Bacterial Species-Specific Hospital Mortality Rate for Intra-Abdominal Infections

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Abstract

Background: Intra-abdominal infections (IAIs) are a major cause of morbidity and death. We hypothesized that the involvement of specific organisms would predict death independently.

Patients and Methods: All patients with IAIs treated at an academic tertiary-care facility over eight years (June 1999–June 2007) were included. The data collected were demographics, co-morbidities, source of infection, intra-abdominal culture results, type of infection (community-acquired vs. nosocomial), type of intervention (operative vs. percutaneous drainage), and outcome. The Charlson Comorbidity Index and multiple organ dysfunction score (MODS) were used in the analysis.

Results: A total of 389 patients were admitted for 452 infection episodes (IEs) during the study period. None of the 129 patients with appendiceal-related infections died, and these patients were excluded from further analysis. Thus, 323 non-appendiceal IEs were evaluated. The overall mortality rate was 8.7%. The mean age of the patients was 54 y, and 50% of them were male. Intra-abdominal cultures were obtained from 303 IEs (93.8%). The most common cause of IAI was post-operative infection (44%). There were 49 distinct species isolated. The most common were *Enterococcus* (105), *Escherichia coli* (75), *Streptococcus* (62), *Staphylococcus* (51), and *Bacteroides* (46). Bivariable analysis revealed multiple risk factors associated with death. Logistic regression demonstrated that independent risk factors for death were age ≥ 65 years (odds ratio [OR] 3.92), cardiac event (OR=8.17), catheter-related blood stream infection (OR=6.16), and growth of *Clostridium* (OR=13.03). The growth of *Streptococcus* was predictive of survival. The C statistic was 0.89.

Conclusions: In addition to age and intrinsic patient factors, the presence of specific bacterial organisms independently predicts death in patients with non-appendiceal IAI.

DESPITE ADVANCES in the diagnosis and treatment of disease, sepsis is ranked tenth among causes of death nationally [1]. A common source of sepsis, intra-abdominal infection (IAI), has a reported mortality rate as high as 30% [2]. These infections encompass a variety of specific diseases, including acute appendicitis, perforated viscus, and post-operative complications, that affect every age and ethnicity and both sexes. Many classification and scoring systems have been developed to guide treatment and predict outcome [3–7]. However, the complexity of these systems limits their usefulness at the bedside, and they do not necessarily apply to patients with IAI. Furthermore, the relation between outcomes and specific bacterial organisms identified in IAI has had limited study.

In a previous report from our institution [8], we identified age ≥ 65 years, catheter-related blood stream infection (CRBSI),

and a cardiac event as independent predictors of death in patients with IAI. In this study, we investigated the impact of specific bacterial organisms on the IAI mortality rate. Specifically, we hypothesized that particular organisms would be associated independently with death in patients with IAI.

Patients and Methods

We conducted a retrospective review of IAI at our institution, a tertiary-care facility and regional Level I trauma center, over an eight-year period (June 1999–June 2007). The MetroHealth Medical Center Institutional Review Board approved the study.

The electronic medical records and hospital database were queried for patients' assigned International Classification of

Disease (ICD)-9 codes for IAI, including intra-abdominal abscess and diffuse peritonitis. The original study population was identified from the administrative database utilizing ICD-9 coding to identify IAIs. Other ICD-9 diagnoses and other data were obtained utilizing the electronic database. All data included in the dataset were confirmed by chart review. Multiple organ dysfunction syndrome scores (MODS) were evaluated for this specific study. Infectious complications were identified prospectively by both surgical intensivists and infection control practitioners.

All patients met one of the following inclusion criteria for secondary peritonitis: (1) New IAI after any non-gynecologic intra-abdominal operation; (2) perforated stomach or duodenum without intervention for >24 h; (3) perforated small or large bowel; (4) histologically or intra-operatively confirmed perforated appendicitis; (5) perforated gallbladder; or (6) other cause of secondary bacterial peritonitis. Traumatic gastrointestinal tract perforations treated within 12 h were excluded. An IAI was defined as an intra-abdominal infection episode (IE) and was classified as appendiceal or non-appendiceal in origin to permit subgroup analysis. An IE involved complete resolution of the IAI.

