



# Metronidazole Dosing Initiative: to BID or not to BID

Antimicrobial Stewardship

August 2024

# Bottom Line Up Front: Recommendations

- **Implement BID metronidazole dosing for all TID/Q8H IV/PO metronidazole orders EXCEPT** when used for treatment of *Clostridiodes difficile* infections, CNS infections, infections caused by ameba (i.e. *Entamoeba histolytica* infection), and treatment of *Helicobacter pylori*
- **Convert all eligible metronidazole IV orders to PO**

# Metronidazole Review

## Metronidazole Pearls



### Mechanism of Action

Toxic metabolites bind and disrupt DNA strands  
Requires low oxidation-reduction environment for prodrug activation → more effective in anaerobic environments



### Bioavailability

Excellent bioavailability (>90%)  
Drug exposures are similar when given PO and IV  
IV metronidazole is ONLY needed if there is a concern that a patient cannot absorb PO metronidazole



### Pharmacokinetics & Pharmacodynamics

Maximum metronidazole concentrations to bacterial MIC (peak:MIC) and area under the curve to bacterial MIC (AUC:MIC) are the PKPD parameters best associated with metronidazole efficacy, although there is limited clinical data to define a target goal



### Adverse Drug Reactions

Neurotoxicity: peripheral neuropathy (more common with prolonged treatment or high doses; usually resolves with stopping metronidazole)  
Gastrointestinal side effects: metallic taste  
Acute pancreatitis/hepatitis: rare

# Metronidazole Dosing

## Pharmacokinetic study of metronidazole BID

### Methods

- 48 patients undergoing surgery
  - 25 patients given metronidazole 400mg PO q12h
  - 23 patients given metronidazole 500mg IV q12h

### Results



### Conclusions

- **Trough concentrations remain above therapeutic concentrations when given IV or PO every 12 hours**

