DUKE ANTIMICROBIAL STEWARDSHIP OUTREACH NETWORK (DASON)

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The STOP-IT trial: a randomized controlled trial on antibiotic duration for intra-abdominal infections

Treatment of intra-abdominal infections typically requires both surgical management to achieve source control and antimicrobial therapy. The Surgical Infections Society (SIS) and Infectious Diseases Society of America (IDSA) recommends that antibiotics be continued for no longer than 4-7 days following source control in their clinical guidelines for the management of complicated intra-abdominal infections(3). However, this recommendation was based exclusively on expert opinion and it is widely ignored in clinical practice. In our experience, patients with complicated intra-abdominal infection commonly receive > 7 days of broad spectrum antimicrobial therapy following source control procedures, despite the preceding guidelines. Thus, duration of antimicrobial therapy following source control for complicated intra-abdominal infections represents an opportunity for antimicrobial stewardship. This month's newsletter will review the findings and implications of the recently-published Study to Optimize Peritoneal Infection Therapy (STOP-IT)(1).

STOP-IT Study Design

STOP-IT was a randomized, controlled trial comparing different durations of antimicrobial therapy for treatment of complicated intra-abdominal infections (1). The primary study outcome was a composite endpoint measuring occurrence of any one of the following: 1) surgical site infection, OR 2) recurrent intra-abdominal infection, OR 3) death within 30 days of the index source control procedure. The study investigators hypothesized that a shorter course of antibiotics would be as effective as a longer one. Study participants were randomized to receive either 1) 4 days of antimicrobial therapy following source control or 2) antimicrobial therapy until 2 days after the resolution of physiologic abnormalities related to systemic inflammatory response syndrome (SIRS), up to a maximum of 10 days, following source control. Treating physicians were allowed to choose any antimicrobial regimen consistent with published IDSA guidelines.

Patients who were 16 and older were eligible to participate in the study if they had a complicated intra-abdominal infection (defined as fever $\geq$ 38.0, leukocytosis $\geq$11,000, or GI dysfunction defined as anorexia limiting to half of normal dietary intake) AND if they had undergone an adequate source control procedure. Study participants were then randomized 1:1 to the experimental or control group, with one exception: enrollment of patients with appendicitis to each treatment arm was allocated separately to ensure sufficient numbers of patients with other types of intra-abdominal infections.

STOP-IT Results

A total of 518 patients were randomized into the control and experimental groups. The two groups were well-balanced in respect to age, sex, ethnicity, characteristics of infection, site of origin, or type of source control procedure between groups. The overall study population had a slight male predominance (55.8%) and the majority of participants were Caucasian. The most common site of origin for intra-abdominal infection was the colon or rectum. Approximately one-third of patients had percutaneous drainage as their source control procedure; resection and anastomosis or closure was used in approximately 25% of patients and simple surgical drainage was utilized in 20%.

Antibiotics were given for 4 days (interquartile range (IQR) 4-5 days) in the experimental arm and 8 days (IQR 5-10 days) in the control arm. Adherence to the study protocol was problematic: only 211 of 258 (81.8%) patients in the experimental arm and 189 of 260 (72.7%) of patients in the control arm adhered to the specified durations of therapy described above. The three most common cause of protocol deviation were: 1) receipt of therapy for too few days, 2) receipt of therapy beyond resolution of SIRS, and 3) receipt of therapy for more than 10 days. All 47 patients within the group randomized to a short course of antimicrobial therapy who had protocol deviations received an antibiotic course longer than 5 days.

No difference was detected between the control group and the experimental group in the composite primary outcome (22.3% versus 21.8%, absolute difference -0.5% (95% confidence interval -7 to 9), p = 0.92). The primary outcome was largely driven by high rates of recurrent intra-abdominal infection in both groups (13.8% in control group and 15.6% in experimental group, p=0.67). A subgroup analysis by type of source control showed no difference between percutaneous drainage and surgical drainage with regard to the composite outcome. There was also no difference in the primary outcome when analyzed by appendiceal source vs. non appendiceal source.

DASON interpretation of STOP-IT results

This is an important study in antimicrobial stewardship. In fact, we'd like to see many more studies similar to this one in the future. Antibiotic duration is an area that desperately needs methodically sound studies to evaluate current practices versus shorter durations. Long durations put patients at risk of the unintended consequences of antibiotic exposures. The STOP-IT trial demonstrates that short-course antimicrobial therapy is at least as effective as

longer courses for complicated intra-abdominal infection. It also supports the existing duration of therapy recommendation in the STS- IDSA guidelines (which are for 4-7 days).

Despite the above findings we think it is difficult to extrapolate the results of this study to everyday practice for several important reasons. First, intra-abdominal infections are heterogeneous, encompassing a broad array of diagnoses from appendicitis to ischemic bowel. Practicing clinicians widely and appropriately base their duration of therapy on the complexity and severity of illness in individual patients. This likely was the reason for the poor compliance with the study protocol that occurred in the study discussed above. These problems also illustrate the challenge of enforcing strict durations of therapy when clinicians believe they have a valid clinical reason to shorten or lengthen the duration of therapy in an individual patient. Simply put, intra-abdominal infections are too variable to treat all of them with the same duration of antibiotic therapy. More work needs to be done to delineate patient groups prone to relapse or experience recurrent infection. Then, perhaps, a more targeted short duration trial toward lower risk patients could make the concept of short durations more palatable to the conservative clinician.

Second, source control was not well-defined in this study. The supplementary material defined source control as "a procedure that eliminated the need of further intervention as deemed by the practitioner." Therefore, source control was a subjectively defined variable rather than an objectively defined variable. We see variability and subjectivity in the type of and timing of source control clinical practice as well. Whether "good" source control was achieved in intra-abdominal infection is by currently based on clinical judgment in most instances and this situation is unlikely to change in the future. Thus we understand and accept the fact that most surgeons base their decisions about duration of antimicrobial therapy in an individual patient on whether they believe there is still undrained abscess contents or retained infected material.

Third, the rates of adverse outcomes in both groups of patients in this study were higher than what we observe within the DICON network. Only one study exists in the literature regarding recurrent intra-abdominal infection after antibiotic discontinuation. This study, published 33 years ago, estimated the incidence of developing repeat intra-abdominal infection after source control and completion of antibiotic therapy. In patients with leukocytosis (WBC >10,000) at the end of antibiotic therapy, the incidence of recurrent intra-abdominal infection was 33% (7 of 21 patients). The authors also looked at patients with a fever of 38.0 C or higher at the time of antibiotic discontinuation, and incidence of recurrent intra-abdominal infection was >70% (11 of 14 patients)(2). This study needs to be repeated or revised to include additional modern metrics and methods to determine if these simple variables can delineate risk factors for treatment failure or success.

Finally, the investigators in the study we discussed above did not measure rates of drug resistance patients with recurrent or relapsed infections. These data could be useful and highly relevant to determine if, as we would expect, the shorter courses of antimicrobial therapy

reduce the risk of subsequent development of emergence of antimicrobial-resistant pathogens in individual patients.

DASON recommendations:

We believe that 4-7 days of antimicrobial therapy, as currently recommended in IDSA guidelines, is appropriate for treatment of most patients with complicated intra-abdominal infections. We cannot definitely state that 4 days is the appropriate duration for all patients as variations in the adequacy of source control, underlying cause of intra-abdominal infection and patient-specific factors make a "one-size-fits-all approach" unrealistic and impractical. However, we continue to believe that adequate source control with either percutaneous or surgical drainage, or both is fundamentally important. And after this is accomplished, it is reasonable to discontinue antibiotics after 4 days of therapy in most patients.

References:

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