SURGICAL INFECTIONS
Volume 10, Number 1, 2009

DOI: 10.1089/sur.2007.041

Choosing Antibiotics for Intra-Abdominal Infections: What Do We Mean by "High Risk"?*

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Abstract

Background: The definition of "high risk" in intra-abdominal infections remains vague. The purpose of this study was to investigate patient characteristics associated with a high risk of isolation of resistant pathogens from an intra-abdominal source.
Methods: All complicated intra-abdominal and abdominal organ/space surgical site infections treated over a ten-year period in a single hospital were analyzed. Infections were categorized by pathogen(s). Organisms designated "resistant" were those that had a reasonable probability of being resistant to the broad-spectrum agents imipenem/cilastatin and piperacillin/tazobactam, and included non-fermenting gram-negative bacilli (e.g., *Pseudomonas aeruginosa*), resistant gram-positive pathogens, vancomycin-resistant enterococci, and fungi. Patient characteristics were analyzed to define associations with the risk of isolation of "resistant" pathogens.
Results: A total of 2,049 intra-abdominal infections were treated during the period of study, of which 1,182 had valid microbiological data. The two genera of pathogens isolated from more than 25% of health care-associated infections and more commonly than from community-acquired infections were *Enterococcus* spp. (29%) and *Candida* spp. (33%). Health care association, corticosteroid use, organ transplantation, liver disease, pulmonary disease, and a duodenal source all were associated with resistant pathogens. By multivariable analysis, several acute and chronic measures of disease were predictive of death, with a strong interaction between solid organ transplantation, resistant pathogens, and death. Other links between specific pathogens and patient characteristics were documented, for example, between fungal infection and a gastric, duodenal, or small bowel source, and between liver transplantation and vancomycin-resistant enterococci.
Conclusions: On the basis of clinical characteristics, it may be possible to identify patients with intra-abdominal infections caused by pathogens that are potentially resistant to broad-spectrum antibacterial agents. Under these circumstances, and if warranted clinically, broadened coverage probably ought to include specific anti-enterococcal and anti-candidal therapy.

The choice of antibiotics for the management of intra-abdominal infections continues to expand. Since the drafting of the Surgical Infection Society (SIS) guidelines for the management of intra-abdominal infections in 2002 [1, 2], ertapenem, moxifloxacin, and tigecycline have been approved by the U.S. Food and Drug Administration (FDA) for this indication, and several other antimicrobial agents, such as doripenem, are in various stages of clinical testing. Although all of these agents (or combinations of agents) have activity against *Enterobacteriaceae* such as *Escherichia coli* and the most commonly isolated anaerobic pathogen *Bacteroides fragilis*, real differences in spectra of activity exist, even within a single class. For example, imipenem/cilastatin has activity against *P. aeruginosa* and *Enterococcus* spp., whereas ertapenem does not, yet both are indicated for complicated intra-abdominal infections. Most guidelines recommend broader-spectrum coverage for "high risk" patients, although the definition of "high risk" remains vague at best.

Two possible interpretations of "high risk" are a greater likelihood of death or a higher likelihood of failure of therapy. Although related, the two are not identical. Because death may be closely related to the underlying medical con-

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* Presented as an educational symposium at the Twenty-Seventh Surgical Infection Society Meeting, Toronto, Ontario, Canada, April 19, 2007.

dition of the patient and time to presentation, patients at high risk of death may die despite adequate interventions. Thus, a frail elderly patient may be "high risk" even from a relatively unimpressive infection. High risk of local failure for intra-abdominal infections, on the other hand, is linked to the adequacy of surgical or percutaneous intervention. In this case, a healthy patient should be considered "high risk" if source control is tenuous or inadequate. In either of these cases, it is unlikely that a broadened spectrum of antibiotics by itself will alter outcomes.

An alternative definition of "high risk" is intra-abdominal infections that have a high likelihood of being caused by pathogens that would not be treated with standard, recommended antimicrobial therapy. The effort to administer adequate initial empiric antimicrobial therapy probably is worthwhile, and the delineation of patient profiles that are "high risk" by this definition may be helpful to the clinician. Traditionally, hospital-acquired infections and tertiary peritonitis have predicted a higher likelihood of resistant pathogens, although these general guidelines do not address either patients with community-acquired infections or risk factors for specific pathogens. The intent of this paper was to analyze a large data set of intra-abdominal infections in order to describe patient characteristics associated with organisms that might not be treated by standard antimicrobial therapy.

Patients and Methods

This research was performed with the approval of the University of Virginia Human Investigation Committee. Data were deidentified for final analysis, and the need for informed consent was waived.

Clinical information for all complicated intra-abdominal and abdominal organ/space surgical site infections (*http://www.cdc.gov/ncidod/dhqp/pdf/nnis/NosInfDefinitions.pdf*) managed in inpatients in the University of Virginia Hospital was collected prospectively from December 1996 to November 2006 as part of a larger data set. Patients were identified by alternate-day chart review and interview by a health care worker. For the analyses presented, abdominal organ/space surgical site infections were included because their physiology and management are similar to those of *de novo* complicated intra-abdominal infections. Demographic, laboratory, and treatment data were collected for each infection. Healthcare-associated infections included those in hospitalized patients or patients with a history of any hospitalization in the 30 days prior to the diagnosis of intra-abdominal infection, including residence in a nursing home or rehabilitation facility. The first analysis sought to confirm which pathogens were isolated more frequently from health care-associated vs. community-acquired infections.

Subsequent analyses attempted to identify patient characteristics that might alert clinicians to the presence of "resistant" pathogens causing intra-abdominal infections. Resistance was defined arbitrarily to reflect clinical significance in the choice of empiric antibiotic therapy.The definition reflected whether a pathogen would have a sufficient likelihood of resistance to imipenem/cilastatin or piperacillin/tazobactam monotherapy that an additional antimicrobial agent might be considered, because these two regimens are recommended routinely for "severe" or "high-risk" infections [1–3]. As such, the following organisms were considered "resistant:" Non-fermenting gram-negative bacilli (including *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, and *Acinetobacter* spp.), methicillin-resistant *Staphylococcus aureus* (MRSA), coagulase-negative staphylococci, vancomycin-resistant enterococci (VRE), and all fungi. We also analyzed all enterococci as a group (vancomycin-resistant and vancomycin-sensitive) because many regimens recommended for intra-abdominal infections; e.g., ciprofloxacin and metronidazole, have unreliable activity against enterococci.