The following information was collected for the study: patient age, gender, source of infection, type of initial intervention (percutaneous drainage vs. operation), Charlson Comorbidity Index score [3], and MODS at presentation and on post-operative day (POD) 7 [6]. Complications were categorized as infectious or non-infectious. Infectious complications included surgical site infection (SSI) urinary tract infection, pneumonia, CRBSI, and post-operative IAI, defined according to the National Healthcare Safety Network (NHSN) surveillance guidelines [9]. Non-infectious complications were wound dehiscence, a major cardiac event (dysrhythmia or myocardial infarction), and deep venous thrombosis or pulmonary embolism. Treatment failure was defined as the need for re-intervention (either reoperation or percutaneous drainage) after treatment of the initial infection. The outcomes were death, treatment failure, cardiac event, prolonged ventilator support (>72 h), pneumonia, CRBSI, urinary tract infection, SSI, and length of intensive care unit (ICU) stay.

Source control was attempted at the time of initial intervention. Intra-operative cultures were obtained at the discretion of the surgeon. Samples from all infections drained percutaneously were sent for culture. Specimens were cultured for aerobic and anaerobic organisms using the Becton, Dickinson and Company (BD) BBL™ Port-A-Cul™ product (Franklin Lakes, NJ). Fungal cultures were performed only when specifically requested; however, typically, such cultures are requested and so were available in most cases.

Antimicrobial treatment was not standardized but generally included initial empiric broad-spectrum antimicrobial agents targeted to the expected microbial flora and later tailored depending on the culture results. Treatment length was not evaluated in this study. However, a typical antimicrobial course lasted seven to ten days or until resolution of signs and symptoms.

The statistical analysis was performed using SPSS (SPSS Inc., Chicago, IL). Continuous and discrete variables were compared using the Student *t*-test and Fisher exact test where appropriate. Continuous data were reported as the mean ± standard error of the mean. A *p* value <0.05 was considered significant. Backward stepwise logistic regression

analysis was performed to assess for independent predictors of death, treatment failure, and complications. All variables with *p* < 0.10 on bivariable analysis were included in the analysis, and a receiver operator characteristic was calculated. Using pathogen species as well as other clinical data, analyses were performed to evaluate the association independently with death, treatment failure, and complications. The microbial variables were limited to species that grew in 10 or more intra-abdominal cultures.

Results

General characteristics

A total of 389 patients were admitted for 452 IEs. The mean age at admission was 51.3 ± 0.8 y, and 52.2% of the patients were male. Twenty-two percent (101) of IEs necessitated ventilation for >72 h, and the mean ICU length of stay was 7 days. Treatment failure occurred in 19.7% of IEs (*n* = 89). The most common complications are listed in Table 1.

Appendiceal infection episodes

Patients with appendiceal infection episodes accounted for 129 of the 452 IEs (28.5%). The mean age for these patients was 44.8 ± 1.5 y, and the mean length of ICU stay was 1.6 ± 0.6 d. This population had zero deaths, no major cardiac events, and 9 treatment failures (7.0%). Of those requiring re-intervention, 5 (3.9% of the total series) had operative intervention and 4 (3.1%) had percutaneous drainage.

TABLE 1. GENERAL POPULATION CHARACTERISTICS

	All (<i>n</i> = 452)	Appendiceal (<i>n</i> = 129)	Non- appendiceal (<i>n</i> = 323)
Age	51.3 ± 0.82	44.8 ± 1.47	53.9 ± 0.95
ICU LOS	7.2 ± 0.76	1.61 ± 0.60	10.2 ± 1.01
Ventilated >72 h (%)	101 (22.3)	6 (4.7)	95 (25.4)
Charlson comorbidity score	1.42 ± 0.09	0.62 ± 0.12	1.75 ± 0.12
Pre-operative MODS	1.78 ± 0.12	0.89 ± 0.11	2.13 ± 0.15
Day 7 post-operative MODS	1.28 ± 0.13	0.17 ± 0.06	1.72 ± 0.17
Mortality rate (%)	28 (6.2)	0	28 (8.7)
Treatment failure (%)	89 (19.7)	9 (7.0)	80 (24.8)
Re-operation	69 (15.3)	5 (3.9)	64 (19.8)
IR drainage	26 (5.8)	4 (3.1)	22 (6.8)
Complications (%)			137 (42.4)
Non-Infectious			
MI	13 (2.9)	5 (3.9)	37 (11.5)
Dysrhythmia	42 (9.3%)	1 (0.8)	13 (4.0)
DVT/PE	14 (3.1)	0	13 (4.0)
Wound dehiscence	11 (2.4)	2 (1.6)	9 (2.8)
Infectious (%)			
CRBSI	52 (11.5)	3 (2.3)	49 (15.2)
Pneumonia	64 (14.2)	4 (3.1)	60 (18.6)
SSI	74 (16.4)	11 (8.5)	63 (19.5)
UTI	38 (8.4)	2 (1.6)	36 (11.1)

