Antibiotic Regimen in Treating Complicated Intra-abdominal Infections

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Introduction

Complicated intra-abdominal infections (cIAI) are a common pathology encountered by trauma, acute care, and critical care surgeons. Perforated viscus, hepatic injury, and pancreatic injury or necrosis all leave patients vulnerable to cIAI. While the causes of cIAI are diverse, their management strategies can be quite similar. It is crucial that antimicrobial therapy be started promptly, and the therapy selected be appropriate to cover organisms typical to these infections. Although beyond the scope of this review, source control—draining abscesses, control of gastrointestinal tract violation, and removal of necrotic tissue—is of utmost importance for successful management of cIAI.

Patients may present with sepsis or septic shock, and mortality risk is significant, with a rate as high as 10.5% in one multinational study [1]. Bacterial resistance can impair the ability of the trauma surgeon to effectively and efficiently treat cIAI, particularly in hospital-associated infections. Factors associated with increased risk of treatment failure or death from cIAI include advanced age greater than 70, malignancy, cardiovascular compromise, liver disease or cirrhosis, renal disease, hypoalbuminemia, diffuse peritonitis, delayed or inadequate source control, delayed or inadequate antimicrobial choice, or presence of resistant pathogens [2]. High-risk patients need broad coverage, even in CA-IAI.

For the purpose of this review, cIAI refers to infections that extend beyond the organ of origin causing localized or diffuse peritonitis [3]. Complicated IAI may further be classified as community-acquired (CA-IAI) or hospital-associated (HA-IAI). These distinctions become important in choosing appropriate

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antimicrobial therapy; however, duration of therapy should not typically be impacted by this difference if adequate source control has been obtained. HA-IAI criteria include those that develop 48 hours or more after source control, admissions greater than 48 hours duration in the last 90 days, residence in a nursing facility during previous 30 days, home therapy or dialysis in the last 30 days, or broad-spectrum antibiotics for 5 days or more in the previous 90 days [2].

In a global sampling of nearly 1900 patients, the majority presented with community-acquired infections, with only about 13% deemed healthcare-associated. Source control was achieved in 91.4% of these patients with either surgery (open or laparoscopic) or percutaneous drainage. The most common cause of cIAI was appendicitis, followed by postoperative infection, cholecystitis, gastroduodenal perforation, colonic, and small bowel perforations [1].

Common organisms found in intra-abdominal infections include Gram-negative bacilli, anaerobes, and Gram-positive cocci. Proximal small bowel contains enterococci and *Escherichia coli*. Distal small bowel contains increasing Enterobacteriaceae species and anaerobes, predominantly Bacteroides. The colon contains high bacterial counts with anaerobes predominating [4]. The most common aerobic organisms isolated from cultures are *Escherichia coli*, *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Streptococcus*, *Pseudomonas*, *Enterobacter*, and *E. faecium* [1]. Resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum beta-lactamase (ESBL) producing organisms, vancomycin-resistant enterococcus (VRE), and *K. pneumoniae* carbapenemase (KPC) organisms present challenges to antibiotic selection.

Several societies have confronted the topic of cIAI antibiotic therapy including the World Society of Emergency Surgery (WSES), Infectious Disease Society of America (IDSA), and the Surgical Infection Society (SIS), with the most updated recommendations from 2017 from both WSES and SIS [2, 3]. Commonly used antibiotic regimens include beta-lactams such as penicillin-like agents, cephalosporins, carbapenems, and fluoroquinolones as single agent or in combination with metronidazole. Less commonly used agents such as aztreonam, tigecycline, vancomycin, and aminoglycosides may be useful in situations of severe allergy or resistance.