Data on demographics, medical history, infection, and outcomes were compared by calculating odds ratios (ORs) with 95% confidence intervals (CI) for categorical variables and Student's *t*-test for continuous variables. One logistic regression analysis was performed with in-hospital death as the outcome. Factors considered to be relevant clinically, including infections with resistant pathogens, were included in the model. One interaction term, identifying patients who were both transplant recipients and from whom resistant organisms were cultured, was also included in the model to account for possible synergism. Data manipulation and analysis were performed using SAS 9.1.3 (SAS Institute, Inc., Cary, NC).

Results

There were 2,049 intra-abdominal infections treated during the period of study; 789 infections were treated without culture, 78 had cultures without growth (usually obtained after antibiotics had been started), and 1,182 had positive cultures. Comparing the infections treated without culture with those treated with positive cultures, the former were more likely to be community-acquired (407/789 [52%] vs. 395/1182 [33%]; $p < 0.0001$) and were associated with a lower Acute Physiology and Chronic Health Evaluation (APACHE) II score [4] at the time of presentation (11.2 ± 0.3 vs. 13.3 ± 0.3 points; $p < 0.0001$). Because the focus of this paper is patients at high risk of having infections caused by resistant pathogens, the rest of the analysis will be limited to the 1,182 infections with positive cultures. Of these cases, 1,074 were complicated intra-abdominal infections, as defined by the U.S. Centers for Disease Control and Prevention (CDC), and 108 were organ/space surgical site infections.

Because health care-associated and community-acquired infections tend to have different microbiology findings, these groups were compared first. Table 1 gives the ORs with 95% confidence intervals for the isolation of specific pathogens from healthcare-associated infections compared to community-acquired infections. The enterococci and *Candida* spp. were the two groups of pathogens more likely to be isolated from health care-associated infections to a clinically relevant extent. Other pathogens, such as MRSA and *Serratia* spp., were statistically more likely to be isolated from health care-associated infections, yet still occurred relatively infrequently ($< 6\%$ of infections) and might not affect the choice of empiric antimicrobial therapy. Surprisingly, several pathogens commonly believed to be associated with health care-associated infections were isolated with similar frequency from the two groups, including *P. aeruginosa*, *Citrobacter* spp., and coagulase-negative staphylococci. Because

TABLE 1. ODDS RATIOS OF ISOLATION OF COMMON BACTERIA FROM HEALTH-CARE ASSOCIATED VS. COMMUNITY-ACQUIRED INTRA-ABDOMINAL INFECTIONS

Pathogen	*Health-care associated* N = *787* (%)	*Community acquired* N = *395* (%)	*Odds ratio*	*95% CI*
Gram-negative bacteria	337 (42.8)	165 (41.8)	1.03	0.82, 1.33
Escherichia coli	106 (13.5)	62 (15.7)	0.84	0.60, 1.17
Klebsiella pneumoniae	52 (6.6)	34 (8.6)	0.75	0.48, 1.18
K. oxytoca	7 (0.89)	9 (2.3)	0.38	0.14, 1.04
Enterobacter cloacae	42 (5.3)	6 (1.5)	3.66	1.54, 8.67
E. aerogenes	14 (1.8)	2 (0.51)	3.56	0.80, 15.73
Pseudomonas aeruginosa	32 (4.1)	12 (3.0)	1.35	0.69, 2.66
Citrobacter spp.	14 (1.8)	7 (1.8)	1.00	0.40, 2.51
Serratia spp.	15 (1.9)	1 (0.25)	7.66	1.01, 58.2
Proteus mirabilis	11 (1.4)	4 (1.0)	1.39	0.44, 4.38
Stenotrophomonas maltophilia	11 (1.4)	3 (0.76)	1.85	0.51, 6.68
Acinetobacter spp.	3 (0.38)	0	—	—
Gram-positive bacteria	413 (52.5)	179 (45.3)	1.33	1.05, 1.70
Staphylococcus aureus	69 (8.8)	29 (7.3)	1.21	0.77, 1.91
MRSA	45 (5.7)	10 (2.5)	2.33	1.16, 4.68
S. epidermidis/CNS	45 (5.7)	15 (3.8)	1.54	0.85, 2.79
All enterococci	229 (29.1)	39 (9.9)	3.75	2.60, 5.39
Enterococcus faecalis	109 (13.9)	29 (7.3)	2.03	1.32, 3.12
E. faecium	130 (16.5)	12 (3.0)	6.32	3.45, 11.56
VRE	71 (9.0)	5 (1.3)	7.73	3.10, 19.3
Streptococcus spp.	62 (7.9)	82 (20.8)	0.33	0.23, 0.47
Anaerobic bacteria	139 (17.7)	99 (25.1)	0.64	0.48, 0.86
Bacteroides fragilis	44 (5.6)	20 (5.1)	1.11	0.65, 1.91
Other *Bacteroides*	14 (1.8)	5 (1.3)	1.41	0.51, 3.95
Prevotella spp.	6 (0.76)	2 (0.51)	1.51	0.30, 7.51
Unspeciated	80 (10.2)	73 (18.5)	0.50	0.35, 0.70
Fungi	262 (33.3)	68 (17.2)	2.40	1.78, 3.24
All *Candida*	209 (26.6)	54 (13.7)	2.28	1.65, 3.17
C. albicans	141 (17.9)	42 (10.6)	1.83	1.27, 2.65
C. glabrata	60 (7.6)	11 (2.8)	2.88	1.50, 5.54
Other *Candida* spp.	32 (4.1)	6 (1.5)	2.75	1.14, 6.63
Unspeciated yeast	52 (6.6)	13 (3.3)	2.08	0.29, 3.87

MRSA = methicillin-resistant *S. aureus*; CNS = coagulase-negative staphylococci; VRE = vancomycin-resistant enterococci (all were *E. faecium*).

the inclusion of solid organ transplant recipients could be a factor in the rate of recovery of certain pathogens, the report of pathogens is repeated in Table 2, excluding these patients. Surprisingly, although the frequency of some pathogens is altered after the exclusion of transplant patients; e. g., VRE, the ORs are changed minimally, and the most important differences clinically are again for enterococci and fungi.

