Clinical outcomes of single versus double anaerobic coverage for intra-abdominal infections

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BACKGROUND

- Intra-abdominal infections (IAIs) are polymicrobial and associated with high rates of morbidity and mortality.[1-3] The organisms involved in IAIs include a mixture of aerobic and anaerobic bacteria, particularly *Bacteroides fragilis*.[4-6]
- The antimicrobial agents recommended for IAIs by the Infectious Diseases Society of America/Surgical Infection Society guidelines include a single-agent therapy with a carbapenem or piperacillin/tazobactam and a combination therapy with metronidazole plus a cephalosporin or fluoroquinolone.[7-8]
- Despite these guideline recommendations, piperacillin/tazobactam, which has anaerobic activity against *Bacteroides* species, is often used with metronidazole in clinical practice resulting in an unnecessary double anaerobic coverage. The consequences of such regimens may result in adverse effects including *Clostrodioides difficile* infections.
- Piperacillin/tazobactam remains as the most active beta-lactam/beta-lactamase inhibitor combination and continues to be very active against the *B. fragilis* with a resistance rate of <1%.[9-10]
- Nevertheless, the impact of double anaerobic coverage on clinical outcomes of IAIs is unknown. Therefore, the aim of this study was to evaluate the clinical outcomes of double anaerobic therapy for post-operative IAIs.

OBJECTIVE

To compare the clinical outcomes of piperacillin/tazobactam to combination therapy with piperacillin/tazobactam and metronidazole in surgically managed intra-abdominal infections.

METHODS

- Study Design:
  - Institutional board approved, retrospective, single center, cohort study
- Study Period:
  - January 1, 2016 to June 30, 2019

Inclusion Criteria	Exclusion Criteria
• Age ≥ 18 years old • Surgically managed IAIs • Treated with piperacillin/tazobactam or combination therapy with piperacillin/tazobactam plus metronidazole	• No surgical intervention • Did not complete therapy with piperacillin/tazobactam or combination therapy with piperacillin/tazobactam plus metronidazole due to death or other reasons
Primary Endpoint	**Secondary Endpoint**
• Length of hospital stay, in-hospital post-operative complications, and re-admission within 30 days of discharge due to post-operative complications • Post-operative complication was defined as septic shock, surgical site infection, post-operative infection(s), or repeat surgery	• In-hospital mortality and hospital-acquired *Clostridioides difficile* infections

- Statistics:
  - Chi-square, multivariate analysis, and aggregate resampling of the sampling distribution were conducted. An alpha of <0.05 was considered statistically significant.

RESULTS

Table 1: Baseline Characteristics	Piperacillin/ tazobactam plus metronidazole (n=67)	Piperacillin/ tazobactam (n=96)	P-value
Age, years, mean (IQR)	53.1 (39-64.5)	46.3 (32-58.3)	0.017
Sex, n (%)			0.442
Male	37 (56.1)	60 (61.9)	
Female	30 (44.8)	36 (54.5)	
Body mass index, kg/m², mean (IQR)	27.7 (22.6-31.2)	28.9 (24.9-32)	0.303
Comorbidities, n (%)			
Hypertension	23 (34.3)	30 (31.3)	0.663
Diabetes	14 (20.9)	12 (12.5)	0.221
Asthma	7 (10.4)	10 (10.4)	0.806
Hyperlipidemia	6 (9)	10 (10.4)	1
HIV	4 (6)	5 (5.2)	1
COPD	2 (3)	4 (4.2)	1
Malignancy	3 (4.5)	3 (3.1)	1
CVA/TIA	2 (3)	4 (4.2)	1
CHF	4 (6)	1 (1)	0.16
Atrial fibrillation	4 (6)	1 (1)	0.16
CAD	2 (3)	2 (2.1)	1
DVT	2 (3)	0	
Hypothyroidism	1 (1.5)	1 (1)	1
Hyperthyroidism	0	2 (2.1)	
ESRD on HD	2 (3)	0	
Charlson Comorbidity Index, median (IQR)	1 (0-3)	0 (0-2)	0.021
Temperature, F (5 days post-op), mean (IQR)	99 (98.4-99.5)	98.7 (98.2-98.9)	0.013
WBC, K/μL (5 days post-op), mean (IQR)	9.6 (7.4-10.7)	9.7 (7.3-10.3)	0.858
ASA pre-operative assessment score, median (IQR)	2 (2-3)	2 (2-3)	0.11
Surgical wound classification, median (IQR)	3 (3-4)	3 (2-3)	0.002