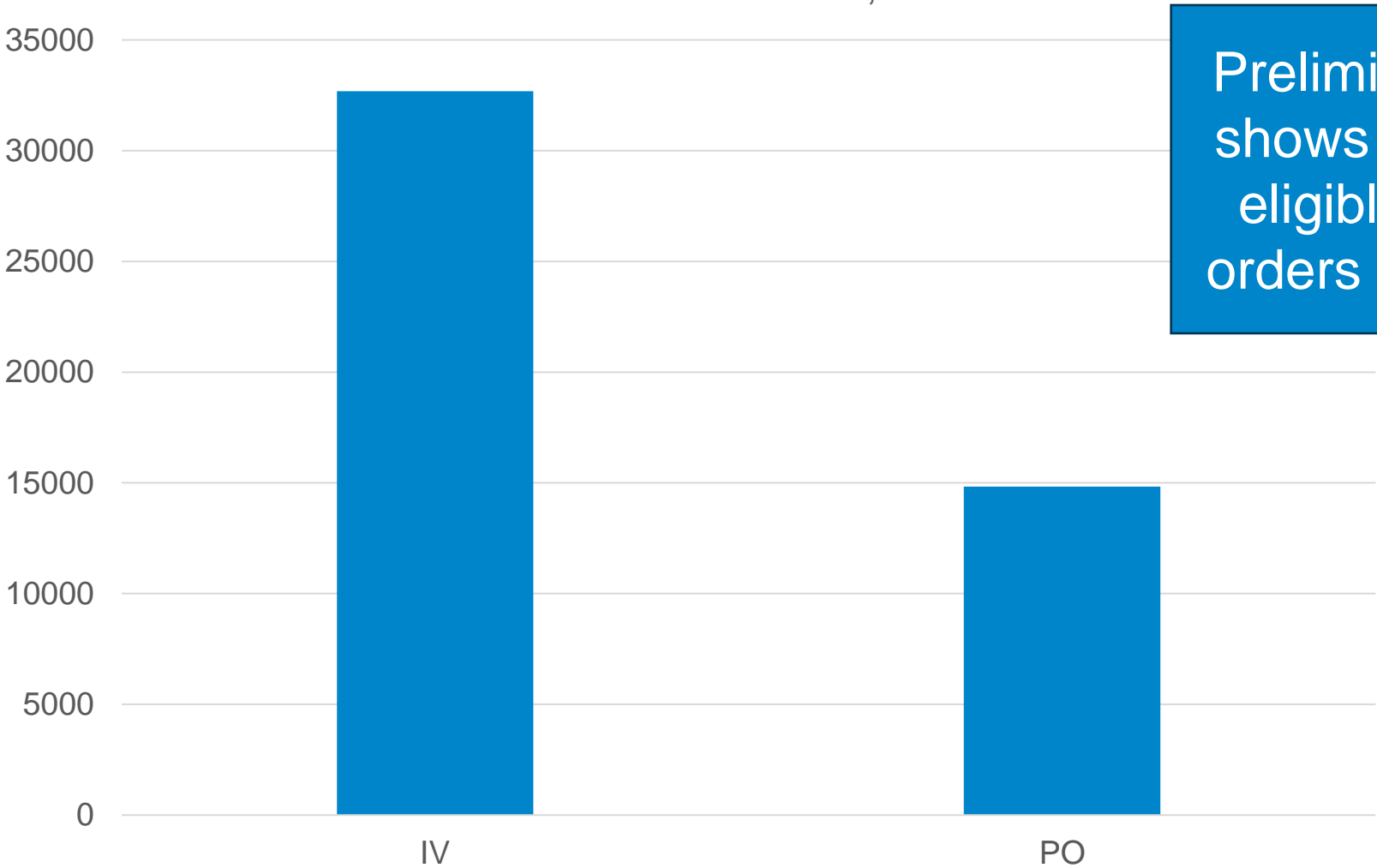
# Metronidazole Dosing

- Clinical studies support Q12H dosing of metronidazole for common infections caused by anaerobes (i.e. anaerobic bacteremia, intra-abdominal infections)

	Study Design	Population	Primary Endpoint	Intervention	Results
Soule et al, 2018	Retrospective pre-post intervention	Patients receiving metronidazole for at least 3 days for presumed anaerobic coverage (84% with intra-abdominal infection) Excluded patients with CNS infections, CDI, parasitic/ameobic infections	Clinical cure (resolution of s/sx of infection at end of therapy or discharge)	Metronidazole Q12H (n = 100) vs metronidazole Q8H (n = 100)	Clinical cure in 83% of patients in Q8H group and 83% of patients in Q12H group
Shah et al 2021	Retrospective study	Patients receiving metronidazole for anaerobic bacteremia (43% with <i>B. fragilis</i> bacteremia, 76% with intra-abdominal source of bacteremia) Excluded patients with CNS infections, CDI	All cause 30-day mortality	Metronidazole Q12H (n = 53) vs metronidazole Q8H (n = 32)	All cause 30-day mortality in 16% of patients in Q8H group and 9% in Q12H group