To help define demographics and outcomes related to intra-abdominal infections with resistant pathogens, Table 3 presents an analysis of associations between multiple clinical variables and the isolation of pathogens considered to be resistant or potentially resistant to standard empiric antimicrobial therapy. The means for continuous variables are given with p values for the differences between infections caused by resistant and non-resistant pathogens. For dichotomous variables, the frequency is given for resistant and non-resistant infections, and ORs with 95% CI are given for their comparison. Outcomes for these infections also are presented. These data confirm that resistant pathogens occur more commonly in hospitalized patients, particularly in the intensive care unit (ICU), and are associated with underlying diseases. Although the mean APACHE II score was significantly higher in patients with resistant infections, the difference of less than three points may be clinically trivial and probably prevents this parameter from being a useful discriminating factor. Gastroduodenal source infections created the highest risk and appendiceal source infections the lowest risk for involvement of resistant organisms. As would be expected, infections with the pathogens of interest were associated with a longer stay and a higher in-hospital mortality rate.

A logistic regression analysis investigating the influence of potential predictors listed in Table 3 on subsequent finding of a resistant organism was performed. The model demonstrated only marginal statistical performance (c statistic 0.674; $R^2 = 0.096$), giving credence to the idea that predicting these cases is difficult. Independent statistically significant effects were seen for age > 70 years (OR = 0.65; p =

TABLE 2. ODDS RATIOS OF ISOLATION OF COMMON BACTERIA FROM HEALTH-CARE ASSOCIATED VS. COMMUNITY-ACQUIRED INTRA-ABDOMINAL INFECTIONS, EXCLUDING PATIENTS WITH SOLID ORGAN ALLOGRAFTS

Pathogen	*Health-care associated* N = *619* (%)	*Community acquired* N = *351* (%)	*Odds ratio*	*95% CI*
Gram-negative bacteria	260 (42.0)	142 (40.5)	1.07	0.82, 1.39
Escherichia coli	84 (13.6)	62 (17.7)	0.73	0.51, 1.05
Klebsiella pneumoniae	42 (6.8)	31 (8.8)	0.75	0.46, 1.22
K. oxytoca	7 (1.1)	9 (3.1)	0.43	0.16, 1.18
Enterobacter cloacae	27 (4.4)	4 (1.1)	3.96	1.37, 11.40
E. aerogenes	12 (1.9)	2 (0.57)	6.82	1.51, 30.71
Pseudomonas aeruginosa	32 (5.2)	7 (2.0)	2.68	1.17, 6.14
Citrobacter spp.	10 (1.6)	7 (2.0)	0.81	0.31, 2.15
Serratia spp.	7 (1.1)	0	—	—
Proteus mirabilis	11 (1.8)	4 (1.1)	1.57	0.50, 4.97
Stenotrophomonas maltophilia	10 (1.6)	2 (0.57)	2.87	0.62, 13.15
Acinetobacter spp.	3 (0.48)	0	—	—
Gram-positive bacteria	322 (52.0)	165 (47.0)	1.11	0.85, 1.44
Staphylococcus aureus	57 (9.2)	29 (8.3)	0.88	0.56, 1.42
MRSA	38 (6.1)	9 (2.6)	2.53	1.21, 5.29
S. epidermidis/CNS	36 (5.8)	13 (3.7)	1.63	0.85, 3.12
All enterococci	168 (27.1)	30 (8.5)	4.00	2.63, 6.03
Enterococcus faecalis	91 (14.7)	23 (6.5)	2.46	1.52, 3.96
E. faecium	73 (11.8)	5 (1.4)	9.25	3.70, 23.12
VRE	36 (5.8)	4 (1.1)	5.36	1.89, 15.18
Streptococcus spp.	46 (7.4)	77 (21.9)	0.30	0.20, 0.44
Anaerobic bacteria	135 (21.8)	94 (26.8)	0.63	0.47, 0.85
Bacteroides fragilis	43 (6.9)	20 (5.7)	1.23	0.73, 2.19
Other *Bacteroides*	14 (2.3)	4 (1.1)	2.01	0.66, 6.15
Prevotella spp.	6 (1.0)	2 (0.57)	1.71	0.34, 8.51
Unspeciated	72 (11.6)	68 (19.4)	0.55	0.38, 0.79
Fungi	226 (36.5)	63 (17.9)	2.63	1.91, 3.61
All *Candida*	184 (29.7)	52 (14.8)	2.43	1.73, 3.42
C. albicans	114 (18.4)	38 (10.8)	1.86	1.25, 2.76
C. glabrata	45 (7.3)	9 (2.6)	2.98	1.44, 6.17
Other *Candida* spp.	25 (4.0)	5 (1.4)	2.91	1.10, 7.68
Unspeciated yeast	42 (6.8)	11 (3.1)	2.29	1.16, 4.51

MRSA = methicillin-resistant *S. aureus*; CNS = coagulase-negative staphylococci; VRE = vancomycin-resistant enterococci (all were *E. faecium*).

0.02), premorbid pulmonary diagnosis (OR = 1.70; p = 0.001), treatment more than 10 days after admission (OR = 1.70; p = 0.002), stomach as the source (OR = 2.86; p = 0.005), duodenum as the source (OR = 4.62; $p < 0.0001$), small bowel as the source (OR = 1.70; p = 0.04), and appendix as the source (OR = 0.34; p = 0.014). It is possible that other factors exist that are independently predictive of specific pathogens but not all resistant pathogens in general. Because it is possible that the presence of patients with allografts might have skewed the results significantly, Table 4 provides data similar to that found in Table 3, but excludes transplant recipients. With the exception of a decrease in the number of infections from a hepatobiliary source, there are minimal differences between the overall cohort and the cohort excluding transplant patients.

