SURGICAL INFECTIONS
Volume 15, Number 4, 2014

DOI: 10.1089/sur.2012.077

Association of Excessive Duration of Antibiotic Therapy for Intra-Abdominal Infection with Subsequent Extra-Abdominal Infection and Death: A Study of 2,552 Consecutive Infections

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Abstract

Background: We hypothesized that a longer duration of antibiotic treatment for intra-abdominal infections (IAI) would be associated with an increased risk of extra-abdominal infections (EAI) and high mortality.
Methods: We reviewed all IAI occurring in a single institution between 1997 and 2010. The IAI were divided into two groups consisting of those with a subsequent EAI and those without; the data for each group were analyzed. Patients with EAI following IAI were matched in a 1:2 ratio with patients who did not develop EAI on the basis of their Acute Physiology and Chronic Health Evaluation (APACHE II) score ± 1 point. Statistical analyses were done with the Student *t*-test, χ^2 analysis, Wilcoxon rank sum test, and multi-variable analysis.
Results: We identified 2,552 IAI, of which 549 (21.5%) were followed by EAI. Those IAI that were followed by EAI were associated with a longer initial duration of antimicrobial therapy than were IAI without subsequent EAI (median 14 d [inter-quartile range (IQR) 10–22 d], vs. 10 d [IQR 6–15 d], respectively, $p < 0.01$), a higher APACHE II score (16.6 ± 0.3 vs. 11.2 ± 0.2 points, $p < 0.01$), and higher in-hospital mortality (17.1% vs. 5.4%, $p < 0.01$). The rate of EAI following IAI in patients treated initially with antibiotics for 0–7 d was 13.3%, vs. 25.1% in patients treated initially for >7 d ($p < 0.01$). A successful match was made of 469 patients with subsequent EAI to 938 patients without subsequent EAI, resulting in a mean APACHE II score of 15.2 for each group. After matching, IAI followed by EAI were associated with a longer duration of initial antimicrobial therapy than were IAI without subsequent EAI (median 14 d [9–22 d], vs. 11 d [7–16 d], respectively, $p < 0.01$), and with a higher in-hospital mortality (14.9% vs. 9.0%, respectively, $p < 0.01$). Logistic regression showed that days of antimicrobial therapy for IAI was an independent predictor of subsequent EAI ($p < 0.001$).
Conclusions: A longer duration of antibiotic therapy for IAI is associated with an increased risk of subsequent EAI and increased mortality.

Intra-abdominal infections (IAI) are a substantial burden for patients, surgeons, and the health-care system. Despite advances in therapeutic techniques, including radiographic and pharmaceutical interventions, overall mortality in patients with IAI exceeds 10%. Source control remains the cornerstone of the management of IAI. This involves mechanical reduction of the infectious burden in the abdomen and the cessation of any ongoing contamination of the abdomen from the gastrointestinal or genitourinary tract. Antimicrobial therapy is an important adjunct to source control in the management of IAI, and the inadequate and inappropriate use of antibiotics is associated with an increased risk of death [1]. Meticulous supportive care, including adequate resuscitation and nutrition, is also necessary to optimize the outcome of patients with IAI.

A major unanswered question in the care of patients with IAI is the appropriate duration of antimicrobial therapy after source control has been achieved. Some surgeons recommend a fixed duration of therapy, generally in the range of 7–10 d, whereas others continue antibiotic adminisration until signs and symptoms indicate that acute infection has resolved. Recent recommendations of the Surgical Infection Society (SIS) and the Infectious Diseases Society of America (IDSA) [2–4] include limiting the duration of antibiotics to no more than seven days if source control has been achieved.

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Despite similar recommendations made almost a decade ago [5–7], numerous clinical reports describe durations of antimicrobial therapy of longer than seven days for the treatment of IAI [8]. This is probably the result of a clinical decision to continue antibiotics until systemic signs and symptoms of infection, such has fever and leukocytosis, have resolved, and the belief that a longer duration of antibiotic administration is relatively risk-free.

