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Do Polymicrobial Intra-Abdominal Infections Have Worse Outcomes than Monomicrobial Intra-Abdominal Infections?

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Abstract

Background: Numerous studies have demonstrated microorganism interaction through signaling molecules, some of which are recognized by other bacterial species. This interspecies synergy can prove detrimental to the human host in polymicrobial infections. We hypothesized that polymicrobial intra-abdominal infections (IAI) have worse outcomes than monomicrobial infections.

Methods: Data from the Study to Optimize Peritoneal Infection Therapy (STOP-IT), a prospective, multicenter, randomized controlled trial, were reviewed for all occurrences of IAI having culture results available. Patients in STOP-IT had been randomized to receive four days of antibiotics vs. antibiotics until two days after clinical symptom resolution. Patients with polymicrobial and monomicrobial infections were compared by univariable analysis using the Wilcoxon rank sum, χ^2, and Fisher exact tests.

Results: Culture results were available for 336 of 518 patients (65%). The durations of antibiotic therapy in polymicrobial ($n=225$) and monomicrobial IAI ($n=111$) were equal ($p=0.78$). Univariable analysis demonstrated similar demographics in the two populations. The 37 patients (11%) with inflammatory bowel disease were more likely to have polymicrobial IAI ($p=0.05$). Polymicrobial infections were not associated with a higher risk of surgical site infection, recurrent IAI, or death.

Conclusion: Contrary to our hypothesis, polymicrobial IAI do not have worse outcomes than monomicrobial infections. These results suggest polymicrobial IAI can be treated the same as monomicrobial IAI.

Intra-abdominal infection (IAI) occurs when bacteria invade the normally sterile abdominal cavity. This condition includes a spectrum of clinical disease states and organs, from localized acute appendicitis to frank, feculent peritonitis [1]. Uncomplicated IAI involves a single organ, without affecting the entire peritoneum. Complicated IAI (cIAI) occurs when the infection spreads and forms an abscess or causes diffuse peritonitis [2]. These IAI can be difficult to detect early and treat. Appropriate source control, resuscitation, and antimicrobial selection are the cornerstones of treatment [3]. Complicated IAI are a prototypical example of a polymicrobial infection [4].

Historically, many believed a single pathophysiologic process, caused by a unique microorganism, produces infections. It is now known that complex interactions are at play that may involve synergism [5–7]. Synergy is particularly important in IAI, because surgical infections are almost always polymicrobial [7,8]. Previous studies have shown that polymicrobial infections exhibit heightened pathogen persistence and disease severity, as well as increased antimicrobial resistance [6]. This process is termed ''polymicrobial synergy,'' which is defined as ''an interaction between two or more microbes in an infection site that results in enhanced disease compared with infections containing the individual microbe acting alone'' [6].

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Table 1. Baseline Demographic Features of Patients, Stratified by Microbial Status

Demographic	*Monomicrobial (n = 111)*	*Polymicrobial (n = 225)*	p
Mean age (SEM)	55.2 (1.47)	52.9 (1.07)	0.20
Gender (N, %)			0.08
Male	69 (62)	117 (52)	
Female	42 (38)	108 (48)	
Race (N, %)			
Caucasian	83 (75)	181 (80)	0.26
Black	23 (21)	38 (17)	0.45
Hispanic	5 (5)	15 (7)	0.43
Asian	2 (1.8)	3 (1.3)	0.67
Native American	1 (1)	1 (0.5)	0.55
Other	2 (2)	2 (1)	0.60
Mean body mass index (SEM)	28.7 (0.80)	29.2 (0.63)	0.64

SEM = standard error of the mean.

In view of these paradigms, we hypothesized that polymicrobial infections have worse outcomes than monomicrobial infections. The primary aim of this study was to compare differences in surgical site infection (SSI), death, and recurrence in patients with monomicrobial vs. polymicrobial cIAI.

Patients and Methods

This study was granted exemption from the University of Virginia's Institutional Review Board because de-identified data from the Study to Optimize Peritoneal Infection Therapy (STOP-IT) trial database were used. A complete description of the study population and randomization protocols can be found in the original STOP-IT paper [9].