Because many if not most community-acquired infections are treated without cultures, a separate analysis of the risk factors for the isolation of resistant pathogens from these infections was compiled (Table 5). Although less frequently than for health care-associated infections, one quarter of the community-acquired infections nevertheless had the organisms of interest recovered. The resistant pathogens recovered from these patients included *P. aeruginosa* (N = 12), *S. maltophilia* (N = 3), MRSA (N = 10), coagulase-negative staphylococci (N = 15), VRE (N = 5), *C. albicans* (N = 42), non-*albicans Candida* spp. (N = 17), and non-speciated yeast (N = 13). Risk factors for the isolation of resistant pathogens were similar to those for all infections, and included corticosteroid use, organ (especially liver) transplantation, pulmonary disease, a gastroduodenal source, and a clinically trivial APACHE II score difference of two points. The length of stay after the initiation of treatment was higher with resistant pathogens, but the in-hospital mortality rates were nearly identical in the two groups.

Because prediction of the presence of specific resistant pathogens might be valuable when choosing antimicrobials empirically, for example, administering fluconazole to patients at risk for candidal infection or linezolid to patients at risk for VRE infections, Table 6 gives data regarding specific clinical characteristics and outcomes for the resistant patho-

TABLE 3. PATIENT CHARACTERISTICS AND OUTCOMES, RESISTANT VS. NON-RESISTANT PATHOGENS, FOR ALL INTRA-ABDOMINAL INFECTIONS

	Resistant pathogens[1] *(N = 493)*	*Non-resistant pathogens (N = 689)*	*Odds ratio*	*95% CI or p value*[2]
Demographics				
Male (%)	275 (55.8)	384 (55.7)	0.99	0.79, 1.26
Age (years)	52.9 ± 0.62	54.1 ± 0.68		0.22
APACHE II score[3]	14.9 ± 0.34	12.2 ± 0.28		<0.0001
Health care-associated (%)	388 (78.7)	399 (57.9)	2.70	2.06, 3.50
In intensive care unit (%)	95 (19.3)	66 (9.6)	2.25	1.60, 3.16
Days from admission to treatment	10.6 ± 0.90	5.0 ± 0.42		<0.0001
Maximum temperature, °C	37.8 ± 0.081	37.9 ± 0.046		0.41
Maximum white blood cell count (1,000/mm^3)	16.2 ± 0.44	16.1 ± 0.32		0.78
Medical conditions (%)				
Current corticosteroid use	147 (29.8)	140 (20.3)	1.67	1.27, 2.18
Solid organ transplant	107 (21.7)	105 (15.2)	1.54	1.14, 2.07
Liver transplant	89 (18.1)	83 (12.1)	1.61	1.16, 2.23
Kidney transplant	17 (3.5)	21 (3.1)	1.14	0.59, 2.18
Kidney/pancreas transplant	10 (2.0)	6 (0.87)	2.36	0.85, 6.53
Diabetes mellitus	103 (20.9)	157 (22.8)	0.89	0.68, 1.19
Cardiac disease	87 (17.7)	113 (16.4)	1.09	0.80, 1.48
Malignant disease	63 (12.8)	98 (14.2)	0.88	0.63, 1.24
Baseline pulmonary disease	68 (13.8)	59 (8.6)	1.71	1.18, 2.47
Ventilator dependence	68 (13.8)	48 (7.0)	2.14	1.45, 3.15
Liver disease	59 (12.0)	50 (7.3)	1.74	1.17, 2.58
Dialysis dependence	47 (9.5)	44 (6.4)	1.55	1.00, 2.37
Crohn's disease/UC	33 (6.7)	47 (6.8)	0.98	0.62, 1.56
Source of infection				
Stomach	28 (5.7)	21 (3.1)	1.92	1.07, 3.41
Duodenum	34 (6.9)	15 (2.2)	3.33	1.79, 6.18
Pancreas	28 (5.7)	44 (6.4)	0.88	0.54, 1.44
Liver/biliary	136 (27.6)	166 (24.1)	1.20	0.92, 1.56
Small bowel	95 (19.3)	119 (17.3)	1.14	0.85, 1.54
Appendix	8 (1.6)	61 (8.9)	0.17	0.081, 0.35
Colorectal	124 (25.2)	188 (27.3)	0.90	0.69, 1.17
Other/unknown	40 (8.1)	75 (10.9)	0.73	0.48, 1.08
Outcomes				
Duration of antibiotic therapy (days)	17.4 ± 0.90	14.0 ± 0.44		0.0008
Length of stay[4]	24.7 ± 1.3	15.4 ± 0.77		<0.0001
In-hospital death (%)	84 (17.0)	59 (8.6)	2.19	1.53, 3.13

[1]Includes *P. aeruginosa, S. maltophilia, Acinetobacter* spp., methicillin-resistant *S. aureus*, coagulase-negative staphylococci, vancomycin-resistant enterococci, or any fungi.

[2]Resistant pathogens/non-resistant pathogens; odds ratios with 95% confidence intervals for categorical variables; p value by Student *t*-test for continuous variables.

[3]At time of diagnosis of intra-abdominal infection.

[4]From initiation of treatment for intra-abdominal infection.

APACHE = Acute Physiology and Chronic Health Evaluation; UC = ulcerative colitis.

gens of interest, including non-fermenting gram-negative bacilli, resistant staphylococci, VRE, and fungi, as well as for all enterococci. The ORs and 95% CI are from comparisons with infections where no resistant pathogens were isolated (see the third column of Table 3), except for all enterococcal infections, which were compared with all other infections not caused by enterococci or resistant pathogens. Not surprisingly, the isolation of resistant pathogens was associated with acquisition in a health care setting, particularly in the ICU. Differences among the specific pathogens or classes were noted. Non-fermenting gram-negative bacilli were associated with underlying lung disease, perhaps secondary to oral or pulmonary colonization. Resistant staphylococcal infections were associated with a pancreatic source and ventilator dependence, perhaps likewise secondary to colonization by this organism. Analysis of MRSA infections alone gave similar results. Infections with any *Enterococcus* were associated with liver disease, including prior liver transplantation, and a hepatobiliary or duodenal source, probably because of the ability of these organisms to grow in bile.