Although the major risk of an inadequate duration of antimicrobial therapy, consisting of recurrent IAI, is obvious and measurable, the risks of excessive and prolonged antibiotic treatment are more diffuse. Possible disadvantages of excessive antimicrobial exposure include increased cost, side effects of the agents used, and the induction of resistance among infecting or colonizing organisms, although each of these outcomes is documented poorly in the literature. One possible downstream effect of unnecessary exposure to antimicrobial agents is an increased susceptibility to subsequent infections, whether as a result of the selection of resistant pathogens per se or of some other, more subtle change in indigenous flora or in the host immune response. The underlying hypothesis for the current study, based in part on these possibilities, was that an association exists between longer courses of antimicrobial therapy for IAI and an increased risk of subsequent EIA among a cohort of hospitalized surgical patients.

Patients and Methods

Our study was a retrospective analysis of a prospectively collected infectious disease data base. This continuously maintained data base includes observations pertaining to all infections occurring in individuals treated as inpatients on the general surgery and trauma units of the University of Virginia Hospital. The study was approved by the University of Virginia Institutional Review Board. Given the observational nature of the data and the de-identification of patients, the need for informed consent was waived.

During the 14-y study period (1997–2010), surgical patients identified as having an infection were followed prospectively during their hospitalization, from the date of diagnosis of infection until death or hospital discharge. Subjects were identified and data were collected through an alternate-day chart review, patient examination, physician interview, and review of pharmacy, laboratory, and microbiologic data. Variables recorded at study entry included age, gender, patient-defined race, patient location at the time of onset of infection (intensive care unit [ICU], home, hospital ward), and pre-infection medical comorbidities (diabetes mellitus, cardiac disease, hypertension, peripheral vascular disease, cerebral vascular disease, chronic kidney disease not requiring dialysis, dependence on dialysis, pulmonary disease, ventilator dependence, active malignant disease, hepatic insufficiency, chronic steroid use, psychiatric diagnoses, thyroid disorder, inflammatory bowel disease (IBD), transplantation, and the need for transfusions of blood cell products, specifically consisting of packed red blood cells or platelets). The Acute Physiology and Chronic Health Evaluation II (APACHE II) score for each patient was determined at the time of initiation of treatment as a measure of severity of illness. Infections were defined according to the criteria of the U.S. Centers for Disease Control and Prevention [9]. The U.S. Food and Drug Administration definition of a complicated IAI was used for the study; only infections of the abdomen that required either surgical or percutaneous intervention were included. The first occurrences of complicated IAI were included and recurrent infections of the abdomen were excluded. Infections occurring at a site other than the abdomen and treated for more than 72 h after the initial diagnosis of IAI were considered as subsequent EAI. Infections diagnosed within 72 h of the initial diagnosis of IAI were not included because they were believed to be simultaneous rather than sequential events. The mortality reported in the study is all-cause, in-hospital mortality.

Data manipulation and statistical analyses were done with IBM SPSS version 19 software (IBM, Somers, NY). Demographics and pre-infection risk factors were tabulated and reported. Normally distributed continuous variables are reported as the mean ± standard error of the mean (SEM). Non-normally distributed continuous variables are reported as the median and inter-quartile range (IQR). Binary categorical variables were compared through χ^2 analysis or the Fisher exact test; continuous variables were compared through use of the Student *t*-test or, for data that were not distributed normally, the Wilcoxon rank sum test. Because the current SIS and IDSA recommendations are that antibiotic therapy for IAI should continue for up to seven days [3,4], we analyzed infections treated for seven or fewer days and compared them with infections treated for more than seven days. Because we detected an imbalance in the entire study-patient cohort in the APACHE II scores of patients with and those without an EAI following an IAI, we used 1:2 matching of these two groups, based on the APACHE II score ± 1 point. We then repeated our comparison of differences in outcomes of the matched groups. We performed backward stepwise logistic regression analysis (Wald) using a priori factors related to various demographic and treatment variables, including days of antimicrobial therapy for IAI. A value of $p \leq 0.05$ was considered significant.