CRBSI=catheter-related blood stream infection; DVT/PE=deep venous thrombosis/pulmonary embolism; IAI=intra-abdominal infections; ICU LOS=intensive care unit length of stay; IR=interventional radiology; MI=myocardial infarction; MODS=multiple organ dysfunction score; SSI=surgical site infection; UTI=urinary tract infection.

TABLE 2. ETIOLOGY OF NON-APPENDICEAL INTRA-ABDOMINAL INFECTION EPISODES (n=323)(%)^a

Source	Lived (n=295)	Died (n=28)	Total
Post-operative	129 (43.7)	13 (46.4)	142 (44.0)
Colon	84 (28.5)	11 (39.3)	95 (29.4)
Small bowel	51 (17.3)	3 (10.7)	54 (16.7)
Stomach	17 (5.8)	0	17 (5.3)
Gallbladder	11 (3.7)	1 (3.6)	12 (3.7)
Other	3 (1.0)	0	3 (0.9)

^aNone of the differences is statistically significant.

Non-Appendiceal Infection Episodes

There were 323 IAs not involving the appendix (Table 1). The mean patient age in this group was 53.9 ± 1.0 y, and the mean length of ICU stay was 10.2 ± 1.0 d. The mortality rate was 8.7% (n=28). Deaths occurred from persistent sepsis with multiple organ failure (n=16), cardiac events (n=6), respiratory failure (n=5), and stroke (n=1). The most common etiologies of IEs were post-operative infection (44%), colonic perforation (29%), small bowel perforation (17%), gastric perforation (5.3%), and gallbladder perforation (3.7%) (Table 2).

Cultures were obtained for 303 (93.8%) of the IEs. By genus, the organisms cultured most frequently, defined as those that grew 10 times or more in the 303 intra-abdominal cultures, were *Enterococcus* (105), *Escherichia coli* (75), *Streptococcus* (62), *Staphylococcus* (51), and *Bacteroides* (46) (Table 3). Of the cultures, 8.6% showed no growth. Forty-one percent of cultures grew one organism. Of the remaining cultures, 21.8%, 21.4%, 12.9%, 5.3%, and 0.3% grew two to six organisms, respectively (Table 4).

Analysis of mortality rate

Bivariable analysis revealed multiple risk factors associated with death (Table 5). Death was significantly associated with age > 65 years, operative management, prolonged mechanical ventilation, and longer ICU stays. Death also was significantly associated with initial treatment failure (p=0.01). Pre-operative and POD 7 MODS > 4 both were associated with a higher mortality rate. *Clostridium* and *Pseudomonas* recovery demonstrated a significant association with death, whereas

TABLE 3. COMMONLY CULTURED ORGANISMS

Species	Infections (n)	Incidence (%)
<i>Enterococcus</i>	105	27
<i>Escherichia coli</i>	75	19
<i>Streptococcus</i>	62	16
<i>Staphylococcus</i>	51	13
<i>Bacteroides</i>	46	12
<i>Candida</i>	40	10
<i>Pseudomonas</i>	39	10
<i>Klebsiella</i>	33	8
<i>Enterobacter</i>	20	5
<i>Clostridium</i>	16	4
<i>Lactobacillus</i>	12	3
<i>Diphtheroids</i>	12	3
No growth	23	6
No culture	20	5

