Title

Longer-Duration Antimicrobial Therapy Does Not Prevent Treatment Failure in High-Risk Patients with Complicated Intra-Abdominal Infections

Journal

Surgical Infections, 18(6)

ISSN

1096-2964

Authors

Hassinger, Taryn E
Guidry, Christopher A
Rotstein, Ori D
et al.

Publication Date

2017-08-01

DOI

10.1089/sur.2017.084

Peer reviewed

SURGICAL INFECTIONS
Volume 18, Number 6, 2017

DOI: 10.1089/sur.2017.084

Longer-Duration Antimicrobial Therapy Does Not Prevent Treatment Failure in High-Risk Patients with Complicated Intra-Abdominal Infections

Taryn E. Hassinger,[1] Christopher A. Guidry,[1] Ori D. Rotstein,[2] Therese M. Duane,[3] Heather L. Evans,[4] Charles H. Cook,[5] Patrick J. O'Neill,[6] John E. Mazuski,[7] Reza Askari,[8] Lena M. Napolitano,[9] Nicholas Namias,[10] Preston R. Miller,[11] E. Patchen Dellinger,[4] Raul Coimbra,[12] Christine S. Cocanour,[13] Kaysie L. Banton,[14] Joseph Cuschieri,[4] Kimberley Popovsky,[1] and Robert G. Sawyer[1]

Abstract

Background: Recent studies have suggested the length of treatment of intra-abdominal infections (IAIs) can be shortened without detrimental effects on patient outcomes. However, data from high-risk patient populations are lacking. We hypothesized that patients at high risk for treatment failure will benefit from a longer course of antimicrobial therapy.

Methods: Patients enrolled in the Study to Optimize Peritoneal Infection Therapy (STOP-IT) trial were evaluated retrospectively to identify risk factors associated with treatment failure, which was defined as the composite outcome of recurrent IAI, surgical site infection, or death. Variables were considered risk factors if there was a positive statistical association with treatment failure. Patients were then stratified according to the presence and number of these risk factors. Univariable analyses were performed using the Kruskal-Wallis, χ^2, and Fisher exact tests. Logistic regression controlling for risk factors and original randomization group, either a fixed four-day antimicrobial regimen (experimental) or a longer course based on clinical response (control), also was performed.

Results: We identified corticosteroid use, Acute Physiology and Chronic Health Evaluation II score ≥5, hospital-acquired infection, or a colonic source of IAI as risk factors associated with treatment failure. Of the 517 patients enrolled, 263 (50.9%) had one or two risk factors and 16 (3.1%) had three or four risk factors. The rate of treatment failure rose as the number of risk factors increased. When controlling for randomization group, the presence and number of risk factors were independently associated with treatment failure, but the duration of antimicrobial therapy was not.

Conclusions: We were able to identify patients at high risk for treatment failure in the STOP-IT trial. Such patients did not benefit from a longer course of antibiotic administration. Further study is needed to determine the optimum duration of antimicrobial therapy in high-risk patients.

[1]Department of Surgery, The University of Virginia Health System, Charlottesville, Virginia.
[2]Department of Surgery, University of Toronto, Toronto, Ontario, Canada.
[3]Department of Surgery, University of North Texas John Peter Smith Hospital, Fort Worth, Texas.
[4]Department of Surgery, University of Washington, Seattle, Washington.
[5]Department of Surgery, Beth Israel Deaconess Medical Center, Boston, Massachusetts.
[6]Department of Surgery, Abrazo West Campus, Goodyear, Arizona.
[7]Department of Surgery, Washington University, St. Louis, Missouri.
[8]Department of Surgery, Brigham and Women's Hospital, Boston, Massachusetts.
[9]Department of Surgery, University of Michigan, Ann Arbor, Michigan.
[10]Department of Surgery, University of Miami Miller School of Medicine, Miami, Florida.
[11]Department of Surgery, Wake Forest School of Medicine, Winston-Salem, North Carolina.
[12]Department of Surgery, University of California, San Diego, San Diego, California.
[13]Department of Surgery, University of California Davis Medical Center, Sacramento, California.
[14]Department of Surgery, University of Minnesota Medical School, Minneapolis, Minnesota.
Presented at the 36th Annual Meeting of the Surgical Infection Society, Palm Beach, Florida, May 18–21, 2016.

Complicated intra-abdominal infections (IAIs) remain a common problem, with a wide range of severity and resulting morbidity. After initial intravenous fluid resuscitation and stabilization, source control and antimicrobial medications remain the mainstays of treatment.

