS)



Bernard, L., *et al.*, Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: an open-label, non-inferiority, randomised, controlled trial. Lancet. 2015.

Oral Versus Standard Antimicrobial Treatment for Pyogenic Native Vertebral Osteomyelitis

DESIGN
Single-center (Italy), retrospective, observational study from November 2008 to June 2018 (N=249)

ORAL GROUP ANTIBIOTICS
Fluoroquinolones +/- Rifampin
Minocycline +/- Rifampin
Other

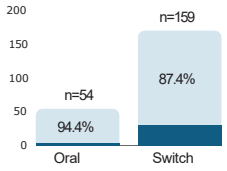
CLINICAL RELEVANCE
- Antibiotic regimens not pre-specified
- Excluded MDRO in outcomes
- Treatment failure: no improvement/progression during treatment
- Most common: *S. aureus*, CoNS., *Strep* spp., *Enterococcus* spp., Enterobacteriaceae
- Follow-up: 1 year

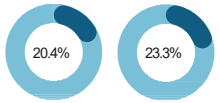
CONCLUSION
An entirely oral treatment, may be as effective as IV treatment in some patients with NVO

RESULTS (ORAL VS SWITCH)

Oral group: treated exclusively with oral antibiotics (<24 hours of IV treatment)

IV/Switch group: initial IV treatment, followed when feasible by oral switch





Treatment-related adverse events

Diabetic Foot Infections (DFIs)

2012 IDSA Guidelines - DFIs

- Prefer IV therapy for all severe and some moderate DFIs, at least initially (*weak, low*)
- Switch to oral agents when patient is clinically stable and culture results are available
- Highly bioavailable oral antibiotics can be used in most mild and moderate infections (*strong, moderate*)

Three Weeks Versus Six Weeks of Antibiotic Therapy for Diabetic Foot Osteomyelitis

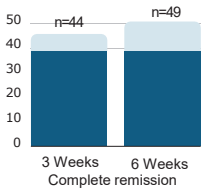
DESIGN
Single-center (Switzerland), prospective, randomized, non-inferiority pilot trial (N=93)

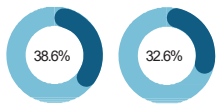
ORAL ANTIBIOTICS
Amoxicillin-clavulanate
Levofloxacin
Clindamycin
TMP-SMX
Doxycycline

CLINICAL RELEVANCE
- Antibiotic regimens **were** pre-specified
- Excluded MDRO in outcomes
- Treatment failure: recurrence or persistence with same site and pathogen
- Most common: *S. aureus*, *Strep* spp., GNOs
- Follow up: median 11 months

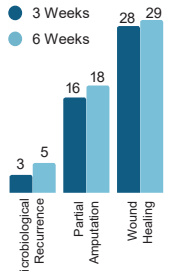
CONCLUSION
A 3-week antibiotic course is non-inferior to 6-week course after debridement for the treatment of DFO

RESULTS (3 VS 6 WEEKS)





Treatment-related adverse events



2 days was the mean duration of IV therapy

DFO – Entirely Oral or Short Initial IV Therapy

Study	Design	Intervention	Results	Take-Away
Senneville 2008 (France)	Multi-center, retrospective study (N=59)	• Antibiotics without surgical intervention based on bone cultures or swab cultures • Fluoroquinolones +/- rifampin or cephalosporins or other combination	Remission: • 81.8% bone culture • 50% swab culture IV for 1st week: • 22.2% treatment failure group • 37.5% remission group	Antibiotics either entirely oral or IV for ≤7 days then oral IV for the first week was not significantly associated with remission
Tone 2015 (France)	Multi-center, prospective, randomized, non-inferiority study (N=40)	• GPCs: Rifampin +/- levofloxacin,TMP-SMX, doxycycline, or linezolid • GNOs: Levofloxacin or ciprofloxacin • 6 vs 12-weeks	6 vs 12-weeks: • Remission in 60% vs 70% • GI adverse events in 15% vs 45%	6-weeks similar to 12-weeks Antibiotics either entirely oral or IV for 5-7 days then oral

