Antimicrobial Stewardship News

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Review of the 2017 Surgical Infection Society Guidelines on the Management of Intra-Abdominal Infection[1]

Introduction

Appropriate management of intra-abdominal infections (IAI) involves prompt source control and appropriate antibiotic therapy. The Infectious Diseases Society of America (IDSA) and Surgical Infections Society (SIS) previously published guidelines for treatment of complicated IAI in 2010.[2] Since that time, newer approaches to source control have been developed and bacteria implicated in IAIs have become more resistant. The SIS recently updated their guidelines for management of IAI. This guideline update was not endorsed by IDSA, which is expected to release a separate guideline update later this year. The goal of this newsletter is to highlight changes in 2017 SIS guidelines that may impact stewardship programs at DASON hospitals.

IAI Classifications

At its most generic, IAI is defined as an infectious process within the abdominal cavity that requires mechanical (surgical) intervention. IAI is classified as *complicated* or *uncomplicated.* Uncomplicated IAI includes acute appendicitis, acute cholecystitis, and uncomplicated diverticulitis. Complicated IAI is the primary focus of published guidelines, and treatment is based on location at time of onset (e.g., community vs. healthcare-associated) and risk for treatment failure and death. The 2017 SIS guideline provides revised parameters for risk assessment and updated criteria for healthcare-association (**Tables 1 & 2**).

Table 1. Risk Classification for Patients with IAI

High Risk for Treatment Failure and Death

• Sepsis or septic shock
• APACHE II ≥ 10
• Diffuse peritonitis
• Delayed/inadequate source control
• ≥ 2 physiologic/phenotypic risk factors:
  ○ Advanced age (≥ 70 years)
  ○ Malignancy
  ○ Significant cardiovascular compromise, hepatic or renal disease

Table 2. Definition for Healthcare-Associated IAI

Healthcare-Associated IAI
• Infection developing ≥ 48h after initial source control • Previously colonized/infected with MDRO • Hospitalized for ≥ 48 hours within prior 90 days • Skilled nursing or LTCF within prior 30 days • Home infusion therapy, wound care, or dialysis within prior 30 days • Broad-spectrum antimicrobials for ≥ 5 days within prior 90 days

It is important to note that defining risk for multidrug-resistant organisms (MDRO) simply as contact with the healthcare system (**Table 2**) has been questioned in recent IDSA guidelines for pneumonia.[3-5] This open issue resulted in **suggestion** rather than **recommendation** for use of these HCAP-derived risk factors in patients with IAI**.**

Treatment

Community-Acquired IAI, Low Risk

The list of preferred agents for low risk (previously "mild to moderate") community-acquired IAI is shown in **Table 3**. Ceftriaxone or cefotaxime (each in combination with metronidazole) continue to have excellent activity against *E. coli* and are recommended in this patient population.[6] Ertapenem is also an option for treatment, but should be reserved for patients with known or

presumed ESBLs due to risk for further development of antibiotic resistance, as well as cost.

Table 3. Treatment for Low-Risk, CA-IAI

Guideline-Preferred	Guideline-Alternative
Cefotaxime + metronidazole Ceftriaxone + metronidazole Ertapenem (for ESBL)	Cefuroxime + metronidazole β-lactam allergy: Moxifloxacin Ciprofloxacin + metronidazole Levofloxacin + metronidazole

There are several notable changes in the recommended agents for empiric treatment in community-acquired IAI. First, cefoxitin is no longer recommended due to increasing resistance in anaerobic bacteria.[7] Second, tigecycline is no longer recommended based on meta-analyses demonstrating increased mortality across several therapeutic indications.[8, 9] Third, the new guidelines recommend reserving fluoroquinolones for patients with documented severe β-lactam allergies based on concern for collateral damage (i.e., *C. difficile* infection) as well as increasing *E. coli* resistance. Finally, and most notably, cefazolin (in combination with metronidazole) is no longer recommended in the SIS guidelines. This change warrants further discussion for antibiotic stewards. The recommendation is **not** based on increasing resistance or evidence of poor clinical outcomes, but rather a lack of direct, comparative, prospective data supporting its efficacy. We continue to believe that cefazolin (in combination with metronidazole) remains an attractive option at most DASON hospitals based on local microbiological data and a large body of clinical experience with this regimen for IAI.

Community-Acquired IAI, High Risk

Patients defined as having high risk, community-acquired IAI should be empirically treated for *P. aeruginosa.* In addition, therapy targeting *Enterococcus* should be considered in select cases (**Table 4**). Risk factors for infection caused by *Enterococcus spp.* include post-operative infection, recent broad-spectrum antibiotics, severe sepsis or septic shock, or known colonization with vancomycin-resistant Enterococci (VRE). Antifungal therapy (such as an echinocandin or fluconazole) may be considered in critically ill patients with an upper GI source.