Table 1: Baseline Characteristics (continued)	Piperacillin/ tazobactam plus metronidazole (n=67)	Piperacillin/ Tazobactam (n=96)	P-value
Diagnosis, n (%)			
Acute appendicitis	13 (19.7)	32 (33)	0.075
Acute cholecystitis	6 (9.1)	35 (36.1)	0.0001
Perforations	27 (40.9)	12 (12.4)	<0.0001
Acute perforated appendicitis	17 (24.2)	13 (14.4)	0.087
Abdominal Abscess	1 (1.5)	1 (1)	1
Gangrenous colon/necrotizing abdominal tissue	1 (1.5)	1 (1)	1
Diverticulitis with abscess	1 (1.5)	1 (1)	1
Cholangitis	0	1 (1)	
Colitis	1 (1.5)	0	
Duration of antimicrobials, days, median (IQR)	7 (5-11)	4 (2-5)	<0.0001
Culture isolates, n (%)			
Escherichia coli	8 (11.9)	3 (3.1)	0.052
Klebsiella pneumoniae	3 (4.5)	0	
Staphylococcus aureus	0	2 (2.1)	
Enterococcus faecium	0	1 (1)	
Enterococcus faecalis	2 (3)	0	
Enterobacter cloacae	0	1 (1)	
Citrobacter freundii complex	1 (1.5)	0	
Enterococcus avium	1 (1.5)	0	
Bacteroides fragilis	1 (1.5)	0	
Pseudomonas aeruginosa	0	1 (1)	
Streptococcus viridans group	1 (1.5)	0	

ASA=american society of anesthesiologists, CVA=cerebrovascular accidents, COPD=chronic obstructive pulmonary disease, CHF=congestive heart failure, CAD=coronary artery disease, HIV=human immunodeficiency virus, DVT=deep vein thrombosis, ESRD=end stage renal diseases, HD=hemodialysis, IQR=interquartile range, post-op=post-operative, TIA=transient ischemic attack, WBC=white blood cell

Table 2: Primary and Secondary Outcomes	Piperacillin/tazobactam plus metronidazole (n=67)	Piperacillin/ tazobactam (n=96)	RR (95% CI)	P-value
Primary Outcomes				
LOS, days, mean	8	5	N/A	<0.0001
In-hospital post-operative complications, n (%)	12 (17.9)	4 (4.2)	0.86 (0.76-0.97)	0.006
Re-admission within 30 days due to post-operative complications, n (%)	1 (1.5)	3 (3.1)	1.97 (0.21-18.5)	0.644
Secondary Outcomes				
In-hospital mortality, n (%)	4 (2.5)	0		
Hospital-acquired *C. difficile* infection, n (%)	1 (1.5)	0		

CI=confidence interval, LOS=length of stay, N/A=not applicable, RR=relative risk

Table 3: Adjusted Primary Outcomes	Mean		Mean Difference	P-value
	Piperacillin/ tazobactam plus metronidazole (n=67)	Piperacillin/ tazobactam (n=96)		
LOS, days	10	6	3.97	<0.0001
In-hospital post-operative complications, (%)	23	8.8	15	<0.0001
Re-admission within 30 days due to post-operative complications, (%)	1.4	3.9	-2.5	<0.0001

LOS=length of stay

DISCUSSION

- Guidelines as well as susceptibility data do not support the use of double anaerobic coverage in IAIs. The Infectious Diseases Society of America and the Surgical Infection Society guidelines do support the use of metronidazole for combination therapy with agents devoid of clinically significant anaerobic activity.[7-8]
- This study demonstrated that double anaerobic coverage was associated with worse clinical outcomes compared to single anaerobic coverage in surgically managed patients with IAIs. In comparison, a recent study demonstrated no additional clinical benefit of double anaerobic coverage for children with perforated appendicitis.[6] Consistent with these findings, this current study suggest that IAIs may be managed with single anaerobic coverage agents alone (e.g., piperacillin/tazobactam).
- When comparing patients treated with piperacillin/tazobactam with those treated with piperacillin/tazobactam plus metronidazole, it is evident that patients treated with double anaerobic coverage were sicker, with higher rates of Charlson Comorbidity Index, 5-day post-operative body temperature, higher risk for surgical site infections, and having more complicated IAIs, such as perforations. This is due to selection bias, as doctors tended to treat with piperacillin/ tazobactam plus metronidazole in patients with severe disease for a longer period of time. To adjust for some of these confounding factors, aggregate resampling of the sampling distribution was performed and similar results were found.
- This study has several limitations. This was a retrospective, single-center study, and thus selection bias was unavoidable since there was a tendency for double anaerobic coverage treatment for more complicated patients. To address this bias, adjusted rates were calculated demonstrating similar results. As the study was retrospective, the ability to complete missing data and to follow patients was limited. Finally, only a small minority of the patients included was immunocompromised; thus, these results cannot be generalized to immunocompromised patients.

CONCLUSION

The results of this study suggest that double anaerobic coverage is associated with worse clinical outcomes than single anaerobic coverage in post-operative IAIs. Therefore, the approach of single anaerobic coverage supports avoiding excessive use of metronidazole without compromising clinical outcomes.

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DISCLOSURES

Authors of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.