Section A -Research paper

Intra-abdominal Infections in the Emergency Intensive Care Unit: Review Article

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Abstract: Intra-abdominal infections (IAIs) are a common cause of sepsis, and frequently occur in intensive care unit (ICU) patients. IAIs include many diagnoses, including peritonitis, cholangitis, diverticulitis, pancreatitis, abdominal abscess, intestinal perforation, abdominal trauma, and pelvic inflammatory disease. IAIs are the second most common cause of infectious morbidity and mortality in the ICU after pneumonia. IAIs are also the second most common cause of sepsis in critically ill patients, and affect approximately 5% of ICU patients. Mortality with IAI in ICU patients ranges from 5 to 50%, with the wide variability related to the specific IAI present, associated patient comorbidities, severity of illness, and organ dysfunction and failures. It is important to have a comprehensive understanding of IAIs as potential causes of life-threatening infections in ICU patients to provide the best diagnostic and therapeutic care for optimal patient outcomes in the ICU.

Keywords: Intra-abdominal infections, ICU, sepsis.

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Introduction:

Intra-abdominal infections (IAIs) are frequent and dangerous entity in intensive care units. IAIs are defined as complicated (cIAIs) when infection extends beyond the affected hollow viscus into the peritoneal space, causing either localized or diffuse peritonitis. Independent of the cause, patients with such severe intra-abdominal infections are at high risk of severe complications, and it represent the second most common cause of sepsis in the intensive care unit (ICU) , therefore considered an important diagnostic and therapeutic challeng **(1).**

Patients may have multiple comorbidities, making them at high risk of treatment failure, and may be already in active sepsis on admission. Other types of infection classically present with treatment for a different medical problem such as cholecystitis as a very common disease in the ICU and the postoperative setting or complicated Clostridium difficile colitis after the extensive use of broad-spectrum

antibiotics, an increasing nosocomial problem in the last few years **(2).**

Despite the improvements in patient care, therapeutic failure still occurs and IAIs remain a leading cause of morbidity and mortality as well as of resource utilization in hospitalized and Surgical Intensive Care Unit (SICU) patients, peritonitis usually arises from either translocation or spillage of intestinal flora into the abdominal cavity. It can be confined to a small area within the abdomen and form an abscess, or it can create a generalized infection along the peritoneum. Perforated appendicitis, for example, tends to cause a confined abscess, whereas upper gastrointestinal (GI) perforation from the duodenum or stomach with a different range of pathogens is more likely to cause diffuse peritonitis, **(**

Table **1)** includes potential infections that can occur in or extend into the abdomen or primarily non inflammatory diseases that can lead to intra- abdominal infections **(3).**

Table 1: Potential etiology of intra- abdominal infections (3).

Gastrointestinal	Anastomotic leak
	Appendicitis
	Clostridium difficile colitis
	Diverticulitis
	Fistula formation
	Gastrointestinal malignancy
	Iatrogenic perforations
	Inflammatory bowel disease
	Meckel diverticulum
	Peptic ulcer disease
	Perforated neoplasm
	Perforating trauma
Biliary	Acalculous cholecystitis
	Acute calculous cholecystitis
	Ascending cholangitis
	Intrahepatic abscess
Retroperitoneal	Acute pancreatitis
	Kidney abscess
	Pyelonephritis
Pelvic	Endometritis
	Extrauterine pregnancy
	Oophoritis
	Ovarial abscess
	Parametritis
	Pelvic inflammatory disease
	Salpingitis
	Tubal abscess
Others	Blunt trauma
	Intrasplenic abscess
	Spontaneous bacterial peritonitis

Epidemiology:

Severe intra-abdominal infection (IAI) represents the second most common cause of sepsis in critically ill patients, affecting approximately 5% of patients presenting to surgical intensive care unit (ICU), An additional 1–2% acquire new abdominal infections while being treated in the ICU **(4)**

Mortality from intra-abdominal sepsis can be as high as 30 to 35 percent, with mortality in patients requiring a second operation reaching 50 percent and in those with an undrained abscess exceeding 90 per cent, often as result of multiple organ failure**(5).**

Classification of Peritonitis:

Peritonitis is a generalized inflammatory reaction involving part of or the entire peritoneal cavity. The extent of the peritoneal reaction and subsequent generalized reaction seems to be dependent on the intestinal origin of bacteria, It can be classified as primary, secondary, and tertiary or can be grouped into simple and complicated disease **(6).**

- **Primary Peritonitis:** an inflammation of the peritoneum without an obvious source of causative organisms or a localized infection within the abdomen.8 Primary peritonitis is usually community acquired and mono bacterial and generally caused by GI flora such as Gram-negative bacilli and enterococci. It rarely requires surgical intervention. Its most common presentation is spontaneous bacterial peritonitis **(7).**
- **Secondary Peritonitis.** The term secondary peritonitis **(Figure 1)** refers to peritonitis in the setting of perforation of a hollow viscus due to an inflammatory or malignant etiology. After this disruption of the anatomical barrier, gross spillage of gastrointestinal flora into the peritoneal cavity may occur **(8)**.