Search Strategy

Our search strategy was to use the terms ((“2000”[Publication Date]: “2020”[Publication Date]) AND (“controlled clinical trial”[Publication Type] OR “meta-analysis”[Publication Type] OR “randomized controlled trial”[Publication Type])) AND ((complicated[All Fields] AND (“infections”[MeSH Terms] OR “infections”[All Fields] OR “infection”[All Fields])) AND intra-abdominal[All Fields]) AND (“anti-bacterial agents”[Pharmacological Action] OR “anti-bacterial agents”[MeSH Terms] OR (“anti-bacterial”[All Fields] AND “agents”[All Fields]) OR “anti-bacterial agents”[All Fields] OR “antibiotics”[All Fields]) on PUBMED. Supplementary search included retrieving guidelines by World Society

Table 10.1 PICO Questions regarding antibiotic regimen in patients with complicated intra-abdominal infections

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with complicated intra-abdominal infections	Antibiotics	Other regimens	Efficacy, mortality, adverse events

Table 10.2 PICO Questions regarding duration of antibiotic therapy in complicated intra-abdominal infection

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with complicated intra-abdominal infections	Short-course antibiotics	Long-course antibiotics	Antibiotic-free days, Recurrent infection, need for additional source control, mortality, emergence of resistant organisms

for Emergency Surgery and Surgical Infection Society from which additional resources were identified.

Clinical questions to be answered including how to determine the most effective antibiotic regimens to treat complicated intra-abdominal infections and the duration of therapy with the goal to avoid recurrent infection, mortality, and with minimal adverse events (Tables 10.1 and 10.2).

Results

Antibiotic Choice

Inappropriate or delayed initial antibiotic therapy has been associated with worsened patient outcomes, including increased length of stay, hospital costs, and mortality [5]. Many randomized controlled trials (RCTs) have compared antibiotic regimens head to head to assess efficacy. When choosing an empiric antibiotic regimen for cIAI, one needs to consider the likely suspected organism, side effects particularly in the setting of pre-existing organ dysfunction, local resistance patterns, and the formulary of the institution. WSES and SIS have performed extensive analyses of antibiotic regimens to treat cIAI utilizing GRADE technique [2, 3]. The reader is referred to these resources for an extensive review of antibiotic regimens.

Favorable Clinical and Microbiological Response

In RCTs comparing antibiotic regimens, favorable clinical response is typically defined as resolution of infectious findings, no need for further surgery or additional antibiotics, or lack of development of secondary, recurrent, or superinfections. Microbiological response is defined as eradication of organisms on subsequent cultures. Table 10.3 [6–24] highlights a sampling of such trials. Unless discussed below, in these trials and meta-analyses, there were either equivalence or no significant differences in clinical or microbiological efficacy.

Table 10.3 Randomized controlled trials and meta-analyses of antibiotic regimens for complicated intra-abdominal infections