Protocol

After informed consent was obtained, patients from 23 sites throughout the United States and Canada were randomly assigned in a 1:1 ratio to receive various durations of antibiotics. The experimental group received a standard four days of antibiotics after the source control intervention. The control group received antimicrobial therapy for two days beyond resolution of clinical symptoms (i.e., fever, leukocytosis, enteral intolerance). Patients were followed up for 30 days from the time source control was achieved.

Data collection and patient characteristics

Patients older than 16 years with cIAI were eligible for enrollment. Additional inclusion requirements were temperature >38° C, peripheral white blood cell count >11,000/mL, or gastrointestinal dysfunction attributable to peritonitis. Percutaneous or surgical intervention for source control also was a requirement. Patients in the database without available culture results, or patients for whom cultures were not sent, were excluded, and patients with culture data demonstrating no growth were excluded.

Variables examined and outcomes measured

Patient demographics, co-morbidities, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, antibiotic duration, and organ of origin were examined. Patients were then stratified microbiologically according to monomicrobial or polymicrobial infection status. Cultures yielding a single organism or category of microbe (i.e., gram-negative bacillus) were defined as monomicrobial. Multiple isolates or categories of isolates were deemed polymicrobial. Pathogens were recorded by site of infection (IAI, SSI, recurrent IAI), and only initial IAI culture information was used for stratification. Infections were defined by site of origin (community acquired, healthcare associated, hospital acquired). The primary endpoint encompassed 30-day complications, including SSI, recurrence, or death, and a composite outcome of all complications.

Statistical analysis

Univariable analysis was utilized to compare patient demographics, co-morbidities, and hospital complications. Categorical variables were compared using the χ^2 or Fisher exact test where appropriate. Continuous variables were compared using the Student *t*-test or Wilcoxon rank sum test where appropriate. Categorical data are reported as frequencies and percentages, and a statistical significance of $p < 0.05$ was used. All statistical analysis was performed with SAS 9.4 (SAS Institute, Cary, NC) software.

Results

Between August 2008 through August 2013, 518 patients were randomized in the STOP-IT study. Out of these, 336 patients (65%) had available culture results with identifiable microorganisms. Of these, 111 patients (33%) had a monomicrobial infection, whereas 225 patients (67%) had a polymicrobial infection.

Table 2. Clinical Demographics of Patients with Monomicrobial and Polymicrobial Infections

Variable	*Monomicrobial (n = 111)*	*Polymicrobial (n = 225)*	p
Antibiotic group (%)			0.51
4-day	52 (47)	114 (51)	–
Control	59 (53)	111 (49)	–
Median maximum WBC (IQR)	15.2 (11, 19)	16.2 (12, 20)	0.21
Median maximum temperature (IQR)	37.6 (37.1, 38.3)	37.8 (37.1, 38.5)	0.29
Median APACHE II score (IQR)	9 (6, 12)	10 (6, 15)	0.20

APACHE = Acute Physiology and Chronic Health Evaluation; IQR = interquartile range; WBC = white blood cells.

Table 3. Co-Morbidities and Patient Location at Time of Infection

Variable (n, %)	*Monomicrobial* (n = *111*)	*Polymicrobial* (n = *225*)	p
Co-morbidities			
Diabetes mellitus	22 (20)	31 (14)	0.15
Steroid use	8 (7)	12 (5)	0.47
Inflammatory bowel disease	7 (6)	30 (13)	0.05
Malignant disease	11 (10)	33 (15)	0.22
Location of infection			
Community acquired	61 (55)	129 (57)	0.73
Healthcare associated	33 (30)	67 (30)	0.91
Hospital acquired	17 (15)	29 (13)	0.63

Patients with monomicrobial and polymicrobial infections were similar in demographic characteristics (Table 1). There were 186 (55%) males and 150 (45%) females in the study. There were no statistically significant differences in mean age, mean body mass index (BMI), or race between the monomicrobial and polymicrobial infection groups. Median maximum white blood cell counts and maximum temperature between the two strata were similar. Median APACHE II scores for monomicrobial and polymicrobial infections were 9 (interquartile range [IQR] 6, 12) and 10 (IQR 6, 15), respectively (Table 2).

