Patients with Complicated Intra-Abdominal Infection Presenting with Sepsis Do Not Require Longer Duration of Antimicrobial Therapy

Rishi Rattan, MD, Casey J Allen, MD, Robert G Sawyer, MD, Reza Askari, MD, Kaysie L Banton, MD, Jeffrey A Claridge, MD, MS, FACS, Christine S Cocanour, MD, FACS, FCCM, Raul Coimbra, MD, PhD, FACS, Charles H Cook, MD, FACS, FCCM, Joseph Cuschieri, MD, FACS, E Patchen Dellinger, MD, Therese M Duane, MD, FACS, FCCM, Heather L Evans, MD, MS, FACS, Pamela A Lipsett, MD, MHPE, FACS, FCCM, John E Mazuski, MD, PhD, Preston R Miller, MD, Patrick J O'Neill, MD, PhD, FACS, Ori D Rotstein, MD, MSc, FRCSC, FACS, Nicholas Namias, MD, MBA, FACS, FCCM

BACKGROUND: A recent prospective, multicenter, randomized controlled trial found that 4 days of antibiotics after source control of complicated intra-abdominal infections resulted in similar outcomes when compared with longer duration. We hypothesized that the subset of patients presenting with sepsis have similar outcomes when treated with the shorter course of antibiotics.

STUDY DESIGN: Patients from the STOP-IT (Study to Optimize Peritoneal Infection Therapy) trial database meeting criteria for sepsis (ie, temperature $<36°C$ or $>38°C$ and a WBC count <4000 cells/mm^3 or $>12{,}000$ cells/mm^3) were analyzed. Patients had been randomized to receive antibiotics until 2 days after the resolution of fever, leukocytosis, and ileus, with a maximum of 10 calendar days of therapy ($n = 45$), or to receive a fixed short-course of antibiotics for 4 ± 1 calendar days ($n = 67$). Outcomes included incidence of and time to surgical site infection, recurrent intra-abdominal infection, *Clostridium difficile* infection, and extra-abdominal infections, as well as hospital days and mortality.

RESULTS: One hundred and twelve of the 588 patients in the STOP-IT database met criteria for sepsis and were adherent to the protocol. With regard to short- vs long-course therapy, surgical site infection (11.9% vs 8.9%; $p = 0.759$), recurrent intra-abdominal infection (11.9% vs 13.3%; $p = 1.00$), extra-abdominal infection (11.9% vs 8.9%; $p = 0.759$), hospital days (7.4 ± 5.5 days vs 9.0 ± 7.5 days; $p = 0.188$), days to recurrent intra-abdominal infection (12.5 ± 6.6 days vs 18.0 ± 8.1 days; $p = 0.185$), days to extra-abdominal infection (12.6 ± 5.8 days vs 17.3 ± 3.9 days; $p = 0.194$), and mortality (1.5% vs 0%; $p = 1.00$) were similar. There were no cases of *C difficile* infection. Days to surgical site infection (6.9 ± 3.5 days vs 21.3 ± 6.1 days; $p < 0.001$) were fewer in the 4-day therapy group.

CONCLUSIONS: There was no difference in outcomes between short and long-course antimicrobial therapy in patients with complicated intra-abdominal infection presenting with sepsis. Our findings suggest that the presence of systemic illness does not mandate a longer antimicrobial course if source control of complicated intra-abdominal infection is obtained. (J Am Coll Surg 2016;222:440–446. © 2016 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

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From the University of Miami Miller School of Medicine, Miami, FL (Rattan, Allen, Namias), University of Virginia Health System, Charlottesville (Sawyer), Virginia Commonwealth University, Richmond (Duane), VA, Brigham and Women's Hospital (Askari), Beth Israel Deaconess Medical Center (Cook), Boston, MA, University of Minnesota Medical Center, Minneapolis, MN (Banton), Case Western Reserve University School of Medicine, Cleveland, OH (Claridge), University of California Davis, Davis (Cocanour), University of California San Diego, San Diego (Coimbra), CA, University of Washington Harborview Medical Center (Cuschieri, Evans), University of Washington (Dellinger), Seattle, WA, Johns Hopkins University School of Medicine, Baltimore, MD (Lipsett), Washington University School of Medicine, St Louis, MO (Mazuski), Wake Forest-Baptist Health, Winston-Salem, NC (Miller), Abrazo West Campus, Goodyear, AZ (O'Neill), and University of Toronto St Michael's Hospital, Toronto, Ontario, Canada (Rotstein).