Intervention antibiotic class	Study	Patients	Intervention	Comparator	Efficacy (Clinical and microbiological)	Mortality	Adverse events (all-cause)	Quality of evidence
Penicillin-like agents	Erasmo et al. (2004) [6]	293	Piperacillin/ Tazobactam ($n = 149$)	Imipenem/ Cilastatin ($n = 144$)	No difference. Clinical: 83.2 vs. 87.5% Micro: 85.1 vs. 91.6%	Not well enumerated	No difference. All: 26.8 vs. 36.1%, Drug-related: 8.1 vs. 8.3%	High
	Catena et al. (2013) [7]	142	Ampicillin/ sulbactam ($n = 71$)	Ertapenem ($n = 71$)	**Favors Ertapenem. Clinical: 86 vs 97%**	Not well enumerated	**Higher infections in ampicillin/sulbatam group.**	Moderate
Cephalosporins	Barie et al. (1997) [8]	323	Cefepime plus metronidazole ($n = 95$)	Imipenem/ Cilastatin ($n = 122$)	**Favors Cefepime in protocol-valid, not in ITT. Clinical: 82 vs. 76% Micro: 82 vs. 76%**	Favors Cefepime. 2 vs. 7%	No difference. 24 vs. 24%	High
	Garbino et al. (2007) [9]	122	Cefepime plus metronidazole ($n = 60$)	Imipenem/ Cilastatin ($n = 61$)	**Favors Cefepime. Clinical: 87 vs. 72% Micro: 71.6 vs. 62.3%**	No difference. One death per group attribute to comorbidity.	No difference. 25 vs. 23%	High
	Mazuski et al. (2016) [10]	1043	Ceftazidime-Avibactam plus metronidazole ($n = 520$)	Meropenem ($n = 523$)	Noninferior. Clinical: 82.5 vs. 84.9% Micro: similar	2.5 vs. 1.5%	No difference. 45.9 vs. 42.9%	High
	Solomkin et al. (2015) [11]	993	Ceftolozane-Tazobactam plus metronidazole ($n = 487$)	Meropenem ($n = 506$)	Noninferior. Clinical: 83 vs. 87.3% High success in ESBL with TOL-TAZ	2.3 vs. 1.6%	No difference. 44 vs. 42.7%	High
	Lucasti et al. (2014) [12]	121	Ceftolozane-Tazobactam plus metronidazole ($n = 82$)	Meropenem ($n = 39$)	**Favors meropenem Clinical: 83.6 vs. 96% Micro: 90.6 vs. 95.8%**	3 deaths in TOL-TAZ, not attributed to drug	No difference. 50 vs. 48%	Moderate

Carbapenems	Solomkin et al. (2003) [13]	633	Ertapenem ($n = 311$)	Piperacillin/ Tazobactam ($n = 304$)	Equivalent. Clinical: 79.3 vs. 76.2% Micro: 86.7 vs. 81.2%	6.4 vs. 3.6%	Not well enumerated	High
	Dela Pena et al. (2006) [14]	370	Ertapenem ($n = 178$)	Piperacillin/ Tazobactam ($n = 183$)	No difference. Clinical:82 vs 85% Micro: 94 vs. 98%	No difference. 2.8 vs. 4.7%	No difference. 54.4 vs. 55.3%	High
	Yellin et al. (2002) [15]	220	Ertapenem 1 g ($n = 59$), Ertapenem 1.5 g ($n = 51$)	Ceftriaxone plus metronidazole ($n = 55$x2)	No difference. Clinical: 1 g 89 vs 83%, 1.5 g 85 vs. 76% Micro: 1 g 88 vs. 85%, 1.5 g 88 vs. 75%	1 death in ertapenem group, not drug-related	No difference. 26% vs. 26%	Moderate
	Navarro et al. (2005) [16]	450	Ertapenem ($n = 225$)	Ceftriaxone plus metronidazole ($n = 225$)	No difference. Clinical: 93.2 vs. 93.1% Micro: 97.9 vs. 96.7%	4 vs 2 deaths, not drug-related	No difference. 49.3 vs. 45.8%	Moderate
Fluoroquinolones	Starakis et al. (2003) [17]	135	Ciprofloxacin plus metronidazole ($n = 69$)	Ceftriaxone plus metronidazole ($n = 66$)	Equivalent. Clinical: 94.2 vs. 89.4% Micro: 93 vs. 88.3%	1 vs 2 deaths	No difference. 14.1 vs. 5.6%	Moderate
	Malangoni et al. (2006) [18]	379	IV/PO Moxifloxacin ($n = 183$)	Piperacillin-tazobactam and amoxicillin-clavulanic acid ($n = 196$)	**Moxifloxacin favored in HA-IAI. No difference overall. Clinical: 80 vs. 78% Micro: 78 vs. 77%**	6 vs 7 deaths, none drug-related	No difference. 84 vs. 83%. High GI complaints.	High
	Solomkin et al. (2009) [19]	364	Moxifloxacin ($n = 180$)	Ceftriaxone plus metronidazole ($n = 181$)	Noninferior. Clinical: 87.2 vs. 91.2% Micro: 89.4 vs. 95.9%	No deaths	No difference. 31.7 vs. 24.3%	High
	Weiss et al. (2009) [20]	595	IV/PO Moxifloxacin ($n = 246$)	Ceftriaxone plus metronidazole and amoxicillin-clavulanate ($n = 265$)	Noninferior. Clinical: 80.9 vs. 82.3% Micro: 78.9 vs. 81.3%	No difference. 4.2 vs. 5.1%	**Higher QT prolongation in moxifloxacin.**	High
	Mavros et al. (2019) [21]	4125 (7 trials)	Moxifloxacin (4 studies), Ciprofloxacin (3 studies)	Beta-lactam based regimens	No difference. ITT RR 0.97 (95% CI 0.94–1.01)	No difference. RR 1.04 (95% CI 0.75–1.43)	No difference. RR 0.97 (95% CI 0.7–1.33)	High