Results

During the 14-y period of the study, 2,552 initial episodes of complicated IAI were managed in our institution, and a subsequent EAI developed in 549 (21.5%) of the patients with these IAI during their hospitalization. Characteristics and outcomes of all patients with IAI who did not develop a subsequent EAI, as compared with those of patients who did develop a subsequent EAI, are described in Table 1. Cases of IAI in which EAI ensued were more commonly caused by hospital-acquired organisms, were more frequent in patients with multiple medical co-morbidities, and were associated with a higher mean APACHE II score than cases in which IAI was not followed by EAI. The duration of antimicrobial therapy for IAI followed by EAI was significantly longer than for IAI that was not followed by EAI (respective median and IQR 14 d [10–22 d], vs. 10 d [6–15 d], $p < 0.01$), and the mortality rate for such cases was significantly higher than in cases of IAI not followed by EAI (17.1% vs. 5.4%, respectively, $p < 0.01$). The rate of subsequent EAI was significantly lower for patients receiving seven or fewer days of antimicrobial treatment for IAI than for those treated for longer than this (13.3% vs. 25.1%, respectively, $p < 0.01$). Table 2 shows the results for the study patient population according to the major diagnostic categories of trauma, transplant, and

Table 1. Characteristics of All Intra-Abdominal Infections in Study Population

Variable	*Infections without subsequent EAI*	*Infections with subsequent EAI*	p *value*
Number	2,003 (78.5%)	549 (21.5%)	-
Age	53.5 ± 0.4	55.7 ± 0.7	0.01
APACHE II score	11.2 ± 0.2	16.6 ± 0.3	< 0.01
Males	1,108 (55.3%)	297 (54.1)	> 0.2
Race			
White	1,674 (83.6%)	460 (83.4%)	> 0.2
Black	258 (12.9%)	75 (13.7%)	
Other	28 (1.4%)	10 (1.8%)	
Location at onset of IAI			
Home	1,414 (70.6%)	200 (36.4%)	< 0.01
Hospital ward	519 (25.9%)	260 (47.4%)	
ICU	70 (3.5%)	89 (16.2%)	
Days, admission to treatment	1 (0–2)	2 (0–8)	< 0.01
Maximum WBC ($10^3/\mu L$)	15.1 ± 0.2	16.3 ± 0.4	< 0.01
Maximum temperature (°C)	37.8 ± 0.0	37.9 ± 0.0	0.04
Diabetes mellitus	393 (19.6%)	117 (21.3%)	> 0.2
Dialysis dependence	62 (3.1%)	41 (7.5%)	< 0.01
Chronic corticosteroids	375 (18.7%)	133 (24.2%)	< 0.01
Cardiac disease	341 (17.0%)	123 (22.4%)	< 0.01
Ventilator dependence	53 (2.6%)	82 (14.9%)	< 0.01
Solid-organ transplant	294 (14.7%)	94 (17.1%)	0.18
Most common pathogens (*n*)	*Candida* spp./yeast 293 *Bacteroides* spp. 237 *Enterococcus* spp. 210 VRE 65 *Escherichia coli* 169 *Streptococcus* spp. 166 *Klebsiella* spp. 108 *Staphylococcus aureus* 94 MRSA 44	*Candida* spp./yeast 143 *Enterococcus* spp. 110 VRE 30 *Bacteroides* spp. 74 *E. coli* 64 *Streptococcus* spp. 31 *Klebsiella* spp. 33 *S, aureus* 28 MRSA 22	
Days of antimicrobial therapy (mean)	11.9 ± 0.2	18.4 ± 0.9	< 0.01
Days of antimicrobial therapy (median)	10 (6–15)	14 (10–22)	< 0.01
Hospital length of stay	6 (4–10)	26 (15–45)	< 0.01
In-hospital deaths	109 (5.4%)	94 (17.1%)	< 0.01

APACHE II = Acute Physiology and Chronic Health Evaluation II; EAI = extra-abdominal infection; IAI = intra-abdominal infection; ICU = intensive care unit; MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant enterococci; WBC = white blood cell count.

general surgery (non-trauma/non-transplant), and shows that outcomes within diagnostic categories were similar to those for the entire patient population.