Correspondence address: Nicholas Namias, MD, MBA, FACS, FCCM, Ryder Trauma Center, T215 (D-40), 1800 NW 10th Ave, Miami, FL 33136. email: nnamias@miami.edu

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Abbreviations and Acronyms
CDI = *Clostridium difficile* infection
CIAI = complicated intra-abdominal infection
IQR = interquartile range
SSI = surgical site infection

Complicated intra-abdominal infections (CIAIs) are an important cause of morbidity and mortality worldwide. They include a wide range of disease processes. The most common source is the appendix, accounting for approximately one-third of CIAI, regardless of geographic location.[1-3] Despite this diversity in organ involvement, mortality seems to be more dependent on intrinsic factors of the individual than the originating organ.[3]

Nevertheless, principles of treatment remain relatively constant—resuscitation of those with sepsis, removal of the source of the inflammatory response, and systemic antimicrobial therapy. Despite this, clinically significant infectious complications arise in approximately 20% of CIAIs.[3] Although source control has been a major foundation, management of sepsis has more recently been unified by the evidence-based Surviving Sepsis Campaign Guidelines.[4] Conversely, although robust data support the use of antimicrobial therapy in CIAIs, the duration of such therapy is less well-studied. Joint guidelines from the Surgical Infection Society and the Infectious Diseases Society of America recommend 4 to 7 days of antimicrobial therapy.[5] Data have existed for several decades, however, suggesting a shorter duration of therapy leads to acceptable outcomes in the contaminated abdomen.[6] Reticence to shorten duration has been based on the notable recurrent infection rate. However, a recent prospective, observational cohort study found that there was no difference in infectious complications after appendectomy for complicated appendicitis when postoperative antibiotic therapy was reduced from 5 days to 3 days.[7] Similarly, a recent prospective, randomized, multicenter trial comparing 4 days of antimicrobial therapy with a longer course for CIAIs demonstrated similar outcomes.[8]

Approximately 10% to 15% of patients with CIAI present with severe sepsis or septic shock.[1,2] This subgroup has a significantly increased risk of mortality.[1] However, the effect of sepsis of less severe acuity on outcomes is less clear. Antimicrobial therapy is a necessary, although not sufficient, component of sepsis management. In addition to the underlying mortality risk of severity of presentation, the morbidity of recurrent infection in patients already compromised by severe sepsis or septic shock is a significant concern. Of equal import are the attendant risks of unnecessary antimicrobial therapy, most notably, morbidity and mortality from *Clostridium difficile* infection (CDI). In a high-risk group of patients with CIAI who present in severe sepsis or septic shock, it is unknown if shortening duration of antimicrobial therapy would change outcomes. In addition, it is also unknown whether outcomes for patients with CIAI presenting with sepsis are different. We hypothesized that there is no difference in outcomes between shorter and longer antimicrobial therapy in patients with CIAI presenting with sepsis.

METHODS

The STOP-IT (Study to Optimize Peritoneal Infection Therapy) trial was a prospective, randomized, multicenter trial conducted between August 2008 and August 2013 at 23 US and Canadian academic medical centers. It was investigator-initiated and open label. Patients were eligible to participate in the study if they were at least 16 years old and had a CIAI, which was defined as infection of any intra-abdominal tissue that met at least one of the following criteria: organisms cultured from purulent intra-abdominal material, abscess or other evidence of intra-abdominal infection; or 2 of the following without recognized cause: temperature $\geq$38°C, nausea, vomiting, abdominal pain, or jaundice, and at least 1 of the following: organisms cultured from intra-abdominal fluid or tissue or organisms cultured from blood with radiographic evidence of intra-abdominal infection.[8]

Patients must have been hospitalized and undergone an intervention to control infection. Enrolled patients must also have had either a WBC >11,000 cells/mm^3, oral temperature $\geq$38°C, or gastrointestinal dysfunction preventing normal dietary intake within 24 hours of initial intervention. Exclusion criteria included viral hepatitis, perforated gastroduodenal ulcer treated within 24 hours of symptoms, iatrogenic bowel injury treated within 12 hours of injury, nonperforated nongangrenous appendicitis or cholecystitis, gangrenous appendicitis without organisms on culture, nonperforated intestinal ischemia, infected necrotizing pancreatitis, primary spontaneous bacterial peritonitis, infection associated with indwelling peritoneal dialysis catheter, pregnancy, primary skin closure of an open surgical incision in the setting of diffuse peritonitis, and lack of adequate source control or high likelihood of death within 72 hours of admission, as determined by the local or principal investigators. Patients underwent central, block randomization in 1:1 fashion, with no more than 10% of patients per block having appendiceal disease. After adequate source control, the