Recently, the duration of antimicrobial therapy has come under scrutiny [1,2]. The 2010 guidelines from the Surgical Infection Society (SIS) and the Infectious Diseases Society of America (IDSA) recommended four to seven days of antimicrobial therapy for an established IAI [3], but the recently published (2017) guideline updates highlight the efficacy of a shorter duration of antimicrobial therapy for patients with adequate source control [4]. Despite these guidelines, there remains no consensus among clinicians about appropriate treatment duration. A major contributing factor to this continued lack of standardization is the belief that certain patients are at an inherently greater risk of treatment failure because of their characteristics and the severity of IAI [5].

To provide further clarification for treatment recommendations, the Study To Optimize Peritoneal Infection Therapy (STOP-IT) trial was conducted. The results revealed no significant difference in complications between a short course and a more traditional longer course of antimicrobial agent [6]. To establish the validity of these results across risk-stratified patient groups, we sought to identify risk factors for treatment failure and to determine if patients with these risk factors were likely to benefit from a longer duration of antimicrobial therapy.

Patients and Methods

The STOP-IT trial included 517 patients enrolled at 23 sites in the United States and Canada over a five-year period. This investigator-initiated, open-label trial randomized patients into an experimental group, receiving four full days of antimicrobial treatment (short course), and a control group, receiving antimicrobial treatment until two days after resolution of physiologic abnormalities related to the systemic inflammatory response syndrome (SIRS) with a maximum of 10 days of therapy (longer course) [6]. The original trial included patients age 16 or older who presented with a complicated IAI, defined as the presence of fever (temperature ≥38.0°C), leukocytosis (≥11,000 peripheral white blood cells/mm^3), or gastrointestinal dysfunction secondary to peritonitis precluding intake of more than half of the normal diet. Additionally, all patients required source control, defined as procedures to eliminate infectious foci, control factors that promote continued infection, and correction or control of anatomic derangements to re-establish normal physiological function. Both the local and the principal investigators were responsible for confirming the adequacy of source control. Treatment failure was defined as the composite outcome of recurrent IAI, surgical site infection, or death [6].

The data set from the STOP-IT trial was used for secondary analysis. Univariable statistical analyses with the Kruskal-Wallis, χ^2, and Fisher exact tests were performed to identify risk factors for treatment failure. Variables were considered relevant risk factors if there was a positive statistical association with treatment failure. Patients were then stratified according to the presence of these factors. Those patients without any of the identified risk factors were considered to be ''low risk,'' whereas patients with at least one factor were considered ''high risk.'' The number of risk factors in the high-risk group was recorded. Logistic regression controlling for the number of risk factors and the original randomization group was performed to determine the correlation between risk and treatment failure.

The results are reported as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Statistical significance was defined with the standard alpha value of <0.05. All statistical analyses were conducted using SAS software, version 9.3 (SAS Institute, Cary, NC).

Results

Patient demographics and infection characteristics grouped by the presence or absence of treatment failure are presented in Table 1. Four variables showed a significant difference between the groups, namely, steroid use, hospital-acquired infection, Acute Physiology and Chronic Health Evaluation (APACHE) II score $\geq$15, and a colonic source of infection. These variables therefore were considered risk factors. Of note, both a biliary source of infection and non-insulin-dependent diabetes mellitus (NIDDM) also showed a significant difference, with fewer patients who had these characteristics suffering treatment failure, and therefore, these conditions were not considered risk factors.

The overall rate of treatment failure was 22.1%. Two hundred thirty-eight patients (46.0%) had zero risk factors, 263 patients (50.9%) had one or two, and 16 patients (3.1%) had three or four. Table 2 presents the rates of treatment failure in the groups with the short and longer antimicrobial duration when patients were sorted by number of risk factors.

Logistic regression controlling for the number of risk factors and the original antimicrobial duration also was performed. Both the presence and the number of risk factors were associated independently with treatment failure, but treatment duration was not, as presented in Table 3 (C-statistic 0.60).

Discussion

This post hoc subgroup analysis of the STOP-IT trial data identified four risk factors associated with treatment failure. There was no significant difference in the rate of failure between randomization groups when grouped by risk factors, regardless of the number of factors present. These results support the generalizability of the initial trial conclusions, namely that a shorter course of antimicrobial therapy is safe and effective even in a higher-risk subset of patients. Despite the lack of a statistically significant difference in the rates of treatment failure between the groups, the raw percentage of treatment failures increased as the number of risk factors increased. This suggests that these higher-risk patients may be destined to fail initial therapy because of still-unidentified factors independent of the duration of antimicrobial treatment. Arguably, subjecting these patients to a prolonged course of antimicrobial therapy simply extends the time until discovery of treatment failure, leading to longer hospitalization and a higher risk of morbidity related to the medications or to secondary and multidrug-resistant infections [7,8].