There were no statistically significant differences in the percentage of community-acquired, healthcare associated, or hospital-acquired illnesses between monomicrobial and polymicrobial infections. Healthcare-associated infections included those occurring while the patient was in a nursing, dialysis, or long-term care-related facility. Hospital-acquired infections are illnesses occurring while the patient is hospitalized [10]. The monomicrobial and polymicrobial groups were also similar in co-morbidity profiles. Inflammatory bowel disease trended toward a greater association with the polymicrobial vs. the monomicrobial group (Table 3).

Table 4. Intra-Operative Variables Associated with Monomicrobial and Polymicrobial Infections

Variable (n, %)	*Monomicrobial* (n = *111*)	*Polymicrobial* (n = *225*)	p
Organ of origin			
Colon	34 (31)	90 (40)	0.09
Small intestine	8 (7)	39 (17)	0.01
Appendix	4 (4)	24 (11)	0.03
Other	8 (7)	19 (8)	0.70
Duodenum	4 (4)	10 (4)	1.0
Esophagus	0 –	2 (1)	–
Liver	8 (7)	8 (4)	0.17
Pancreas	8 (7)	4 (2)	0.02
Stomach	11 (10)	10 (4)	0.06
Abdominal wall	8 (7)	3 (1)	0.01
Procedure			
Open surgery	65 (59)	138 (61)	0.62
Percutaneous drainage	46 (41)	87 (39)	0.63
Site closure			
Laparoscopic port site	5 (5)	6 (3)	0.52
Delayed closure	14 (13)	22 (10)	0.43
Primary closure	28 (25)	52 (23)	0.67
Secondary closure	18 (16)	58 (26)	0.05
Presence of drain	46 (41)	87 (39)	0.63

Table 5. Clinical Outcome Variables between Monomicrobial and Polymicrobial Infections

Median (IQR)	*Monomicrobial* (n = *111*)	*Polymicrobial* (n = *225*)	p
Antibiotic days	5 (4, 10)	5 (4, 10)	0.78
Hospital length of stay	7 (4, 11)	7 (4, 12)	0.89
Normalization of white blood cell count	3 (1, 8)	3 (1, 5)	0.31
Normalization of temperature	1 (1, 2)	1 (1, 2)	0.99
Enteral feeding tolerance	3 (1, 5)	4 (1, 6)	0.20

IQR = interquartile range.

The organ of origin was notably different in the two groups. Appendiceal and small intestine infections had significantly greater associations with polymicrobial infections, whereas pancreatic and abdominal wall infections were more likely to be monomicrobial. The type of site closure during the source control procedure (laparoscopic or open surgery or percutaneous drain) did not differ between the groups. Patients with polymicrobial infections were, however, more likely to undergo secondary closure of their sites (Table 4). The two groups were alike in the number of days before the white blood cell count and temperature normalized and in the median total inpatient days (Table 5).

Outcome assessment

Univariable analysis showed no statistically significant differences in outcomes between monomicrobial and polymicrobial infections. Recurrent IAI occurred in 15 patients with monomicrobial infections (14%) and in 38 (17%) with polymicrobial infections; subsequent SSIs were noted in 10

Table 6. Outcome Variables Stratified by Microbiology Findings

Outcome Variable (n, %)	*Monomicrobial*	*Polymicrobial*	p
Recurrent IAI	15 (14)	38 (17)	0.43
Surgical site infection	10 (9)	17 (8)	0.64
Death	0	2 (1)	0.90
Complications	23 (21)	52 (23)	0.62
Any, four-day group	12 (23)	24 (21)	–
Any complication, extended group	11 (19)	28 (25)	–

patients with monomicrobial and 17 with polymicrobial infections. Lastly, death occurred in zero patients with monomicrobial infections and two with polymicrobial infections. The likelihood of the original composite outcome, comprised of SSI, recurrent IAI, or death, was no different in the two groups (Table 6). A subgroup analysis of the STOP-IT randomization arms, the four-day antibiotic group or control group, characterized by monomicrobial or polymicrobial status, demonstrated no differences in composite outcome.