Characteristics of EAI subsequent to IAI are shown in Table 3. The most common site of EAI after initial IAI was the blood stream, and the most common pathogens were *Candida* spp., *Enterococcus* spp., and *Pseudomonas aeruginosa*. Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) were prevalent, particularly in pneumonia and blood stream infections (BSI). The all-cause in-hospital mortality for all EAI was 25.1%. The median length of stay after the diagnosis of infection was 22 d, with an IQR of 9–46 d. The highest all-cause, in-hospital mortality (35.2%) was seen in patients with pneumonia, and was caused most frequently by infection with *P. aeruginosa* or MRSA.

Clostridium difficile-associated diarrhea (CDAD) was diagnosed in 83 patients. The mean duration of antimicrobial therapy for IAI in these patients was 15.6 ± 1.0 d (median 13 d, IQR 10–22 d), which was similar to that for patients with subsequent EAI, in which the mean duration of therapy was 18.4 ± 0.9 d (median 14 d, IQR 10–22 d), but was longer than that for patients without subsequent EAI. Matching in a 1:2 ratio on the basis of the APACHE II score ± 1 point was done because of the imbalance in APACHE II score at the time of initial IAI of patients with these infections followed by EAI and of those in whom IAI was not followed by EAI. Successful matching was possible of 469 patients with IAI and a subsequent EAI with 938 patients who had IAI without a subsequent EAI. The demographics and outcomes of the two groups are described in Table 4. The mean and median APACHE II scores of the two groups were similar. However, despite similar severities of illness the duration of antimicrobial therapy was longer and mortality was higher among patients in whom EAI followed IAI than among those with IAI alone.

After matching, data were re-analyzed on the basis of whether the initial IAI was community-acquired or health care-associated. Of community-acquired infections, 348 were not followed by EAI and 112 were followed by EAI.

Table 2. Characteristics of Intra-Abdominal Infections by Diagnosis

Variable	*Infections without subsequent EAI*	*Infections with subsequent EAI*	p *value*
Trauma			-
Number	54 (51.9%)	50 (48.1%)	
Age	38.1 ± 2.4	46.9 ± 3.0	0.02
APACHE II score	12.3 ± 1.1	17.6 ± 1.0	< 0.01
Males	43 (79.6%)	35 (70.0%)	> 0.2
Maximum WBC (10^9 cells/L)	17.0 ± 1.0	15.6 ± 1.2	> 0.2
Maximum temperature (°C)	38.0 ± 0.1	38.4 ± 1.0	> 0.2
Most common pathogens (*n*)	*Candida* spp./yeast 7 *Bacteroides* spp. 3 *Enterococcus* spp. 3 VRE 0 *Escherichia coli* 2 No cultures 33	*Candida* spp./yeast 10 *Enterococcus* spp. 7 VRE 3 *Bacteroides* spp. 6 *E. coli* 4 No cultures 24	
Days antimicrobial therapy (mean)	8.5 ± 0.9	17.2 ± 2.1	< 0.01
Days antimicrobial therapy (median)	7 (3–13)	14 (6–23)	< 0.01
In-hospital deaths	7 (13.0%)	3 (6.0%)	> 0.2
Transplant			-
Number	294 (75.8%)	94 (24.2%)	
Age	50.8 ± 0.7	50.5 ± 1.1	> 0.2
APACHE II score	15.3 ± 0.4	18.7 ± 0.7	< 0.01
Males	206 (70.1%)	65 (69.1%)	> 0.2
Maximum WBC (10^9 cells/L)	12.3 ± 0.5	17.0 ± 1.2	0.01
Maximum temperature (°C)	37.8 ± 0.1	37.5 ± 0.1	> 0.2
Most common pathogens (n)	*Enterococcus* spp. 64 VRE 28 *Candida* spp./yeast 46 *E. coli* 17 *Bacteroides* spp. 12	*Enterococcus* spp. 35 VRE 10 *Candida* spp./yeast 26 *E. coli* 7 *Bacteroides* spp. 6	
Days antimicrobial therapy (mean)	14.5 ± 0.8	26.2 ± 4.7	< 0.01
Days antimicrobial therapy (median)	14 (8–18)	18 (11–26)	< 0.01
In-hospital deaths	17 (5.8%)	24 (25.5%)	< 0.01
General surgery (non-trauma/non-transplant			-
Number	1656 (80.3%)	405 (19.7%)	
Age	54.5 ± 0.4	58.0 ± 0.8	< 0.01
APACHE II score	10.5 ± 0.2	16.0 ± 0.4	< 0.01
Males	860 (51.4%)	197 (48.6%)	> 0.2
Maximum WBC (10^3/μL)	15.5 ± 0.2	16.2 ± 0.5	0.14
Maximum temperature (°C)	37.7 ± 0.0	38.0 ± 0.1	< 0.01
Most common pathogens (n)	*Candida* spp./yeast 240 *Bacteroides* spp. 207 *E. coli* 150 *Streptococcus* spp. 148	*Candida* spp./yeast 107 *Enterococcus* spp. 68 VRE 17 *Bacteroides* spp. 62 *E. coli* 53	
Days antimicrobial therapy (mean)	11.5 ± 0.2	16.8 ± 0.6	< 0.01
Days antimicrobial therapy (median)	10 (6–15)	14 (10–22)	< 0.01
In-hospital deaths	85 (5.1%)	67 (16.5%)	< 0.01