TABLE 4. NUMBERS OF ORGANISMS IN 303 INTRA-ABDOMINAL CULTURES (% OF SERIES)^a

No. of organisms cultured	Patient lived	Patient died	Total
None	25 (8.3)	1 (0.3)	26 (8.6)
One	108 (35.6)	16 (5.3)	124 (40.9)
Two	61 (20.1)	5 (1.7)	66 (21.8)
Three	61 (20.1)	4 (1.3)	65 (21.4)
Four	12 (11.6)	4 (1.3)	16 (12.9)
Five	12 (4.0)	4 (1.3)	16 (5.3)
Six	1 (0.3)	0	1 (0.3)

^aNone of the differences is statistically significant.

Streptococcus was inversely associated with death. The anatomic source of IAI was found not to be significant. There also was no association between the number of organisms growing in a culture and death.

Multivariable logistic regression demonstrated that age > 65 years, cardiac event, CRBSI, and growth of *Clostridium* were independent predictors of death (Table 6). *Streptococcus* was a strong independent predictor of survival. The C statistic for this analysis was 0.89.

A separate analysis by microbial species showed a higher mortality rate with infections that yielded *Bacteroides* other than *B. fragilis* (p=0.008), *Enterococcus faecalis* and *E. faecium* (p=0.008), or *Clostridium perfringens* (p=0.05). *Pseudomonas aeruginosa* nearly reached significance (p=0.059).

TABLE 5. BIVARIABLE ANALYSIS FOR DEATH

Risk Factor	Percent who had factor among those who lived (N=295)	Percent who had factor among those who died (N=28)	p value
Age ≥ 65 y	26	61	<0.001
Charlson comorbidity score ≥ 2	23	68	0.031
Operative management	75	96	0.008
Ventilation > 72 h	27	57	0.001
Cardiac event	10	54	<0.001
CRBSI	12	54	<0.001
Pre-operative MODS ≥ 4	21	43	0.016
Post-operative day 7 MODS ≥ 4	17	54	<0.001
Needed re-intervention	23	46	0.01
Pneumonia	17	39	0.006
More than one species	55	63	NS
Colonic etiology	29	39	NS
<i>Streptococcus</i>	21.7	7.4	0.051
<i>Clostridium</i>	4.0	18.5	0.008
<i>Pseudomonas</i>	11.6	25.9	0.034
<i>Candida</i>	12.7	18.5	NS
<i>Klebsiella</i>	11.2	7.4	NS
<i>Staphylococcus</i>	16.7	18.5	NS
<i>Bacteroides</i>	14.5	22.2	NS
<i>Enterococcus</i>	32.2	44.4	NS
<i>Enterobacter</i>	6.5	7.4	NS
No growth	8.0	3.7	NS

CRBSI=catheter-related blood stream infection; MODS=multiple organ dysfunction syndrome score; NS=not significant.

TABLE 6. LOGISTIC REGRESSION ANALYSIS FOR DEATH

Characteristic	Odds ratio	95% Confidence interval	p value
Age ≥ 65 years	3.92	1.44–10.68	0.008
Cardiac event	8.17	2.96–22.56	<0.001
Catheter-related blood stream infection	6.16	2.30–16.52	<0.001
<i>Streptococcus</i> infection	0.14	0.02–0.83	0.031
<i>Clostridium</i> infection	13.03	3.09–54.82	<0.001

Analysis of Initial Treatment Failure

As death was associated with treatment failure, a separate bivariable analysis for treatment failure was performed, which demonstrated that cardiac events, CRBSI, pneumonia, and POD 7 MOD score ≥ 4 were associated with treatment failure. Interestingly, no specific bacterial genus was associated with initial treatment failure. Age, initial intervention, anatomic source, and initial MODS likewise had no association with treatment failure (Table 7). Of note, fungus seen on Gram stain was highly associated with treatment failure ($p < 0.01$). Furthermore, four of the five patients with *Candida* organisms other than *C. albicans* and *C. glabrata* required a re-intervention.