(continued)

Table 10.3 (continued)

Intervention antibiotic class	Study	Patients	Intervention	Comparator	Efficacy (Clinical and microbiological)	Mortality	Adverse events (all-cause)	Quality of evidence
Tigecycline	Oliva et al. (2005) [22]	825	Tigecycline ($n = 413$)	Imipenem-cilastatin ($n = 412$)	Noninferior. Clinical: 73.5 vs. 78.2% Micro: 80.6 vs. 82.4%	17 vs. 12 deaths	**Higher rates of secondary infections, dyspnea, pneumonia, and hypoproteinemia in tigecycline group**	High
	Towfigh et al. (2010) [23]	448	Tigecycline ($n = 228$)	Ceftriaxone plus metronidazole ($n = 220$)	Noninferior. Clinical: 64 vs. 71% Micro: Monomicrobial 68 vs. 71.5%, Polymicrobial 67 vs. 68.3%	4 vs 3 deaths	**Tigecycline: higher nausea, oral thrush, leukocytosis, and DVT. Ceftriaxone: higher edema, atelectasis, taste change**	High
Aminoglycosides	Falagas et al. (2017) [24]	3177 (28 trials)	Clindamycin/ aminoglycoside	Beta-lactam monotherapy	**Beta-lactams more effective. OR 0.67 (95% CI 0.55–0.81)**	No difference. OR 1.25 (95% CI 0.74–2.11)	Higher nephrotoxicity in aminoglycoside regimens OR 3.7 (95% CI 2.09–6.57)	High

Aminoglycosides in combination with clindamycin were once the gold standard to treat intra-abdominal infections. In a 2005 Cochrane review of antibiotic regimens to treat secondary peritonitis, any other regimen was favored over then gold standard combination aminoglycoside and clindamycin for clinical success (OR 0.65, 95% CI 0.46–0.92). Microbiological success also was favored in other regimens versus aminoglycosides (OR 0.49, 95% CI 0.31–0.76) [4]. A meta-analysis of 28 RCTs of beta-lactams over aminoglycoside plus clindamycin regimens, beta-lactams were favored for clinical success (OR 0.67, 95% CI 0.55–0.81) [24].

In a single institution RCT, ampicillin/sulbactam was statistically significantly less effective than ertapenem, 86% versus 93% in mild-to-moderate localized peritonitis [7]. In another small RCT, ampicillin/sulbactam was an independent predictor of treatment failure compared to moxifloxacin [25]. Cefepime and metronidazole were compared to imipenem-cilastatin in two RCTs conducted 10 years apart. Clinical and microbiological efficacy of cefepime and metronidazole were 82–87% and 71.6–82%, respectively. In both studies, cefepime and metronidazole performed statistically better than imipenem–cilastatin, with clinical cure of 72–76% and bacteriological success in 62.3–76% [8, 9]. Moxifloxacin as a single agent has been compared to piperacillin–tazobactam and ceftriaxone plus metronidazole [18, 19]. In a subgroup analysis of HA-IAI, moxifloxacin (IV/PO) performed better than piperacillin–tazobactam converted to amoxicillin–clavulanate (82 vs. 55%) [18]. In a small study comparing ceftolozane–tazobactam plus metronidazole with meropenem in cIAI, meropenem had higher clinical success rates in the modified intention to treat group; though, this was attributed to higher rates of missing data in the ceftolozane group [12].