APACHE II = Acute Physiology and Chronic Health Evaluation II; EAI = extra-abdominal infection; VRE = vancomycin-resistant enterococci; WBC = white blood cell count.

The initial APACHE II score for patients without subsequent EAI was 15.2 ± 0.4, vs. 12.5 ± 0.6 points for patients with subsequent EAI ($p < 0.01$), yet the duration of antimicrobial therapy for the initial IAI was shorter for the patients who did not develop a subsequent EAI than for those who did, with a mean of 10.5 ± 0.4 d and median of 9 d (IQR 5–14 d), vs. a mean of 14.1 ± 1.1 d and median of 22 d (IQR 12–38), respectively ($p < 0.05$). The all cause, in-hospital mortality for the two groups was similar, at 30/348 (8.6%) vs. 12/112 (10.7%), respectively. Among patients with health care-associated infections (590 of which were not complicated by subsequent EAI and 357 of which were followed by EAI), the APACHE II scores were similar, at 15.2 ± 0.3 vs. 16.0 ± 0.4 ($p > 0.05$). The duration of antimicrobial therapy for the initial IAI was also shorter for patients without than for those with a subsequent EAI, with a mean of 12.7 ± 0.3 d and median of 12 d (IQR 7–12 d), vs. a mean of 20.0 ± 1.4 d and median of 26 d (IQR 15–45 d), respectively ($p < 0.01$). The

TABLE 3. CHARACTERISTICS OF EXTRA-ABDOMINAL INFECTIONS FOLLOWING INTRA-ABDOMINAL INFECTIONS

Site of infection	*Blood*	*Lung*	*Urine*	*Incision*[a]	*Vascular catheter*
Number	324	287	287	224	157
Age	53.7 ± 0.8	57.4 ± 0.9	57.2 ± 0.9	54 ± 1.0	52.9 ± 1.2
APACHE II score[b]	17.3 ± 0.4	19.7 ± 0.4	15.2 ± 0.4	13.7 ± 0.5	17.4 ± 0.5
Males	185 (57.1%)	177 (61.7%)	109 (38.0%)	106 (47.3%)	76 (48.4%)
Race					
White	258	221	237	186	132
Black	53	53	36	33	21
Other	13	13	14	5	4
Location at onset					
Home[c]	8	0	8	11	1
Hospital ward	125	64	150	117	49
ICU	191	221	129	96	107
Most common pathogens (*n*)	*Enterococcus* 95 VRE 33 CNS 85 *Candida*/yeast 58 *P. aeruginosa* 19 *E. coli* 15 *Serratia* 15	*P. aeruginosa* 86 *S. aureus* 53 MRSA 42 *Klebsiella* 25 *Stenotrophomonas maltophilia* 27 *Acinetobacter* 22 *Enterobacter* 22	*Candida*/yeast 101 *Enterococcus* 56 VRE 34 *P. aeruginosa* 34 *E. coli* 25 *Klebsiella* 19	*Candida*/yeast 49 *Enterococcus* 34 VRE 12 *P. aeruginosa* 18 *E. coli* 15 *Klebsiella* 12 *S. aureus* 12 MRSA 5	CNS 52 *Candida*/yeast 38 *Enterococcus* 25 VRE 2 *S. aureus* 15 MRSA 12 *Klebsiella* 7
Days of antimicrobial therapy	14 (9–19)	13 (8–18)	8 (5–14)	12 (6–17)	12 (7–17)
Hospital LOS[d]	23 (10–52)	28 (15–56)	18 (7–44)	17 (7–34)	28 (12–65)
In-hospital deaths	95 (29.3%)	101 (35.2%)	70 (24.4%)	29 (12.9%)	39 (24.8%)