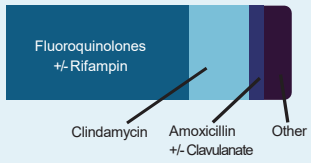
Prosthetic Joint Infections (PJIs)

2012 IDSA Guidelines - PJIs

Debridement and Retention of Prosthesis (DAIR) or 1-Stage Exchange		
Staph PJI	Initial IV + rifampin then rifampin + companion oral drug	• Fluoroquinolone • TMP-SMX • Doxycycline
Unable to use rifampin	IV therapy	• Pathogen-specific
PJI due to other organisms	Pathogen-specific IV or highly bioavailable oral therapy	• Fluoroquinolone • Clindamycin • Linezolid
2-Stage Exchange		
	IV or a highly bioavailable oral therapy	• Fluoroquinolone • TMP-SMX • Doxycycline • Clindamycin • Linezolid

Antibiotic Therapy for 6 or 12 Weeks for Prosthetic Joint Infection (DAPITO Trial)

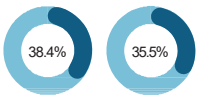
DESIGN
Multicenter (France), open-label, randomized, controlled, non-inferiority trial from November 2011 through January 2015 (N=404)

ANTIBIOTICS


CLINICAL RELEVANCE
- Antibiotic regimens not pre-specified
- MDROs **included** in both groups
- Treatment failure: persistent infection, new infection, or probable failure
- Most common: *S. aureus*, *Strep* spp., GNOs
- Follow up: 2 years

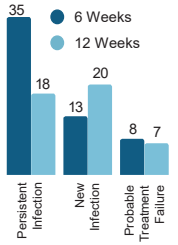
CONCLUSION
A 6-week antibiotic course is **NOT** non-inferior to 12-week course in the treatment of PJIs

RESULTS (6 VS 12 WEEKS)



Treatment-related adverse events

9 days was the median duration of IV therapy

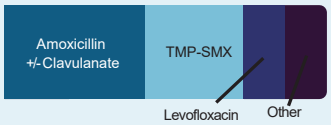


Excellent Outcomes with the Selective Use of Oral Antibiotic Therapy for Bone and Joint Infections: A Single-Center Experience

DESIGN

Single-center (US), retrospective, study, July 2019 through December 2019. PO group: started/switched to oral therapy; IV group: IV antibiotics only (N=40)

ANTIBIOTICS



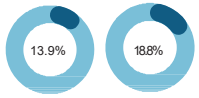
CLINICAL RELEVANCE

- Antibiotic regimens not pre-specified
- MDROs included in both groups
- Treatment failure: death, unplanned surgery, or unplanned suppressive antibiotics
- Most common: *S. aureus*, CoNS, *Strep.* spp., Enterobacteriaceae
- Follow up: 2 years

CONCLUSION

Study's criteria was effective at identifying patients who are likely to do well with oral therapy

RESULTS (PO VS IV)



Treatment-related adverse events

Treatment failure
- 0/23 vs 6/17

Unplanned surgery at surgery
- 0/23 vs 3/17

Initiation of chronic antibiotic suppression
- 0/23 vs 5/17

10 days was the mean time to switch in the PO group for PJIs

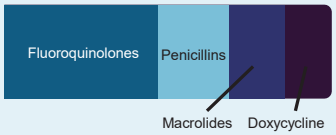
Infection types:

Oral Versus Intravenous Antibiotics for Bone and Joint Infections (OVIVA)

DESIGN

Multi-center, parallel group, randomized, open label, non-inferiority trial (N=1054)