TABLE 4. PATIENT CHARACTERISTICS AND OUTCOMES, RESISTANT VS. NON-RESISTANT PATHOGENS, FOR ALL INTRA-ABDOMINAL INFECTIONS EXCLUDING PATIENTS WITH SOLID ORGAN ALLOGRAFTS

	Resistant pathogens[1] *(N = 371)*	*Non-resistant pathogens (N = 599)*	*Odds ratio*	*95% CI or p value*[2]
Demographics				
Male (%)	275 (51.5)	319 (53.3)	0.93	0.72, 1.21
Age (years)	53.7 ± 0.8	54.1 ± 0.68		0.52
APACHE II score[3]	14.3 ± 0.4	12.2 ± 0.28		<0.0001
Healthcare-associated (%)	290 (78.2)	329 (54.9)	2.94	2.19, 3.94
In intensive care unit (%)	77 (20.8)	50 (8.3)	2.88	1.96, 4.22
Days from admission to treatment	9.9 ± 1.1	4.1 ± 0.4		<0.0001
Maximum temperature, °C	37.9 ± 0.1	37.9 ± 0.1		0.99
Maximum white blood cell count (1,000/mm^3)	16.0 ± 0.4	16.6 ± 0.3		0.23
Medical conditions (%)				
Current corticosteroid use	53 (14.3)	43 (7.2)	2.12	1.38, 3.24
Diabetes mellitus	79 (21.3)	126 (21.0)	1.02	0.74, 1.40
Cardiac disease	63 (17.0)	103 (17.2)	0.99	0.70, 1.39
Malignant disease	52 (14.0)	96 (16.0)	0.85	0.59, 1.23
Baseline pulmonary disease	55 (14.8)	58 (9.7)	1.62	1.09, 2.41
Ventilator dependence	56 (15.1)	41 (6.8)	2.42	1.58, 3.70
Liver disease	20 (5.4)	19 (3.2)	1.74	0.92, 3.30
Dialysis dependence	30 (8.1)	30 (5.0)	1.67	0.99, 2.82
Crohn's disease/UC	30 (8.1)	43 (7.2)	1.14	0.70, 1.45
Source of infection				
Stomach	28 (7.5)	21 (3.5)	2.25	1.26, 4.02
Duodenum	34 (9.2)	15 (2.5)	3.91	2.11, 7.32
Pancreas	26 (7.0)	40 (6.7)	1.05	0.63, 1.76
Liver/biliary	53 (14.3)	95 (15.9)	0.88	0.61, 1.27
Small bowel	83 (22.4)	111 (18.5)	1.27	0.92, 1.74
Appendix	8 (2.2)	60 (10.0)	0.20	0.09, 0.42
Colorectal	113 (30.5)	194 (32.4)	0.91	0.69, 1.21
Other/unknown	26 (7.0)	62 (10.4)	0.65	0.40, 1.05
Outcomes				
Duration of antibiotic therapy (days)	16.4 ± 0.6	13.2 ± 0.44		<0.0001
Length of stay[4]	25.1 ± 1.6	14.9 ± 0.8		<0.0001
In-hospital death (%)	53 (14.3)	50 (8.3)	1.82	1.21, 2.75

[1]Includes *P. aeruginosa, S. maltophilia, Acinetobacter* spp., methicillin-resistant *S. aureus*, coagulase-negative staphylococci, vancomycin-resistant enterococci, or any fungi.

[2]Resistant pathogens/non-resistant pathogens; odds ratios with 95% confidence intervals for categorical variables; p value by Student *t*-test for continuous variables.

[3]At time of diagnosis of intra-abdominal infection.

[4]From initiation of treatment for intra-abdominal infection.

APACHE = Acute Physiology and Chronic Health Evaluation; UC = ulcerative colitis.

Vancomycin-resistant enterococci were even more closely associated with immunosuppression, liver disease, and a hepatobiliary source. Finally, the isolation of fungi was associated with steroid use, pulmonary disease, and a gastroduodenal or small bowel source. In general, outcomes were worse for resistant pathogens, with the highest mortality rate observed after infections caused by fungi or VRE.

Table 7 gives results of a multivariable analysis of risk factors for death after intra-abdominal infections to analyze the importance of resistance in outcome. When developing the model, a strong interaction between solid organ transplantation and death after infections with resistant organisms was revealed. In terms of crude mortality rate, the following observations were made: Mortality rate for non-transplant patients with non-resistant infections 49/584 (8.4%) vs. 54/386 (14.0%) for non-transplant patients with resistant infections ($p = 0.008$); mortality rate for solid organ transplant patients with non-resistant infections 10/105 (9.5%) vs. 30/107 (28.0%) for solid organ transplant patients with resistant infections ($p = 0.001$). Therefore, the final model included the interaction term "Resistant organism + solid organ transplant." The logistic regression model demonstrated excellent statistical performance (c statistic 0.887; $R^2 = 0.226$). Not surprisingly, multiple measures of acute and chronic illness were associated with death, although after APACHE II score, the strongest predictor was intra-abdominal infection with a resistant organism in the setting of solid organ transplantation. These data suggest that after adjusting for other