[a]Incisional surgical site infections only.
[b]Scored at time of diagnosis of EAI.
[c]Patients who returned to the hospital after discharge with a new EAI.
[d]Length of stay from time of diagnosis of EAI.
APACHE II = Acute Physiology and Chronic Health Evaluation II; CNS = coagulase-negative staphylococci, including *S. epidermidis*; ICU = intensive care unit; LOS = length of stay; MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant enterococci.

Table 4. Demographics and Outcomes in Matched Intra-Abdominal Infections

Variable	*Infections without subsequent EAI*	*Infections with subsequent EAI*	p *value*
Number	938	469	-
Age	57.2 ± 0.5	55.4 ± 0.7	0.04
APACHE II score (mean)	15.2 ± 0.2	15.2 ± 0.3	> 0.2
APACHE II score (median)	15 (11–19)	15 (10–20)	> 0.2
Males	551 (58.7%)	297 (54.1%)	> 0.2
Race			
White	799 (85.2%)	460 (83.4%)	> 0.2
Black	115 (12.3%)	75 (13.7%)	
Other	24 (2.5%)	10 (1.8%)	
Location at onset of IAI			
Home	600 (64.0%)	200 (36.4%)	< 0.01
Hospital ward	277 (29.5%)	260 (47.4%)	
ICU	61 (6.5%)	89 (16.2%)	
Days, admission to treatment	1 (0–4)	2 (0–8)	< 0.01
Maximum WBC (10^9 cells/L)	16.0 ± 0.3	16.0 ± 0.4	> 0.2
Maximum temperature (°C)	37.8 ± 0.0	38.0 ± 0.0	< 0.01
Diabetes mellitus	217 (23.1%)	106 (22.6%)	> 0.2
Dialysis dependence	58 (6.2%)	32 (6.8%)	> 0.2
Chronic corticosteroids	375 (27.6%)	110 (23.5%)	< 0.01
Cardiac disease	212 (22.6%)	108 (23.0%)	> 0.2
Ventilator dependence	46 (4.9%)	59 (12.6%)	< 0.01
Solid organ transplant	217 (23.1%)	80 (17.1%)	< 0.01
Most common pathogens (*n*)	*Candida* spp./yeast 183 *Enterococcus* spp. 144 VRE 57 *Bacteroides* spp, 123 *E. coli* 84 *Streptococcus* spp. 69 *Klebsiella* spp. 50 *S. aureus* 48 MRSA 27	*Candida* spp./yeast 121 *Enterococcus* spp. 89 VRE 27 *Bacteroides* spp. 63 *E. coli* 59 *Klebsiella* spp. 27 *Streptococcus* spp. 26 *S. aureus* 23 MRSA 18	
Days of antimicrobial therapy (mean)	11.9 ± 0.3	18.6 ± 1.1	< 0.01
Days of antimicrobial therapy (median)	11 (7–16)	14 (9–22)	< 0.01
Hospital length of stay	7 (4–12)	25 (14–44)	< 0.01
In-hospital deaths	84 (9.0%)	70 (14.9%)	< 0.01

EIA = extra-abdominal infection; IAI = intra-abdominal infection; ICU = intensive care unit; MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant enterococci; WBC = white blood cell count.

mortality for patients without a subsequent EAI was lower than for those in whom IAI was followed by EAI, at 54/590 (9.2%) vs. 58/357 (16.2%), respectively ($p < 0.01$).