ORAL ANTIBIOTICS



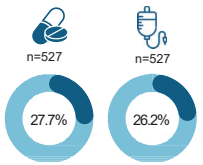
CLINICAL RELEVANCE

- Antibiotic regimens not pre-specified
- MRSA in both groups
- Treatment failure: presence of at least one clinical, microbiologic, or histologic criterion
- Most common: *S. aureus*, CoNS, *Strep.* spp., *Pseudomonas* spp.
- Follow up: 1 year

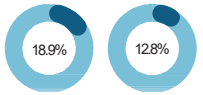
CONCLUSION

Oral therapy non-inferior to IV therapy for complex orthopedic infection, as assessed by treatment failure at 1 year

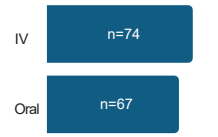
RESULTS (PO VS IV)



At least one serious adverse event



Early discontinuation of therapy



Treatment failure within 1 year

14 vs **11**

Median hospital length of stay (days)

Potential Oral Regimens for Bone and Joint Infections

Type of Infection	Empiric Oral Antibiotic					
	Fluoroquinolone	TMP-SMX	Doxycycline	Amoxicillin +/- clavulanate	Linezolid	Clindamycin
Osteomyelitis w/o implant	✓	✓	✓		✓	✓
Diabetic foot osteomyelitis	✓	✓	✓	✓	✓	✓
Osteomyelitis with retained implant, including PJI						
<3 months after procedure (early)	✓	✓	✓		✓	✓
≥3 months after procedure (late onset)	✓	✓	✓		✓	✓

Summary – Bone and Joint Infections

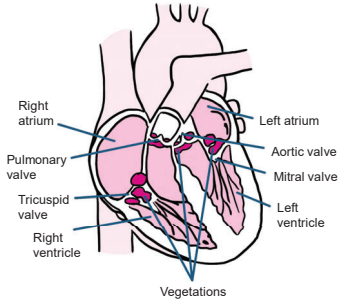
- Most data for oral treatment is available for osteomyelitis and PJIs
- Starting with oral treatment may be appropriate in some patients
- Optimal time for oral switch has not been well established
- The OVIVA trial is the main landmark trial

USHP

Infective Endocarditis (IE)

IE Background

- Mortality due to IE ranges from 25-40%
- Left-sided IE accounts for 90-95% of cases
- Right-sided IE associated with IVDU, devices, and catheters
- Guidelines recommend long term IV therapy
- Most data with Gram positive infections



Baddour, L. M., *et al.*, Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications. AHA Scientific Statement. 2015
Cuervo, G., *et al.*, Current Challenges in the Management of Infective Endocarditis. Front Med. 2021
Shmueli, H., *et al.*, Right-Sided Infective Endocarditis 2020: Challenges and Updates in Diagnosis and Treatment. JAHA. 2020

2015 AHA Guidelines – Infective Endocarditis

Isolated Organism	Regimen
Viridans group *Streptococcus*	Penicillin G (+ gentamicin if PCN resistant) Ceftriaxone + gentamicin Vancomycin
Staphylococcus spp.	Nafcillin or oxacillin Cefazolin Vancomycin (if methicillin resistant) Daptomycin (if methicillin resistant) If prosthetic valve IE: + rifampin and gentamicin
***Enterococcus* spp.**	Ampicillin or penicillin + gentamicin Ampicillin + ceftriaxone Vancomycin + gentamicin
HACEK Organisms	Ceftriaxone Ampicillin Ciprofloxacin

HACEK: Haemophilus species, Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae

Osman, D. R., *et al.*, Diagnosis and Management of Prosthetic Joint Infection: Clinical Practice Guidelines by the Infectious Diseases Society of America (Archived). Clin Infect Dis 2012

Oral Antibiotic Treatment of Right-Sided Staphylococcal Endocarditis in Injection Drug Users: Prospective Randomized Comparison with Parenteral Therapy

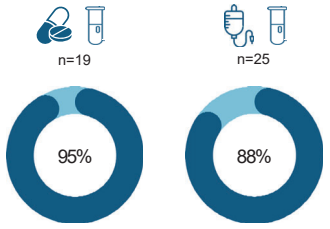
DESIGN
Single-center (US), randomized, prospective, comparison trial from November 1990 through August 1993 (N=85)