Mortality

As seen in Table 10.3, mortality was either not well enumerated in RCTs comparing antibiotic regimens in cIAI or rates were low and not statistically different. The 1997 Barie et al. study comparing cefepime plus metronidazole with imipenem/cilastatin demonstrated lower mortality rates in the cefepime group [8]. Tigecycline stands out for mortality risk and carries a black box warning after meta-analyses not specific to intra-abdominal infections were performed and revealed a small, but statistically significant increased risk of mortality in patients who received tigecycline [26, 27].

Adverse Events

Antibiotic regimens for cIAI have rarely been attributed to serious adverse outcomes. Commonly, antibiotics cause gastrointestinal distress including nausea, vomiting, diarrhea, *Clostridium difficile* infection, and transaminitis. Other adverse events include nephrotoxicity and QT prolongation. Ampicillin–sulbactam use was complicated by more frequent superficial and deep surgical site infections when compared to Ertapenem [7]. Compared to beta-lactam antibiotics, aminoglycosides were associated with higher odds of nephrotoxicity (OR 3.7, 95% CI 2.09–6.57), but not ototoxicity [24]. Moxifloxacin was associated with higher rates of QT prolongation when compared to ceftriaxone and metronidazole [20]. Tigecycline use is

associated with higher rates of secondary infections, dyspnea, pneumonia, nausea, oral thrush, and DVT against comparators [22, 23].

Duration of Antibiotic Therapy

Duration of antibiotic therapy for cIAI has been investigated recently given the lack of evidence-based recommendations. The data come from patient populations that have undergone adequate source control. Duration of therapy in patients who have not had source controlling procedures is less clear, and this requires individualized clinical decision making.

Two multi-institutional randomized control trials attempted to answer the question if shorter antibiotic duration could effectively treat cIAI following source control. The STOP IT trial compared short-course antibiotics with a median 4 days versus discontinuation of antibiotics 2 days after resolution of fever, leukocytosis, and ileus with a maximum duration of 10 days of antibiotics, with a median duration of 8 days. The primary outcome of the STOP IT trial was an aggregate measure of subsequent surgical site infections, recurrent intraabdominal infection, or death within 30 days. While the study population did not meet the number of participants needed to meet statistical power, there was no difference found between the two groups at interim analysis, and the study was halted early [28]. The DURAPOP trial compared a short course of 8 days to longer course of 15 days of antimicrobial therapy in a critically ill population with cIAI with the primary outcome being antibiotic-free days between day 8 and 28 [29]. Other important secondary outcomes in these studies included but were not limited to extra-abdominal infection, need for additional source control, and antibiotic resistance emergence. In both the STOP IT and DURAPOP trials, the authors concluded that there was no apparent benefit to longer-course antibiotic therapy in their study populations [28, 29].

Antibiotic-Free Days

In the DURAPOP study, antibiotic-free days were the primary outcome for which the study was powered to detect a difference. Shorter-course therapy is associated with more antibiotic-free days in both the STOP IT (Median 25 vs. 21 days) and DURAPOP (Median 15 vs. 12 days) studies [28, 29].

Recurrent Infection and Extra-Abdominal Infection

No differences were detected in recurrent infection in either the DURAPOP or the STOP IT trials, but neither of these studies were powered for this individual outcome. In the STOP IT trial, short-course infection recurrence was 15.6%, while long-course was 13.8%. Surgical site infections in these patients were 6.6% and 8.8%, in short and long course groups. Extra-abdominal infections occurred in 8.9% of the short-course and 5% of the longer-course group [28]. DURAPOP included recurrent infection only in those who underwent additional procedures—13 of 14 versus 14 of 19 patients, and superinfection in those still admitted at day 28–11 of

32 versus 14 of 44, long course versus short course, respectively. These were not statistically significant [29].