A priori factors chosen for the model of EAI subsequent to IAI included age, APACHE II score, gender, occurrence in the ICU, hospital-acquired IAI, diabetes mellitus, chronic steroid use, presence of a transplanted organ, days from admission to treatment of IAI, and days of antimicrobial therapy for IAI (Table 5). Independent predictors of EAI after initial treatment of IAI included (in decreasing order of the Wald χ^2 statistic) APACHE II score, days of antimicrobial therapy for IAI ($p < 0.001$), hospital-acquired IAI, ICU status at the time

Table 5. Predictors of Extra-Abdominal Infection after Intra-Abdominal Infection

Factor	*Wald statistic*	*Exp* (β)	*95% CI for Exp* (β)	p *value*
APACHE II score (per point)	121.5	1.08	1.07–1.10	< 0.001
Number of days of antimicrobial therapy for IAI (per day)	60.3	1.04	1.03–1.05	< 0.001
Hospital-acquired IAI	23.8	1.82	1.43–2.32	< 0.001
ICU status at time of IAI	12.7	2.00	1.27–2.92	< 0.001
Organ transplant	10.5	0.62	0.47–0.83	0.001
Days, admission to IAI (per day)	9.8	1.02	1.01–1.04	0.002

APACHE II = Acute Physiology and Chronic Health Evaluation II; CI = confidence interval; IAI = intra-abdominal infection; ICU = intensive care unit.

of IAI, non-transplant status, and days from admission to treatment of IAI. Characteristics in the Hosmer–Lemeshow test were a χ^2 statistic = 11.2, degrees of freedom = 8, and significance = 0.19.

Discussion

The management of IAI is complex and includes adequate resuscitation, appropriate mechanical intervention to achieve source control, and the administration of antimicrobial agents active against the pathogens found in the IAI. Although the spectrum of pathogens involved in IAI is fairly well known and many antimicrobial regimens are acceptable for treating such infection according to current guidelines, the optimal duration of antimicrobial therapy remains unknown.

Few randomized studies have examined the efficacy of different courses of antimicrobial therapy in the setting of IAI. Taylor et al. randomized 94 patients with complicated appendicitis to receive either at least five days of antibiotic therapy or therapy of no set duration, with both groups having their antibiotic therapy stopped on the basis of clinical resolution of infection [10]. Outcomes of the two groups were similar, but the duration of antimicrobial therapy was 5.9 d in the five-day treatment group and 4.3 d in the group with no set duration of therapy ($p = 0.014$). More recently, Basoli et al. found similar outcomes for three days of ertapenem versus five or more days of ertapenem in the management of 90 patients with IAI of moderate severity, related principally to appendicitis, who were randomized to either regimen[11]. There were no deaths in either group, and there were a total of eight infectious complications, with no difference in the incidence of complications in the two treatment groups.

Given this relative lack of data from prospective studies, the duration of antimicrobial therapy for IAI has commonly been based on custom and expert opinion [2–6,12,13]. Although recommendations for the duration of antimicrobial therapy for IAI routinely range from five to seven days after adequate source control has been achieved, our data demonstrate that these guidelines are met rarely. One possible reason for this is the belief that additional days of antibiotics are relatively risk-free. However, this may not be the case. Hedrick et al. presented evidence that shorter, fixed courses of antibiotic therapy in the treatment of IAI were associated with less risk of complications, including a reduced risk of recurrent IAI, than were longer courses of antibiotic therapy [8]. These data suggest that substantial morbidity may be associated with long-term antimicrobial administration, even after controlling for underlying illness.