TABLE 5. PATIENT CHARACTERISTICS AND OUTCOMES, RESISTANT VS. NON-RESISTANT PATHOGENS, FOR COMMUNITY-ACQUIRED INFECTIONS

	Resistant pathogens[1] *(N = 105)*	*Non-resistant pathogens (N = 290)*	*Odds ratio*	*95% CI or p value*[2]
Demographics				
Male (%)	58 (55.2)	150 (51.7)	1.15	0.55, 1.36
Age	52.7 ± 1.6	53.5 ± 0.99		0.65
APACHE II score[3]	12.8 ± 0.64	10.8 ± 0.40		0.0090
Maximum temperature, °C	37.8 ± 0.10	37.6 ± 0.08		0.89
Maximum white blood cell count (1,000/mm^3)	15.2 ± 0.94	15.3 ± 0.50		0.91
Medical conditions (%)				
Current corticosteroid use	28 (26.7)	39 (13.5)	2.34	1.35, 4.05
Solid organ transplant	18 (17.2)	26 (9.0)	2.10	1.10, 4.02
Liver	14 (13.3)	20 (6.9)	2.07	1.01, 4.28
Kidney	2 (1.9)	6 (2.1)	0.92	0.18, 4.63
Kidney/pancreas	1 (0.95)	3 (1.03)	0.92	0.095, 8.94
Diabetes mellitus	20 (19.5)	63 (21.7)	0.85	0.48, 1.49
Cardiac disease	20 (19.5)	44 (15.2)	1.32	0.73, 2.36
Malignant disease	12 (11.4)	37 (12.8)	0.88	0.44, 1.76
Baseline pulmonary disease	21 (20.0)	27 (9.3)	2.44	1.31, 4.53
Liver disease	8 (7.6)	19 (6.6)	1.18	0.50, 2.78
Dialysis dependence	4 (3.8)	5 (1.7)	2.26	0.59, 8.57
Crohn's disease/UC	8 (7.6)	18 (6.2)	1.24	0.53, 2.96
Source of infection				
Stomach	10 (9.5)	10 (3.5)	2.94	1.12, 7.30
Duodenum	11 (10.5)	7 (2.5)	4.73	1.79, 12.55
Pancreas	8 (7.6)	10 (3.5)	2.31	0.89, 6.02
Liver/biliary	23 (21.9)	71 (24.5)	0.87	0.51, 1.48
Small bowel	18 (17.1)	32 (11.0)	1.67	0.89, 3.12
Appendix	4 (3.8)	46 (15.9)	0.21	0.074, 0.60
Colorectal	26 (24.8)	93 (32.1)	0.70	0.42, 1.16
Other/unknown	5 (4.8)	21 (7.2)	0.64	0.24, 1.74
Outcomes				
Duration of antibiotic therapy	15.1 ± 1.2	12.9 ± 0.80		0.15
Length of stay (days)[4]	16.2 ± 1.9	10.8 ± 0.78		0.011
In-hospital death (%)	7 (6.7)	18 (6.2)	1.08	0.44, 2.67

[1]Includes *P. aeruginosa, S. maltophilia, Acinetobacter* spp., methicillin-resistant *S. aureus*, coagulase-negative staphylococci, vancomycin-resistant enterococci, or any fungi.
[2]Resistant pathogens/non-resistant pathogens; odds ratios with 95% confidence intervals for categorical variables; p value by Student *t*-test for continuous variables.
[3]At time of diagnosis of intra-abdominal infection.
[4]From initiation of treatment for intra-abdominal infection.
APACHE = Acute Physiology and Chronic Health Evaluation; UC = ulcerative colitis.

variables, the added burden of resistance affects immunosuppressed transplant patients disproportionately.

Discussion

The optimal management of intra-abdominal infections depends on several factors, including adequate source control, physiologic resuscitation and support, and administration of appropriate antibiotics. A deficiency in any of these areas could increase the risk of failure, manifested as recurrent infection or death. For the purpose of the current paper, however, "high risk" is meant to refer to patients at increased risk of having pathogens that may not be sensitive to the broad-spectrum antibacterial agents recommended for serious intra-abdominal infections.

Generally, the most important factors in predicting the presence of resistant pathogens in intra-abdominal infections appear to be acquisition in a health care setting (particularly if the patient becomes infected in the ICU or has been hospitalized for more than one week), corticosteroid use, organ transplantation, baseline pulmonary or hepatic disease, and the duodenum as the source of infection. On the other hand, sex, age, diabetes mellitus, malignant disease, and severity of illness per se probably are not significant differentiating factors in terms of pathogen sensitivity. This does not imply, however, that severity of illness should not be considered when choosing antibiotics, because it is plausible that a delay in the administration of effective antibiotics may be more burdensome to critically ill patients than to those who are relatively healthy.

Table 6. Patient Characteristics and Odds Ratios (85% Confidence Intervals) of Finding that Characteristic among Patients with Specific Resistant Pathogens Compared with Intra-Abdominal Infections with No Resistant Pathogens