Both biliary infections and NIDDM reached statistical significance, with a negative association with treatment failure. In the original trial, both biliary tree and gallbladder

Table 1. Patient Demographics and Infection Characteristics According to Failure or Success of Treatment

	No Treatment Failure (N = 403)	*Treatment Failure (N = 114)*	P *Value*	*Odds Ratio (95% CI)*
Characteristics				
Age y (range)	53.00 (40.00–63.00)	52.50 (39.00–67.00)	0.94	1.00 (0.99– 1.01)
Female (%)	180 (44.67)	49 (43.00)	0.75	0.93 (0.61– 1.42)
Body mass index (range)	27.00 (23.00–32.00)	28.50 (23.00–34.00)	0.36	1.01 (0.99– 1.03)
Cerebrovascular disease (%)	16 (3.97)	3 (2.63)	0.78	0.65 (0.18– 2.29)
Pulmonary disease (%)	41 (10.17)	10 (8.77)	0.66	0.85 (0.41– 1.75)
Coronary artery disease (%)	58 (14.39)	12 (10.53)	0.29	0.70 (0.36– 1.35)
Peripheral vascular disease (%)	22 (5.46)	4 (3.51)	0.40	0.63 (0.21– 1.87)
NIDDM (%)	38 (9.43)	4 (3.51)	0.04	0.35 (0.12– 1.00)
IDDM (%)	26 (6.45)	10 (8.77)	0.39	1.39 (0.65– 2.98)
Chronic kidney disease (%)	11 (2.73)	5 (4.39)	0.37	1.64 (0.56– 4.81)
Hemodialysis (%)	7 (1.74)	2 (1.75)	1.00	1.01 (0.21– 4.93)
Inflammatory bowel disease (%)	38 (9.43)	15 (13.16)	0.25	1.45 (0.77– 2.75)
Hepatic insufficiency (%)	15 (3.72)	2 (1.75)	0.39	0.46 (0.10– 2.05)
Malignancy (%)	45 (11.17)	14 (12.28)	0.74	1.11 (0.59– 2.11)
Steroid use (%)	19 (4.71)	12 (10.53)	0.02	2.38 (1.12– 5.06)
Transfusion (%)	32 (7.94)	11 (9.65)	0.56	1.24 (0.60– 2.54)
Infection data				
CAI (%)	252 (62.53)	69 (60.53)	0.70	0.92 (0.60– 1.41)
HAI (%)	105 (26.05)	22 (19.30)	0.14	0.68 (0.41– 1.14)
HospAI (%)	46 (11.41)	23 (20.18)	0.02	1.96 (1.13– 3.40)
APACHE II (range)	9 (5–13)	10 (6–15)	0.01	1.05 (1.01– 1.08)
APACHE II >15 (%)	78 (19.35)	33 (28.95)	0.03	1.70 (1.06 2.73)
Mean WBC maximum (mm^3/mL) (range)	15.60 (11.40–9.50)	15.85 (12.00–20.00)	0.41	1.02 (1.00– 1.04)
Mean temperature maximum (°C) (range)	37.60 (37.10–38.30)	37.75 (37.00–38.50)	0.38	1.15 (0.90– 1.46)
Gram positive (%)	159 (39.45)	47 (41.23)	0.73	1.08 (0.71– 1.64)
Gram negative (%)	148 (36.72)	44 (38.60)	0.72	1.08 (0.71– 1.66)
Anaerobic (%)	85 (21.09)	29 (25.44)	0.32	1.28 (0.79– 2.07)
Fungi (%)	43 (10.67)	15 (25.44)	0.46	1.26 (0.68– 2.38)
Site (%)				
Esophagus	2 (0.50)	1 (0.88)	0.53	1.78 (0.16–19.76)
Stomach	25 (6.20)	6 (5.26)	0.71	0.84 (0.34– 0.10)
Duodenum	16 (3.97)	7 (6.14)	0.32	1.58 (0.64– 3.94)
Liver	14 (3.47)	4 (3.51)	1.00	1.01 (0.33– 3.13)
Biliary tree	51 (12.66)	5 (4.39)	0.01	0.32 (0.12– 0.81)
Pancreas	14 (3.47)	2 (1.75)	0.54	0.50 (0.11– 2.22)
Small intestine	60 (14.89)	13 (11.40)	0.35	0.74 (0.39– 1.40)
Colon	128 (31.76)	49 (42.98)	0.03	1.62 (1.05– 2.48)
Appendix	56 (13.90)	17 (14.91)	0.78	1.09 (0.60– 1.95)
Abdominal wall	10 (2.48)	3 (2.63)	1.00	1.06 (0.29– 3.93)
Other	27 (6.70)	7 (6.14)	0.83	0.91 (0.39– 2.15)