The most common EAI in our patient population was blood stream infection, as opposed to urinary tract infections and surgical site infection, which have been considered to be the most common nosocomial infections in other similar studies [14]. We, of all surgical patients, believe that this discrepancy may stem from the inclusion, in the population used for compiling most of the national data regarding nosocomial infections, regardless of their primary illness. The patients in our study who developed an EAI subsequent to an IAI were already being treated for serious IAI, and therefore represented a select population. Unfortunately, because our data set does not capture central venous catheter usage or the number of days of such catheterization, we can only speculate that a higher percentage of the patients who develop EAI after IAI have central venous catheters than does the general population of patients who develop nosocomial infections. It is also possible that pathologic features of IAI, such as the virulence of the causative pathogen or its ability to translocate, makes patients more susceptible to blood stream infections.

Our data demonstrate that EAI following IAI is associated both with a greater severity of illness during the IAI and with characteristics that mark the patients who develop such EAI as having longer and more intense exposure to health care, including ICU status, in-hospital acquisition of infection, and multiple co-morbidities. These findings suggest that some patients have an increased susceptibility or decreased responsiveness to treatment for medical illnesses (including infections), and that the duration of therapy for IAI is merely a marker of patients who are genetically at risk for infection. Further clarification of the relationships among genetics, the host response, and microbial pathogenesis will be required to understand further these truly complex interactions.

Duration of therapy has only rarely been studied in forms of severe illness other than IAI, but most notably in ventilator-associated pneumonia (VAP). Of particular interest is the report of Chastre et al. of a randomized, controlled trial of eight versus 15 days of antimicrobial therapy in 401 patients with VAP [15]. Overall, there were no differences in cure rate or mortality between the two treatment groups, and the patients assigned to eight days of antimicrobial therapy had a significantly shorter duration of therapy than those treated for 15 d. Interestingly, patients with pneumonia caused by non-fermentative gram-negative bacilli, principally *P. aeruginosa,* had a higher rate of recurrence of pneumonia but no difference in mortality. Additionally, the patients given 15 d of antimicrobial therapy had a higher incidence of subsequent infections with resistant pathogens. The rates of extrapulmonary infections in the eight-day and 15-d treatment groups were similar. The results of the Chastre et al. study led to recommendations for an abbreviated course of antibiotic use in patients with VAP caused by organisms other than *P. aeruginosa* after the clinical resolution of their illness. Mueller et al., in an observational case-control pilot study, demonstrated that the use of repeat bronchoalveolar lavage as a guide to the duration of antibiotic therapy during an episode of VAP in trauma patients led to a decreased duration of such therapy without any differences in relapse of pneumonia, ventilator-free ICU days, ICU-free hospital days, or mortality as compared with these variables in matched controls [16].

The major weakness of our study is the retrospective nature of its data collection and analysis. To overcome this weakness, we utilized two statistical methods, matching and logistic regression, to account for differences in severity of illness in patients with and those without EIA subsequent to IAI. Using these methods, we found that patients with a longer duration of antimicrobial therapy for IAI and those who develop EIA subsequent to IAI share many characteristics that mark them as being at high risk for infection, including a high prevalence of hospital acquisition of infection, an elevated APACHE II score, and multiple co-morbidities. Although statistical methods can be used to a certain degree to account for these differences, only a prospective study of different durations of antibiotic therapy for these patients will be able to determine whether shorter or longer courses of such therapy will minimize morbidity and

provide the best outcomes of treatment. However, it is imperative that such a study include patients with complicated infections and a high severity of illness, or it will be difficult or impossible to extrapolate the results and conclusions of the study to more difficult cases of infection. Currently the SIS is attempting to answer this need by conducting a randomized study (ClinicalTrials.gov number NCT00657566), in which the representation of appendiceal disease is limited to 10%.

In conclusion, our research demonstrates that a relationship exists between longer courses of antibiotic therapy for IAI and an increased risk of subsequent infections distant from the abdomen. Furthermore, these subsequent infections appear to be associated with an increased risk of mortality. Results of a randomized trial, including an analysis of these events, are needed to more clearly guide surgeons about the most appropriate duration of antimicrobial therapy for complicated IAI.

Author Disclosure Statement

No competing financial interests exist.

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