Analysis of Complications

Bivariable analysis found multiple variables to be associated with non-infectious complications (Table 8). Growth of

TABLE 7. BIVARIABLE ANALYSIS FOR TREATMENT FAILURE

Risk factor	Percent with no reintervention (N=243)	Percent with reintervention (N=80)	p value
Age ≥ 65 years	27.2	36.3	NS
Charlson comorbidity score ≥ 2	45.3	56.3	NS
Operative management	76.1	78.8	NS
Ventilation for >72 h	24.3	45.0	0.001
Cardiac event	9.1	27.5	<0.001
CRBSI	12.3	23.8	0.019
Pre-operative MODS ≥ 4	21.8	26.3	NS
Post-operative day 7 MODS ≥ 4	45.3	56.3	<0.001
Pneumonia	15.2	28.8	0.012
More than one species	53.3	62.2	NS
Colon etiology	30.0	27.5	NS
<i>Streptococcus</i>	19.7	23.0	NS
<i>Clostridium</i>	5.2	5.4	NS
<i>Pseudomonas</i>	13.1	12.2	NS
<i>Candida</i>	16.2	12.2	NS
<i>Klebsiella</i>	11.4	9.5	NS
<i>Staphylococcus</i>	17.0	16.2	NS
<i>Bacteroides</i>	16.2	12.2	NS
<i>Enterococcus</i>	31.9	37.8	NS
<i>Enterobacter</i>	6.6	6.8	NS
No growth	8.3	5.4	NS

CRBSI=catheter-related blood stream infection; MODS=multiple organ dysfunction score; NS=not significant.

TABLE 8. NONINFECTIOUS COMPLICATIONS

Risk Factor	Percent with no complications (N=265)	Percent with complication (N=58)	p value
Age ≥ 65 years	25.3	48.3	0.001
Charlson Comorbidity score ≥ 2	44.9	62.1	0.02
Operative management	74.0	89.7	0.01
Ventilation for >72 h	22.6	60.3	<0.001
Pre-operative MODS ≥ 4	20.8	32.8	0.058
More than one species	52.0	71.7	0.01
Colonic etiology	28.7	32.8	NS
No growth	9.2	0	0.019
<i>Enterococcus</i>	29.2	52.8	0.001
<i>Pseudomonas</i>	10.4	24.5	0.011
<i>Candida</i>	11.6	20.8	NS
<i>Streptococcus</i>	20.4	20.8	NS
<i>Clostridium</i>	4.8	7.5	NS
<i>Bacteroides</i>	15.2	15.1	NS

MODS=multiple organ dysfunction score; NS=not significant.

Enterococcus and *Pseudomonas* was each associated significantly with non-infectious complications ($p = 0.001$ and 0.011 , respectively). There also was a significant association between growth of more than one organism and a non-infectious complication. Interestingly, there were no non-infectious complications among patients who had no growth in their IAI cultures. Logistic regression analysis showed that being ventilated for >72 h, age >65 years, and having a culture that grew more than one organism were independent predictors of a non-infectious complication (Table 9).

The variables that were associated with infectious complications are listed in Table 10. Bivariable analysis did not reveal an association between a specific bacterial species and an infectious complication.

Discussion

Intra-abdominal infections cause substantial morbidity and many deaths. In previous work at our institution, we demonstrated that age, major cardiac events, and CRBSI were independent predictors of death in patients with IAI [8]. Our current investigation demonstrated that the presence of specific organisms also is associated with a higher mortality rate. Appendiceal IAIs were excluded from this analysis because of the low morbidity and mortality rates, both in our study and in the literature [10]. We had no deaths in this series of patients. Our results demonstrated that *Clostridium* cultured from IAIs were an independent predictor of death, whereas

TABLE 9. LOGISTIC REGRESSION ANALYSIS FOR NON-INFECTIOUS COMPLICATIONS

Characteristic	Odds ratio	95% Confidence interval	p value
Ventilation >72 h	5.20	2.70–10.05	<0.001
Age ≥ 65 years	2.59	1.36–4.96	0.004
More than one species	2.82	1.39–4.96	0.004