# Current Use of IV and PO Metronidazole at LH

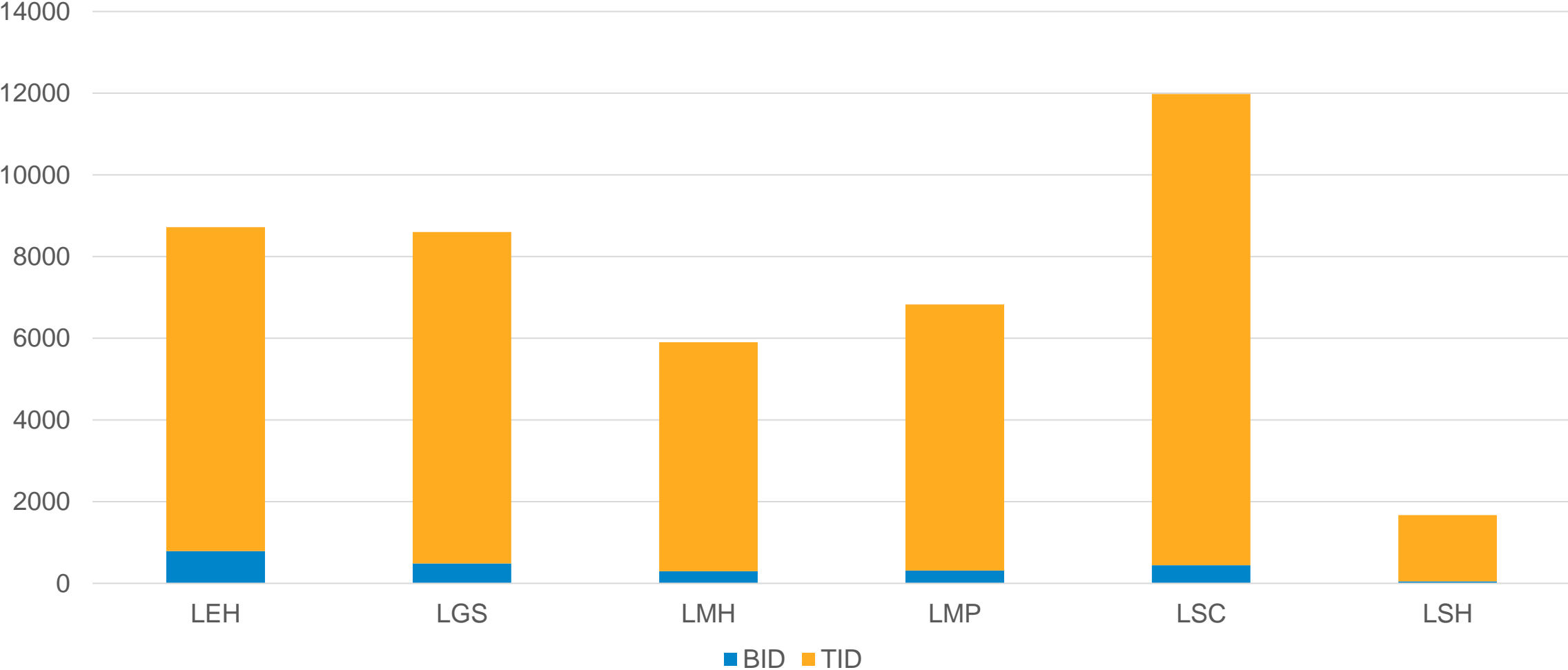
IV and PO Metronidazole Use, FY 2024



Preliminary data at Legacy shows that very few (<5%) eligible IV metronidazole orders are converted to PO

# Current Use of Metronidazole Q12H at LH

Use of BID and TID Metronidazole Across Legacy



# Let's be financial stewards

## Metronidazole is relatively inexpensive

- ~\$3.00 per IV dose
- ~\$0.50 per PO dose



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- IV metronidazole is in the **top 20 anti-infective spend for FY2024**, alongside other high spend anti-infectives include remdesivir (~\$500 per dose), ceftaroline (~\$300 per dose), amphotericin B (~\$2,000 per dose)

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## How can we help?

- **Implement BID metronidazole dosing!**
  - If all TID and q8h metronidazole orders were converted to BID in FY2024, we would have saved **~\$30,000**
- **Convert all eligible IV orders to PO!**
  - If all eligible IV metronidazole orders were converted to PO in FY2024, we would have saved **~\$11,000**

# Recommendations

- **Implement BID metronidazole dosing for all TID/Q8H IV/PO metronidazole orders EXCEPT** when used for treatment of *Clostridioides difficile* infections, CNS infections, infections caused by ameba (i.e. *Entamoeba histolytica* infection), and treatment of *Helicobacter pylori*
  - Recommend implementation of default frequency in Epic orderable
  - Recommend alt alert for Q8H and TID metronidazole
- **Convert all eligible metronidazole IV orders to PO**
  - Recommend pharmacist utilization of IV to PO protocol



**Thank you!**