Clinical outcomes of a twice daily metronidazole dosing strategy for *Bacteroides* bloodstream infections

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INTRODUCTION

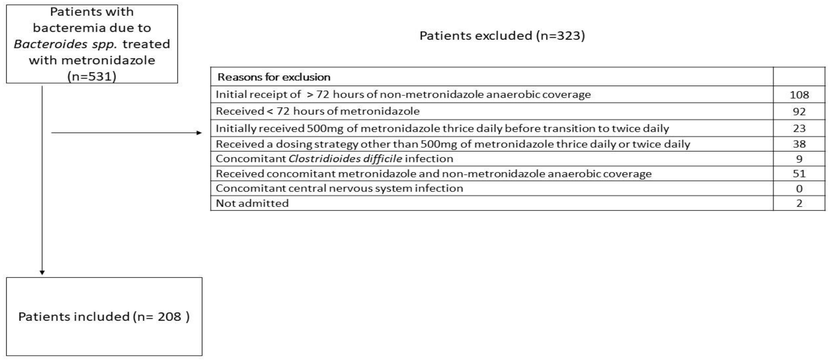
- Despite over a half century of experience with metronidazole, the optimal dose has yet to be been identified
- Although current prescribing guidance recommends metronidazole be administered at 500mg every 6-8 hours for the treatment of anaerobic infections, pharmacokinetics data would support a dose of 500mg every 12 hours
- The purpose of this study was to compare the efficacy metronidazole at a dose of 500mg twice versus thrice daily among patients with bacteremia secondary to *Bacteroides spp*

METHODS

- This was a multicenter, retrospective study of adult patients admitted to one of eleven hospitals with bacteremia secondary to *Bacteroides spp* who were treated with metronidazole during admission between October 2010 and June 2021
- Patients were excluded if they received > 72 hours of non-metronidazole anaerobic coverage initially, received < 72 hours of metronidazole, initially received 500mg of metronidazole thrice daily before transition to twice daily, received a dosing strategy other than 500mg of metronidazole thrice daily or twice daily, had concomitant *Clostridioides difficile* infection, received concomitant non-metronidazole anaerobic coverage, or had a concomitant central nervous system infection
- The primary endpoint was clinical failure which was a composite of all-cause 30-day mortality, escalation of antimicrobial therapy, 30-day readmission or recurrence due to an anaerobic infection, positive repeat blood cultures for *Bacteroides spp*., or failure to resolve leukocytosis or fever
  - Patients were considered to have escalated antimicrobial therapy if, in the setting of ongoing signs of infections, antimicrobial therapy was either broadened or the frequency of metronidazole was increased from twice daily to thrice daily
- Outcomes of patients who received 500mg twice daily of metronidazole were compared to patients who received 500mg thrice daily in the bivariate model
- A multivariate logistic regression model was performed on all variables with a P-value < 0.05 in the bivariate model
- Concomitant antimicrobials were excluded in the multivariate model due to institution formulary differences and stewardship restriction policies

RESULTS

Figure: Inclusion criteria



Reasons for exclusion	
Initial receipt of > 72 hours of non-metronidazole anaerobic coverage	108
Received < 72 hours of metronidazole	92
Initially received 500mg of metronidazole thrice daily before transition to twice daily	23
Received a dosing strategy other than 500mg of metronidazole thrice daily or twice daily	38
Concomitant *Clostridioides difficile* infection	9
Received concomitant metronidazole and non-metronidazole anaerobic coverage	51
Concomitant central nervous system infection	0
Not admitted	2