TABLE 10. INFECTIOUS COMPLICATIONS

Risk factor	Percent with no complication (N=202)	Percent with complication (N=121)	p value
Age ≥ 65 years	27.2	33.1	NS
Charlson comorbidity score ≥ 2	43.1	56.2	0.029
Operative management	69.8	88.4	<0.001
Ventilation for >72 h	11.9	58.7	<0.001
Cardiac event	5.4	27.3	<0.001
Pre-operative MODS ≥ 4	13.4	38.8	<0.001
More than one species	55.8	54.9	NS
Colonic etiology	30.2	28.1	NS
No growth	7.9	7.1	NS
<i>Enterococcus</i>	30.5	38.1	NS
<i>Pseudomonas</i>	11.1	15.9	NS
<i>Candida</i>	13.2	13.3	NS
<i>Streptococcus</i>	23.2	15.9	NS
<i>Clostridium</i>	4.2	7.1	NS
<i>Bacteroides</i>	15.8	14.2	NS

MODS= multiple organ dysfunction score; NS=not significant.

Streptococcus was significantly predictive of survival. Additionally, cultures that grew *Bacteroides* species other than *B. fragilis*, *Enterococcus* (*E. faecalis* or *E. faecium*), or *C. perfringens* demonstrated a significant association with a higher mortality rate.

We are not aware of other studies investigating the relation between death and a specific infecting organism. However, there are publications addressing the diagnosis, management, and treatment of IAIs and intra-abdominal sepsis. Swenson et al. investigated patient characteristics associated with the growth of resistant pathogens from an intra-abdominal source. This study noted relations between the anatomic source of infection, patient characteristics, growth of resistant pathogens, and death [11]. The authors concluded that clinical characteristics may help identify patients potentially infected with resistant pathogens, specifically *Candida* and enterococci.

Montravers et al. investigated *Candida* peritonitis and noted that the infection was an independent predictor of death [12]. Fungal cultures were not performed routinely, and *Candida* was not associated with death. However, fungus seen on Gram stain was associated with treatment failure. Furthermore, Szeto et al. found a higher mortality rate from peritonitis in patients undergoing peritoneal dialysis who had cultures positive for *Pseudomonas* or *Enterococcus* [13]. Our study demonstrated a significant association of *Pseudomonas* with death, but logistic regression analysis failed to confirm *Pseudomonas* as an independent predictor of death. This fact likely is attributable to a Type II error and lack of power in our study.

There were other limitations to this study. It was retrospective and based on ICD-9 code assignments in the administrative database. Patients thus may have been excluded on the basis of coding errors, which may have contributed to the small sample, leading to a Type II error. Also, the low overall mortality rate limited our ability to identify factors associated with death. Additionally, specific populations such as patients with solid organ allografts were not evaluated. Our findings therefore should not be applied to a transplant population.

Source control and appropriate antimicrobial management are fundamental to the successful management of IAIs. However, this study did not examine specifically the adequacy of source control or the appropriateness of the antimicrobial treatment. Additionally, infectious complications were not differentiated by hospital-acquired or community-acquired status, yet these factors may contribute to death or treatment failure. We also did not use an Acute Physiology and Chronic Health Evaluation II score, which is associated with outcomes in many studies of infections. Lastly, the initial source of the post-operative infections was not identified.

Our previous work demonstrated that whether an infection was community-acquired or nosocomial had less impact on the patient mortality rate than did intrinsic patient characteristics [8]. The patient's physiologic and co-morbidity scores support the relation between co-morbidities, greater physiologic derangements, and death. Now we can further address the impact of the specific infecting organism on the likelihood of death. In our work, enterococcal species (*E. faecalis* and *E. faecium*) as well as *Bacteroides* other than *B. fragilis* and *Clostridium* were clear predictors of death. Our study demonstrates that IAIs associated with positive cultures of these specific organisms are associated with poorer outcomes. The specific cause and effect relation of these associations remains unclear. The growth of these organisms may occur in sicker patients and therefore herald overall host deterioration. Also, it is possible that these infections are more difficult to treat because of inadequate empiric antimicrobial coverage [14] or the selection of virulence factors resulting in resistant organisms [15]. As we look to improve and refine treatment regimens for IAIs, the ability to recognize organisms associated with death may alert the treating surgeon to a potentially poor outcome and trigger more aggressive treatment.

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Author Disclosure Statement

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