ANTIBIOTICS
Ciprofloxacin + Rifampin
Oxacillin or Vancomycin

CLINICAL RELEVANCE
- Antibiotic regimens **were** pre-specified
- Fluoroquinolone-resistance and MRSA in the IV group only
- Treatment failure: CV complications, worsening infection, sustained bacteremia
- Only *Staph.* spp. infections included
- Follow up: 1month

CONCLUSION
Select patients with right-sided *Staph.* spp. IE, oral fluoroquinolones plus rifampin are effective and associated with less drug toxicity than IV therapy

RESULTS (PO VS IV)



Blood culture test of cure

Heldman, A. W., et al., Oral Antibiotic Treatment of Right-sided Staphylococcal Endocarditis in Injection Drug Users: Prospective Randomized Comparison with Parenteral Therapy . Am J Med 1996

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis (POET)

DESIGN

Multi-center (Denmark), randomized, non-inferiority trial from July 2011 through August 2017 (N=400)

ORAL ANTIBIOTICS

***Staph* (non-MRSA)**
- Dicloxacillin + rifampicin
- Amoxicillin + rifampicin

Strep
- Amoxicillin + rifampicin
- Amoxicillin + moxifloxacin

E. faecalis
- Amoxicillin + moxifloxacin
- Amoxicillin + linezolid

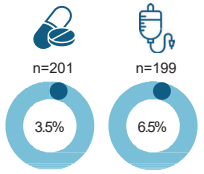
CoNS
- Fusidic acid + linezolid
- Linezolid + rifampicin

CLINICAL RELEVANCE
- Antibiotic regimens **were** pre-specified
- MDROs excluded
- Treatment failure: PO group switching to IV
- Included: *Staph* spp. (non-MRSA), *E. faecalis*, *Strep* spp., CoNS
- Follow up: 6 months

CONCLUSION

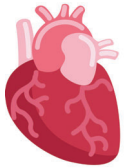
In stable patients with left-sided endocarditis, switching to oral antibiotic treatment was non-inferior to continued IV treatment

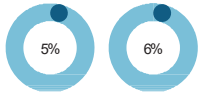
RESULTS (PO VS IV)



All-cause mortality

Other components of primary composite outcomes were similar





Treatment-related adverse events

Long-Term Outcomes in POET Patients

- Median 5.4-year follow-up
- Primary composite outcome (PO vs IV)
  - 32.8% vs 45.2%
  - Difference driven mainly by lower incidence of death from any cause in the PO group
- Conclusion: No indication for increased treatment failure in patients transitioned to oral compared to those continued on IV during long-term follow up

Future Data – RODEO Trial

- Oral switch versus standard intravenous antibiotic therapy in left-sided endocarditis due to susceptible staphylococci, streptococci or enterococci (RODEO)
- Two simultaneous multi-center open-label prospective randomized trials
  - Assessing non-inferiority of oral switch compared to entirely IV therapy in left-sided IE
  - One trial is assessing infections caused by staphylococci (RODEO-1) and the other is assessing streptococci or enterococci (RODEO-2)
- Plan to include 324 participants in each trial
- Methods and outcomes are similar to the POET trial

Potential Oral Regimens for Infective Endocarditis

Causative Pathogen	Oral Antibiotic
***Staphylococcus* spp.** (non-MRSA)	Amoxicillin Fluoroquinolone Linezolid TMP-SMX
***Streptococcus* spp.**	Amoxicillin +/- rifampin or fluoroquinolone
***Enterococcus* spp.**	Amoxicillin +/- fluoroquinolone or linezolid

Summary – Infective Endocarditis

- Starting with oral treatment may be preferred in some patients
- The optimal time for oral switch has not been well established
- POET is the main landmark trial
- RODEO 1 & 2 trials will likely add much needed additional data

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