Discussion

Intra-abdominal infections are a source of significant morbidity and death and can be difficult to treat [11]. It is well known that successful management involves early diagnosis, appropriate antibiotic selection, and surgical intervention for source control [4,12]. Further complicating treatment of cIAI is the polymicrobial nature of these infections, along with an increasing trend in resistant organisms [13,14]. Aerobes predominating in IAI include *Escherichia coli, Klebsiella* spp., *Streptococcus* spp., *Proteus* spp., and *Enterobacter* spp. *Bacteroides* spp., *Peptostreptococcus* spp., and *Clostridium* spp. cause prevailing anaerobic infections. Additionally, post-operative infections are dominated by enterococci, staphylococci, and streptococci [12]. To our knowledge, this is the first study to evaluate outcome differences in polymicrobial and monomicrobial infections with available culture data and speciation in both community-acquired and nosocomial infections. Although many studies have demonstrated the polymicrobial nature of IAI infections, and others have evaluated the greater acuity associated with polymicrobial infections, few have compared the two groups.

Several studies demonstrate the synergistic nature of bacterial species, with a prevailing notion that the microbiologic composition of the infection predicts disease prognosis and outcome [5,6,8]. For example, Meleney's synergistic gangrene is the gangrenous lesion produced by the combination of *S. aureus* with streptococci, which is not reproduced with either organism acting alone. However, in combination, these organisms produce progressive gangrene of the abdominal wall after appendiceal abscess drainage [8]. Similarly, Altemeier demonstrated higher-acuity intraperitoneal infections with preferential mixing of certain *E. coli* strains, but not with solitary strains. These strains produced fatal reactions in guinea pigs, which were not reproduced when the strains were injected alone [8]. The mechanisms for synergy are complex and occur through a variety of pathways, including contact-dependent interaction, metabolic interactions, quorum sensing through low-molecular-weight signals, or a combination of these [5,6].

Our study reveals several important findings. First, roughly one third of the infections were monomicrobial (33%), which contradicts the belief that almost all cIAI are polymicrobial. A possible explanation for this observation may be the variable speciation techniques at different institutions. As our ability to isolate microbes improves, we may see that many infections previously thought to be monomicrobial actually are polymicrobial. Second, our results show that polymicrobial infections do not have worse outcomes in terms of recurrent IAI, SSI, death, or composite outcomes, in spite of any bacterial synergy that may be occurring. It is possible that bacterial synergy has little clinical significance, and timely source control plus appropriate antibiotic selection may alleviate or outweigh the toxic effects of bacterial synergy. Additionally, source control procedures debride the surgical incision and may facilitate antimicrobial action [15]. Prompt antibiotic administration is key; therapy initiated after 8 h increases morbidity and mortality rates in both community-acquired and hospital-acquired IAI [12,16].

We expected polymicrobial infections to be associated with aborad pathology, such as appendiceal or colorectal origins. Interestingly, our results show that although colon-related infections were the most common, there was no difference in microbiology in the monomicrobial and polymicrobial groups. Appendiceal and small bowel infections were significantly associated with polymicrobial culture results ($p = 0.03$ and $p = 0.01$, respectively). This emphasizes that antimicrobial therapy should be chosen by general infection location (intra-abdominal) rather than empirically adjusting the choice on the basis of the organ of origin.

Our report has several important limitations, including the post hoc analysis of STOP-IT data, which limits the generalizability of the results. Second, because stratification by microbiology findings was not the primary aim of the original study, we do not have information on whether the infection was post-operative or primary. The outcomes, namely SSI, intra-abdominal recurrence, and death, have low frequencies. Interpretation of these P values should be made with caution, because we may not have enough events to characterize the difference between the two groups accurately. Furthermore, the lack of difference between monomicrobial and polymicrobial outcomes may be attributable to a type II error.

Conclusion

Despite these limitations, this study suggests outcome similarities between monomicrobial and polymicrobial IAI. These results imply that polymicrobial infections should be managed in a fashion similar to monomicrobial infections, especially when considering source control options or antimicrobial duration.

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Author Disclosure Statement

The authors have no relevant financial disclosures to declare.

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