Baseline demographics	MDZ every 12 hours (n=68)	MDZ every 8 hours (n=140)	P-value
Age, median (IQR)	67 (53-79.3)	68 (58.8-77)	0.599[a]
Female gender, n (%)	33 (48.5)	68 (48.6)	0.996[b]
Weight in Kg, median (IQR)	76.8 (65.1-97.2)	77 (64-91)	0.429[a]
Charleson comorbidity index, median (IQR)	3 (1-6)	3 (1-5.25)	0.814[a]
PITT Bacteremia score, median (IQR)	1 (0-2)	1 (0-1)	0.216[a]
Admitted prior to 2016, n (%)	3 (4.4)	43 (30.7)	< 0.001[c]
Pre-infection length of stay, median (IQR)	0 (0-0)	0 (0-5)	< 0.001[a]
Initial oral metronidazole use, n (%)	38 (55.8)	23 (16.4)	< 0.001[b]
Time to active therapy, median (IQR)	1 (0-2)	1 (0-2)	0.558[a]
Empiric days of therapy of non-metronidazole anaerobic coverage, median (IQR)	0 (0-2)	0 (0-0)	< 0.001[a]
Source of infection, n (%)			
Transient GI translocation	24 (35.3)	44 (31.4)	
Biliary	6 (8.8)	9 (6.4)	
Intrabdominal abscess	7 (10.3)	16 (11.4)	
Complicated diverticulitis/appendicitis	4 (5.9)	5 (3.6)	
Uncomplicated diverticulitis/appendicitis	1 (1.5)	18 (12.9)	
Osteomyelitis/Sacral ulcer	14 (20.5)	8 (5.7)	
GI obstruction/perforation	3 (4.4)	10 (7.1)	
Diabetic foot infection/ SSTI[d]	2 (2.9)	4 (2.9)	
Other/ Unknown	7 (10.3)	26 (18.6)	
Managed surgically, n (%)	30 (44.1)	60 (42.9)	0.863[b]
Source control achieved within 5 days if managed surgically, n (%)	N=30 19 (63.3)	N=60 40 (66.7)	0.754[b]

a Mann-Whitney U
b Chi-square test
c Fishers exact test
d Skin and soft tissue infection

Univariate outcome comparison between groups

Variable	MDZ every 12 hours (n=68)	MDZ every 8 hours (n=140)	P-value
Clinical failure, n (%)	17 (25)	44 (31.4)	0.339[b]
30-day mortality, n (%)	9 (13.2)	26 (18.6)	0.335[b]
Post infection length of stay, median (IQR)	8 (5-12.3)	9 (6-15.3)	0.045[a]
Escalation of antimicrobial therapy, n (%)	7 (10.3)	17 (12.1)	0.694[b]
30-day readmission due to anaerobic infection, n (%)	1 (1.5)	3 (2.1)	> 0.999 [c]
Resolution of fever, n (%)	N=45 45 (100)	N=67 65 (97)	0.242[c]
Resolution of leukocytosis, n (%)	N=37 29 (78.4)	N=68 52 (76.8)	0.824[b]
Positive repeat blood cultures, n (%)	N=62 0 (0)	N=106 1 (0.9)	> 0.999[c]

a Mann-Whitney U
b Chi-square test
c Fishers exact test

Multivariate model for clinical failiure

Multivariate model for clinical failure	OR	95% CI	P-value
Thrice daily metronidazole dosing	0.74	0.33-1.65	0.457
Days to active *Bacteroides* therapy	1	0.81-1.22	0.968
Days of initial non-metronidazole anaerobic therapy	0.91	0.59-1.34	0.646
Pre-infection days of stay	1.02	0.99-1.05	0.106
Admission prior to 2016	1.09	0.49-2.39	0.829
Initial oral metronidazole use	0.45	0.18-1.03	0.066

CONCLUSIONS

- In the largest study to date of patients with *Bacteroides spp*. bacteremia treated with metronidazole we determined that twice daily dosing strategies were as effective as thrice daily metronidazole dosing strategies for the composite outcome of clinical failure
- Metronidazole twice daily dosing for anaerobic infections may mitigate adverse effects and serve as a cost containment strategy
- Further studies are encouraged to confirm these findings and define the optimal strategies for treatment of anaerobic infections