Need for Additional Source Control

The DURAPOP study did not show difference in reoperation or additional drainage procedures between the shorter- and longer-course antibiotic regimens, 40% and 28%, respectively [29]. STOP IT does not investigate this outcome.

Mortality

In both the STOP IT and the DURAPOP trials, there was no statistically significant difference in mortality rates among short or longer-duration antibiotic therapy. STOP IT 30-day mortality rates were quite low with 1.2% in shorter-course group and 0.8% in longer-course group, highlighting the less critically ill population included in this study [28]. DURAPOP 45-day mortality rates were 11% vs 15% for short- and long-course antibiotic therapies, respectively [29]. Neither study was powered to detect a difference in this as an individual outcome.

Emergence of Resistant Organisms

In the STOP IT trial, emergence of resistant organisms was an uncommon occurrence and did not differ between the groups. Surgical site infection or recurrent infection with a resistant organism occurred in 2.3% of short-course and 3.5% of long-course groups. Extra-abdominal infection with resistant organisms occurred in 0.8 and 2.3% in the short and long-course groups, respectively [28]. There was no difference in the rates of emergence of resistant organisms between the groups in the DURAPOP study, with 43% of the short-course group and 50% of the longer-course group. It should be noted that the high rate of resistance in DURAPOP was from both surveillance cultures and clinical isolates taken as part of the protocol [29].

Recommendations Based on Data

Antibiotic Choice

1. We recommend using piperacillin–tazobactam as a single agent option for empiric therapy in high-risk community-acquired cIAI and hospital-associated cIAI.
2. We suggest avoiding ampicillin–sulbactam as empiric therapy for cIAI.
3. We recommend ceftriaxone and metronidazole as an option for empiric treatment of community-acquired cIAI.
4. We recommend cefepime and metronidazole as an option for empiric therapy in high-risk community-acquired cIAI and hospital-associated cIAI.
5. We recommend ertapenem as an option for community-acquired cIAI.
6. We suggest that carbapenem antibiotics other than ertapenem be used with suspected or confirmed ESBL organisms in cIAI.

7. We suggest that fluoroquinolones be employed in setting of allergy, culture-proven sensitivity given concern for increasing Gram-negative resistance.
8. We suggest that tigecycline with its broad coverage, although higher associated adverse outcomes including mortality, should be considered only as a last resort therapy.
9. We suggest novel cephalosporin/beta-lactamases be used in the setting of MDRO cIAI keeping in mind antibiotic stewardship.
10. We recommend utilizing aminoglycoside-based regimens only in response to resistant pathogens sensitive to these agents and not as initial empiric therapy.
11. We suggest metronidazole as anti-anaerobic agent of choice given increasing resistance of *Bacteroides* species to clindamycin.

Duration of Therapy

1. We recommend 3–5 days of antibiotic therapy following adequate source control in non-critically ill patients.
2. We suggest 3–8 days of therapy in critically ill or septic patients following initial source control, individualizing care based on the needs of the patient's clinical picture.
3. We suggest that clinician judgment be employed in determining antibiotic duration in circumstances of persistent sepsis or inability to obtain adequate source control in cIAI.

Personal View of the Data

For complicated intra-abdominal infections, our first-line therapy is either piperacillin–tazobactam or cefepime and metronidazole for higher risk CA-IAI or HA-IAI. For low-risk CA-IAI, we typically select ceftriaxone or ciprofloxacin, plus metronidazole. If and when culture results are available, antibiotics are accordingly tailored. We typically choose an antibiotic duration of 5 days from source control in both non-critically and critically ill patients. This duration is most frequently altered in critically ill patients with persistent sepsis.

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