Two major changes in the recommendations for high risk CA-IAI include 1) the addition of new antibiotics for MDROs and 2) downgrading ceftazidime + metronidazole from a preferred to an alternative regimen. The latter change stems from a lack of randomized controlled trials providing contemporary efficacy data. Of note, ceftazidime susceptibilities to *E. coli* remain > 90% in most hospitals.[5]

Table 4. Treatment for High-Risk, CA-IAI

Guideline-Preferred	Guideline-Alternative
Piperacillin/tazobactam Cefepime + metronidazole Doripenem Imipenem Meropenem	Ceftazidime + metronidazole β-lactam allergy: FQs (see Table 3), or Aztreonam + metronidazole + vancomycin
When Enterococcal Coverage Desired	
If not being treated with piperacillin/tazobactam or imipenem/cilastatin, add: vancomycin or ampicillin	

Healthcare-Associated IAI

Recommendations for HA-IAI are similar to those for high risk CA-IAI (See **Table 4**), with a few additions. Empiric coverage for *Enterococcus spp.* should be considered more seriously, particularly if the patient has a post-operative infection, recent exposure to broad-spectrum antibiotics, signs of severe sepsis or septic shock, or is known to be colonized with VRE. Ampicillin- and vancomycin-resistant Enterococci are of greater concern in HA-IAI patients, therefore options for coverage include vancomycin, or linezolid or daptomycin for VRE. In addition, agents targeting *Staphylococcus aureus* and fungal pathogens may be warranted.

Durations of Therapy

The SIS guidelines promote shorter durations of antibiotic therapy based on recent studies for certain infections (**Table 5**). In patients with adequate source control, older studies suggested no difference in outcome with 5 days of antibiotic therapy compared to longer durations. More recent studies found that 3 days

of antibiotic therapy for mild to moderate IAI was as effective as five or more days.[10] The STOP-IT trial (reviewed in detail in the Oct 2015 DASON Newsletter) demonstrated that 4 days of treatment was as effective as longer, symptom-based treatment.[11] Therefore, in patients with adequate source control, the new guidelines have shortened the duration recommendation to 4 days.

Table 5. Durations of Therapy

Condition	Duration
Adequate source control	Max 96 hours (4 days)
Established IAI, without definite source control	5 to 7 days
Bacteremia secondary to IAI with adequate source control	7 days
Low risk, uncomplicated acute colonic diverticulitis	Defer antibiotics
Gastroduodenal perforations operated on within 24 hours	Max 24 hours
Traumatic bowel perforations operated on within 12 hours	
Acute or gangrenous appendicitis/cholecystitis in absence of perforations	
Ischemic, non-perforated bowel	
Severe, necrotizing pancreatitis	Do not use antibiotics

The guidelines also newly incorporate a 7-day maximum duration of therapy for most patients with transient bloodstream infections and source control. This was based on a systematic review and meta-analysis which found similar outcomes between ≤ 7 days of therapy versus longer courses. Patients at high risk for treatment failure, such as those receiving immunosuppressive medications or patients with ongoing sepsis or septic shock may require a longer duration of treatment.

Transition to PO

As noted in prior guidelines, oral antibiotics should be used to complete the defined short course of treatment rather than to extend therapy beyond the guideline recommended duration. Oral treatment options are shown in **Table 6.**

Table 6. Oral Treatment Options for IAI

Guideline-Preferred	Guideline-Alternative
Ciprofloxacin + metronidazole	Amoxicillin/clavulanate Moxifloxacin Levofloxacin + metronidazole TMP/SMX + metronidazole $1^{st}/2^{nd}/3^{rd}$ Generation Cephalosporin + metronidazole

The question of whether transitioning to oral antibiotics is equivalent to completion of therapy with IV has rarely been evaluated in studies. Only the combination of ciprofloxacin and metronidazole has been evaluated in this capacity and has demonstrated comparable outcomes.[12] Therefore, ciprofloxacin and metronidazole is considered preferred therapy per the guidelines. Evidence for alternative options is based on randomized controlled trials that have allowed for de-escalation to oral antibiotics within the protocol, without demonstration of adverse effects.

Choice of oral step-down agents can be difficult due to increasing rates of resistance in Gram-negative bacteria. Amoxicillin/clavulanate, in particular, should be used with caution due to concern for resistant *E. coli.* Thus, patient-specific culture and susceptibility data should guide choice for Gram-negative coverage. In general, anaerobes should also be covered even if not present in cultures because of the difficulty in isolating these pathogens in the lab. At DASON, we believe the listed alternative agents are reasonable options taking into account local resistance patterns and patient-specific data. In general, we recommend avoidance of fluoroquinolones and avoidance of class switching whenever possible.

Take Home Points

1. The guideline definition for HA-IAI includes use of healthcare exposure criteria to identify patients at risk for more resistant pathogens. However, the ability of such criteria to appropriately distinguish patients at risk for drug resistant organisms is questionable. These criteria are only **suggested** for use, rather than **recommended**.
2. The cephamycins (cefoxitin and cefotetan) should not be used for IAI due to increasing anaerobic resistance.
3. Preferred vs. alternative antibiotic choice recommendations support reserving use of fluoroquinolones only for patients with β-lactam allergies.
4. Use of cefazolin and metronidazole at individual hospitals should be based on local efficacy and resistance data. Although this combination is "not recommended" per SIS guidelines based on a lack of clinical trial data, we continue to consider it a reasonable alternative for community-acquired, low risk IAI.
5. Maximum duration of therapy for patients with adequate source control has been decreased to 4 days in non-bacteremic patients, and 7 days in IAI with secondary bacteremia.

References

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