Categorical variables are listed as N (%) and continuous variables as median (interquartile range).

APACHE = Acute Physiology and Chronic Health Evaluation; CAI = community-acquired infection; CI = confidence interval; HAI = healthcare-associated infection; HospAI = hospital-associated infection; IDDM = insulin-dependent diabetes mellitus; NIDDM = non-insulin-dependent diabetes mellitus; WBC = white blood cells.

infections were classified as biliary infections. Although patients with non-perforated, non-gangrenous cholecystitis were not included in the trial, the nature of the disease process allows less complicated and more definitive source control with removal of the entire infected organ via cholecystectomy [6,9]. The severity of NIDDM, including the home treatment regimen, was not recorded in the original trial, making its association with the absence of treatment failure challenging to determine.

When interpreting these results, it is important to recognize the small number of patients experiencing treatment failure and the resulting small number of patients with risk factors for failure. The STOP-IT trial required appropriate source control prior to enrollment. Thus, these findings should be

Table 2. Stratification of Patients by Number of Risk Factors in Longer-Course and Short-Course Antibiotic Treatment

Number of Risk Factors	*Longer Course (%)*	*Short Course (%)*	P *Value*
	126	112	
0	19 (15.15)	19 (17.00)	0.69
	129	134	
1 or 2	35 (27.10)	31 (23.10)	0.45
	5	11	
3 or 4	4 (80.00)	6 (54.50)	0.59

Table 3. Risk-Adjusted Association Between Treatment Group and Number of Risk Factors in Treatment Failure

	χ^2	P *Value*	*Odds Ratio (95% Confidence Interval)*
Treatment group			
Longer-course antibiotics	Reference		
Short-course antibiotics	0.29	0.60	0.89 (0.58– 1.37)
Number of risk factors			
0	Reference		
1 or 2	6.33	0.01	1.77 (1.14– 2.77)
3 or 4	16.04	<0.0001	9.00 (3.07–26.36)

applied only to similar patients, as source control may be more important to treatment success than the duration of antimicrobial therapy. This idea is supported by Bloos et al., who showed a statistically significant difference in the number of deaths by 28 days according to the time to source control while finding no difference in time to antimicrobial therapy or inadequate empiric therapy [10]. Similarly, Burnham et al. found no difference in outcomes related to time to appropriate antimicrobial therapy as long as it was started within 12 hours of a positive culture [11].

Practice guidelines for complicated IAI with source control have established that antimicrobial treatment duration should not exceed seven days, as longer therapy is not associated with better outcomes [3]. Despite this, significant variability in the duration of antimicrobial therapy continues, with data suggesting that the average length of therapy remains 10 to 14 days. The tendency to continue antimicrobial therapy is likely the result of the significant rate of additional infectious complications after treatment of complicated IAIs [7,12]. It is important to note that some of these complications may be related to inadequate source control, not to failure of antimicrobial therapy [13].

In addition to the STOP-IT trial, several other studies have investigated the safety and efficacy of a shorter course of antimicrobial therapy for complicated IAIs, with results suggesting failure rates similar to those of traditional therapy [14,15]. These smaller studies focused primarily on mild-to-moderate IAIs, excluding the typical patient population encountered in an academic center or critical care setting, where high-risk patients are more common.

Swenson et al. attempted to better define what makes a patient with a complicated IAI high risk, as defined by failure of antimicrobial therapy rather than failure of source control. Risk factors were identified as health care-associated infection, corticosteroid use, organ transplantation, liver disease, pulmonary disease, and a duodenal source of infection [5]. The lists are not identical, but there is overlap between these risk factors and those identified in the current analysis. Although intuitively, it seems that these high-risk patients should benefit from a longer course of antimicrobial therapy, this idea remains poorly defined in the literature and is not supported by our data.