	Non-fermenting gram negative[1] (N = 35)	*Resistant staphylococci*[2] (N = 74)	*All enterococci*[3] (N = 161)	*VRE*[4] (N = 39)	*Fungi*[5] (N = 267)
Demographics					
Male	1.73 (0.84, 3.59)	1.23 (0.75, 2.01)	0.88 (0.62, 1.24)	0.75 (0.40, 1.44)	0.90 (0.68, 1.20)
Age	50.7 ± 3.38	50.0 ± 1.58	55.1 ± 1.22	50.5 ± 2.31	54.2 ± 0.92
APACHE II score[6]	15.9 ± 1.5	13.2 ± 0.9	15.0 ± 0.6	16.7 ± 1.0	14.7 ± 0.5
Healthcare-associated	1.59 (0.76, 3.29)	1.83 (1.08, 3.11)	3.16 (2.09, 4.78)	6.35 (2.24, 18.09)	2.40 (1.74, 3.32)
In intensive care unit	2.80 (1.22, 6.41)	2.40 (1.29, 4.47)	3.11 (1.91, 5.05)	4.72 (2.31, 9.62)	1.86 (1.23, 2.81)
Days from admission to treatment	13.0 ± 3.4	8.4 ± 2.3	11.9 ± 1.5	23.3 ± 4.1	7.1 ± 0.9
Maximum temperature, °C	38.2 ± 0.2	38.0 ± 0.1	37.9 ± 0.1	37.9 ± 0.2	37.9 ± 0.1
Maximum white blood cell count (1,000/mm^3)	20.0 ± 2.0	15.8 ± 1.4	17.5 ± 0.8	16.7 ± 1.9	15.9 ± 0.5
Medical conditions					
Corticosteroid use	1.16 (0.52, 2.61)	0.68 (0.35, 1.33)	2.61 (1.78, 3.84)	7.00 (3.55, 13.82)	1.52 (1.11, 2.12)
Solid organ allograft	0.93 (0.35, 2.44)	0.67 (0.31, 1.45)	3.13 (2.08, 4.72)	7.20 (3.70, 14.01)	1.25 (0.86, 1.81)
Liver	0.94 (0.32, 2.74)	0.76 (0.34, 1.72)	3.47 (2.24, 5.39)	6.94 (3.55, 13.53)	1.28 (0.86, 1.93)
Kidney	0.94 (0.12, 7.16)	0.44 (0.058, 3.29)	0.98 (0.36, 2.68)	1.72 (0.39, 7.62)	1.10 (0.51, 2.45)
Kidney/pancreas	—	—	1.41 (0.27, 7.36)	3.00 (0.35, 25.51)	2.17 (0.66, 7.18)
Diabetes mellitus	0.44 (0.15, 1.26)	1.34 (0.79, 2.29)	1.46 (0.98, 2.19)	0.28 (0.089, 0.93)	0.96 (0.68, 1.35)
Cardiac disease	1.05 (0.43, 2.60)	0.36 (0.15, 0.94)	0.84 (0.52, 1.37)	0.58 (0.20, 1.67)	1.35 (0.95, 1.93)
Malignant disease	0.78 (0.27, 2.25)	1.05 (0.54, 2.07)	1.13 (0.69, 1.86)	0.33 (0.077, 1.37)	0.85 (0.56, 1.30)
Baseline pulmonary disease	2.67 (1.12, 6.37)	1.48 (0.70, 3.12)	1.06 (0.58, 1.94)	1.94 (0.78, 4.83)	1.77 (1.15, 2.74)
Ventilator dependence	2.23 (0.83, 6.00)	2.33 (1.15, 4.72)	2.61 (1.49, 4.58)	4.01 (1.80, 8.92)	1.95 (1.23, 3.10)
Liver disease	1.20 (0.35, 4.05)	1.77 (0.83, 3.76)	2.51 (1.45, 4.34)	5.02 (2.36, 10.68)	1.38 (0.84, 2.27)
Dialysis dependence	3.03 (1.19, 7.69)	1.06 (0.41, 2.77)	4.37 (2.46, 7.78)	3.78 (1.64, 8.72)	1.05 (0.60, 1.87)
Crohn's disease/UC	—	1.43 (0.62, 3.28)	0.22 (0.07, 0.70)	0.74 (0.17, 3.16)	1.27 (0.68, 1.99)
Source of infection					
Stomach	—	0.88 (0.20, 3.84)	1.25 (0.49, 3.23)	1.71 (0.39, 7.61)	2.16 (1.12, 4.17)
Duodenum	2.72 (0.60, 12.40)	0.62 (0.080, 4.73)	2.82 (1.03, 7.69)	1.18 (0.15, 9.19)	4.03 (2.06, 7.90)
Pancreas	0.43 (0.058, 3.22)	2.29 (1.10, 4.77)	2.73 (1.49, 4.99)	1.68 (0.57, 4.93)	0.57 (0.28, 1.15)
Liver/biliary	1.44 (0.69, 3.01)	1.09 (0.62, 1.89)	1.83 (1.25, 2.67)	2.70 (1.41, 4.19)	0.97 (0.70, 1.36)
Small bowel	0.29 (0.067, 1.23)	1.12 (0.60, 2.07)	1.17 (0.74, 1.84)	0.55 (0.19, 1.57)	1.45 (1.02, 2.05)
Appendix	1.32 (0.45, 3.89)	—	0.11 (0.03, 0.44)	0.27 (0.037, 2.01)	0.12 (0.04, 0.38)
Colorectal	1.07 (0.50, 2.26)	0.99 (0.58, 1.69)	0.46 (0.29, 0.73)	0.39 (0.15, 1.02)	1.02 (0.74, 1.40)

Table 6. Patient Characteristics and Odds Ratios (85% Confidence Intervals) of Finding that Characteristic among Patients with Specific Resistant Pathogens Compared with Intra-Abdominal Infections with No Resistant Pathogens (Cont'd)

	Non-fermenting gram negative[1] (N = 35)	*Resistant staphylococci*[2] (N = 74)	*All enterococci*[3] (N = 161)	*VRE*[4] (N = 39)	*Fungi*[5] (N = 267)
Other/unknown	1.36 (0.51, 3.62)	0.99 (0.46, 2.14)	0.74 (0.40, 1.35)	0.94 (0.32, 2.71)	0.52 (0.30, 0.91)
Outcomes					
Duration of antibiotic therapy	14.9 ± 1.3	14.8 ± 0.9	15.5 ± 0.8	18.2 ± 1.6	18.1 ± 1.6
Length of stay (days)[7]	25.7 ± 6.3	24.8 ± 3.5	21.5 ± 1.7	23.9 ± 3.2	23.8 ± 1.8
In-hospital death	1.78 (0.67, 4.76)	1.29 (0.59, 2.83)	1.62 (0.94, 2.80)	3.68 (1.71, 7.93)	1.88 (1.23, 2.89)

Shaded boxes indicate $p < 0.05$ by Student's *t*-test or 95% confidence does not cross 1 compared to infections with no resistant organisms (see Table 3), except for values for all enterococcal infections, which are compared with all infections without resistant pathogens or *Enterococcus* spp.

[1]Includes *P. aeruginosa, S. maltophilia,* and *Acinetobacter* spp.

[2]Includes methicillin-resistant *S. aureus* and coagulase-negative staphylococci.

[3]Includes vancomycin-resistant and -resistant strains.

[4]Vancomycin-resistant enterococci; all were *E. faecium*.

[5]Includes all *Candida* spp., non-speciated yeast, *Aspergillus* spp., and other fungi.

[6]At time of diagnosis of intra-abdominal infection.

[7]From initiation of therapy for intra-abdominal infection.

UC = ulcerative colitis.

One of the underlying premises of trying to match empiric antimicrobial therapy with probable pathogens on the basis of presenting patient characteristics is the idea that early adequate therapy for all isolated pathogens will lead to better outcomes. This concept is far from proved. The need to diagnose and treat both enterococci and *Candida* spp. specifically continues to be unclear, with recommendations generally leaning toward treatment only in immunosuppressed or critically ill patients [1, 3]. On the other hand, Montravers et al. reported a mortality rate of 16% for patients with postoperative peritonitis who received adequate initial empiric antimicrobial therapy vs. 45% for those who did not [5], implying that for complex cases of intra-abdominal infection, a more aggressive spectrum of empiric therapy may be warranted.