This subgroup analysis is strengthened by the relatively large sample in the STOP-IT trial, as well as its well-matched control and experimental groups. Limitations include the small number of immunocompromised patients and the exclusion of patients deemed to have inadequate source control. Caution therefore should be applied in generalizing the results to these types of patients, as it is possible that these populations would indeed benefit from an extended course of antimicrobial therapy. Additionally, treatment failure in complicated IAI is more likely in patients with delayed (>24 hours) procedural intervention for source control as well as in the presence of multidrug-resistant pathogens causing the initial IAI, but these data were not collected in the original trial [10, 11].

The highest-risk group of patients (identified as having three or four risk factors) was small, with only 16 patients falling into this subset. With 23 high-volume centers enrolling patients in the STOP-IT trial, this small number of patients indicates that patients with three or four risk factors are not encountered routinely, suggesting that when discussing high-risk patients, those in the one or two risk-factor subset are much more common.

Conclusion

This subgroup analysis was able to identify risk factors for treatment failure among patients enrolled in the STOP-IT trial. Importantly, in patients with these risk factors, there remained no difference in the rates of treatment failure between randomization groups, indicating that even patients at high risk of treatment failure did not benefit from a longer duration of antimicrobial therapy. These findings support the use of a short course of antibiotics in most critically ill patients or in those deemed at low to moderate risk. Additional study will be needed to evaluate the optimum duration of antimicrobial therapy in high-risk patients.

Contributions of the Authors

Conception and design: TEH, CAG, RGS. Data acquisition: CAG. Analysis and interpretation: TEH, CAG, RGS. Manuscript drafting and editing for important intellectual content: All authors.

Acknowledgment

Funding for this study was provided by National Institutes of Health Grant R01 GM081510.

Author Disclosure Statement

No competing financial interests exist.

References

1. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 2013;39:165–228.
2. Blot S, De Waele JJ. Critical issues in the clinical management of complicated intra-abdominal infections. Drugs 2005;65:1611–1620.
3. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Surg Infect 2010;11:79–109.

4. Mazuski JE, Tessier JM, May AK, et al. The Surgical Infection Society Revised Guidelines on the Management of Intra-Abdominal Infection. Surg Infect 2017;18:1–76.
5. Swenson BR, Metzger R, Hedrick TL, et al. Choosing antibiotics for intra-abdominal infections: What do we mean by ''high risk''? Surg Infect 2009;10:29–39.
6. Sawyer RG, Claridge JA, Nathens AB, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med 2015;372:1996–2005.
7. Inui T, Haridas M, Claridge JA, Malangoni MA. Mortality for intra-abdominal infection is associated with intrinsic risk factors rather than the source of infection. Surgery 2009;146:654–661.
8. Marshall JC, Maier RV, Jimenez M, Dellinger EP. Source control in the management of severe sepsis and septic shock: An evidence-based review. Crit Care Med 2004; 32(11 Suppl):S513–526.
9. Brill A, Ghosh K, Gunnarsson C, et al. The effects of laparoscopic cholecystectomy, hysterectomy, and appendectomy on nosocomial infection risks. Surg Endosc 2008; 22:1112–1118.
10. Bloos F, Thomas-Ruddel D, Ruddel H, et al. Impact of compliance with infection management guidelines on outcome in patients with severe sepsis: A prospective observational multi-center study. Crit Care 2014;18:R42.
11. Burnham JP, Lane MA, Kollef MH. Impact of sepsis classification and multidrug-resistance status on outcome among patients treated with appropriate therapy. Crit Care Med 2015;43:1580–1586.
12. Riccio LM, Popovsky KA, Hranjec T, et al. 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. Surg Infect 2014;15:417–424.
13. Tellor B, Skrupky LP, Symons W, et al. Inadequate source control and inappropriate antibiotics are key determinants of mortality in patients with intra-abdominal sepsis and associated bacteremia. Surg Infect 2015;16:785–793.
14. Schein M, Assalia A, Bachus H. Minimal antibiotic therapy after emergency abdominal surgery: A prospective study. Br J Surg 1994;81:989–991.
15. Basoli A, Chirletti P, Cirino E, et al. A prospective, double-blind, multicenter, randomized trial comparing ertapenem 3 vs or ≥5 days in community-acquired intraabdominal infection. J Gastrointest Surg 2008;12:592–600.

Address correspondence to:
Dr. Taryn E. Hassinger
Department of Surgery
The University of Virginia Health System
PO Box 800300
Charlottesville, VA 22908-0679

*E-mail:*teh3rz@virginia.edu