For certain infections such as straightforward community-acquired infections or infections with diffuse fecal soilage, where thousands of species of organisms co-exist, the utility of peritoneal cultures is unclear. Some authorities argue for the practice [6], whereas others argue just as strongly against it [7]. Commonly, it is recommended that patients with postoperative, tertiary, and other forms of health care-associated peritonitis undergo culture because of the greater likelihood of isolation of nosocomial pathogens, and there is some evidence to support this approach [1, 3]. For example, Montravers et al., using multivariable analysis, noted that the isolation of *Candida* spp. from the abdomen was predictive of death in nosocomial but not community-acquired infections, implying that cultures might not be worthwhile in community-acquired peritonitis [8]. These data are similar to our own, where Candida spp. were the most common resistant isolates from community-acquired infections, yet there was no increase in the mortality rate (5.9%) despite the use of antifungal agents in only about one-half of these cases (data not shown), whereas we have reported that for all infected surgical patients, the isolation of fungi is an independent predictor of death [9]. Thus, the routine culturing of the peritoneal cavity during community-acquired intra-abdominal infections cannot be recommended because there is little evidence that this practice alters outcomes.

One weakness of our study is that we do not have reliable data on two important aspects that should be considered when deciding on the empiric therapy for intra-abdominal infections, namely recent antibiotic use and documented colonization with resistant pathogens. Data from studies of tertiary peritonitis show clearly that antimicrobial therapy for infection influences the flora of subsequent intra-abdominal infections [10, 11]. Although we did not specifically study antimicrobial use prior to the treatment of intra-abdominal infection in our population, it is likely that a large part of the relation between health care-associated and ICU-acquired infections and the isolation of resistant pathogens relates to previous antibiotic exposure. We have demonstrated that confirmed colonization with resistant gram-positive pathogens is highly associated with subsequent infections with those pathogens among surgical patients [12].

One point that cannot be overemphasized in interpreting our data is the selected patient population. As a tertiary referral center with a large number of transplant recipients, our results certainly are not typical compared with those of many other hospitals. In addition, even our community-acquired infections may not represent a normal distribution, because many patients are referred to us because of co-morbidities. Therefore, the relatively low rate of isolation of *E.*

Table 7. Results of Logistic Regression Analysis Examining Influence of Clinical Factors on In-Hospital Death

	Odds value	*95% Confidence interval*	P *value*
Demographics			
Male sex	0.87	0.55, 1.37	0.54
Age ≥ 70 years	3.81	2.22, 6.54	<0.0001
APACHE II[1] ≥ 20	5.24	3.23, 8.53	<0.0001
In intensive care unit	3.53	1.78, 7.02	0.0003
Days from admission to treatment ≥ 10	1.32	0.76, 2.27	0.32
Maximum temperature ≥ 38.5°C	0.31	0.18, 0.54	<0.0001
Maximum white blood cell ≥ 20,000/mm^3	1.18	0.73, 1.90	0.50
Medical conditions			
Corticosteroid use	1.32	0.65, 2.64	0.44
Solid organ allograft	0.47	0.14, 1.57	0.22
Diabetes mellitus	1.15	0.69, 1.91	0.59
Cardiac disease	2.12	1.26, 3.57	0.0048
Malignant disease	3.41	1.97, 5.93	<0.0001
Baseline pulmonary disease	1.54	0.85, 2.81	0.16
Ventilator dependence	1.78	0.87, 3.68	0.11
Liver disease	2.84	1.42, 5.68	0.0032
Dialysis dependence	2.39	1.25, 4.56	0.0084
Infection with resistant organism[2]	1.39	0.83, 2.30	0.21
Interaction terms[3]			
Resistant organism + solid organ allograft	5.18	1.60, 16.8	0.0061

[1]At time of diagnosis of intra-abdominal infection.
[2]Includes *P. aeruginosa, S. maltophilia, Acinetobacter* spp., methicillin-resistant *S. aureus*, coagulase-negative staphylococci, vancomycin-resistant enterococci, or any fungi.
[3]Tests for synergistic effect of one or more terms in combination, independent of individual contribution of each.
APACHE = Acute Physiology and Chronic Health Evaluation.
c statistic = 0.887; $R^2 = 0.226$.

coli and *B. fragilis* may well be secondary to the biased population that presents to our medical center, different from those at other hospitals or enrolled in pharmaceutical trials. These differences in patient population should be taken into account when interpreting our data. In addition, even the flora isolated from hospital-acquired infections will differ among centers. For example, Montravers et al. [13] noted that fewer than 10% of patients with non-postoperative nosocomial intra-abdominal infections had fungi isolated, vs. 37% in our health care-associated population, highlighting the variable nature of patients who superficially might seem homogeneous.

The data presented are intended to help guide empiric therapy that is, by definition, a guess. The implications of our observations need to be tempered by the characteristics of the local flora; for example, some hospitals have few or no VRE, and an agent specific for this pathogen should not be part of any empiric regimen. Nevertheless, some general suggestions can be made for the specific pathogens studied. Empiric therapy for non-fermenting gram-negative bacilli or resistant staphylococci, including MRSA, probably can be reserved for patients known to be colonized or infected previously with these pathogens. Some form of enterococcal coverage should be considered for anything other than straightforward community-acquired infections in immunocompetent hosts, and empiric therapy for VRE probably is indicated for liver transplant patients. Similarly, empiric therapy with an antifungal agent may be reasonable for any infection other than those acquired in the community, and may be indicated especially for infections from an upper gastrointestinal source.

Overall, our data support the idea that health care association and the presence of iatrogenic immunosuppression should lead one to consider the broadening of empiric antimicrobial therapy for intra-abdominal infections [1, 2]. Naturally, local endemicity patterns also need to be considered, such as the rate of colonization with VRE. Our data suggest further that emphasis ought to be put on adequate empiric enterococcal and fungal activity for these patients, as resistant gram-negative bacilli are still uncommon isolates. In addition, certain associations imply even more targeted therapy in certain patient populations, such as using empiric antimicrobials with VRE activity in liver transplant recipients with intra-abdominal infections. Of course, prospective data from other centers are needed to confirm these relations, and local epidemiology always needs to be considered when empiric antibiotic regimens are chosen.

Author Disclosure Statement

This study was supported partially by National Institutes of Health grant 1 R01 AI49989-03. Dr. Sawyer has acted as an advisor for Pfizer, Merck, Wyeth, and Schering-Plough.

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