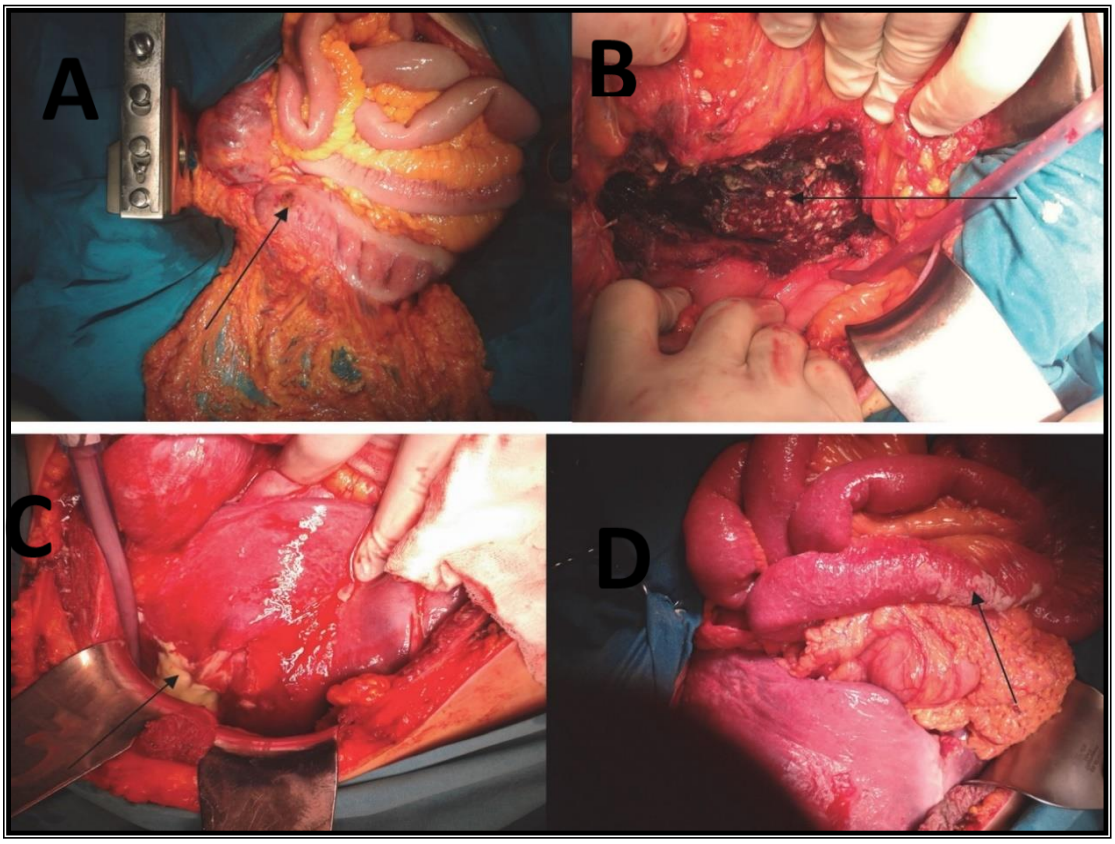

Figure 1: Secondary peritonitis. A. Fibrin on small bowel loops. B. Infected pancreatic necrosis C. Perforated liver abscess. D. Colon perforation (8).

- **Tertiary Peritonitis.** Tertiary peritonitis is described as persistent or recurrent peritonitis after failure of medical and interventional treatment **(9)**.

Pathogenesis and risk factors:

Figure 2 summarizes the general and independent risk factors for infections and sepsis. Additional to these "general" risk factors for sepsis, the surgical patient is permanently threatened by surgical complications caused by impaired healing of anastomoses or sutures for abdominal closure. Several trials have analyzed patient-related risk factors that lead to impaired healing, resulting in increased anastomotic leakage, surgical-site infections, and intra-abdominal sepsis. These factors, in part, overlap with the general risk factors, but are of major importance for abdominal surgery. Besides intraoperative complications and episodes of intraoperative hypotension, patient-related factors such as male gender, age, smoking, and diabetes mellitus correlate with increased anastomotic leakage rate. The same holds true for medication (corticosteroids, chemotherapeutics, immunosuppressants) and radiation **(10).**

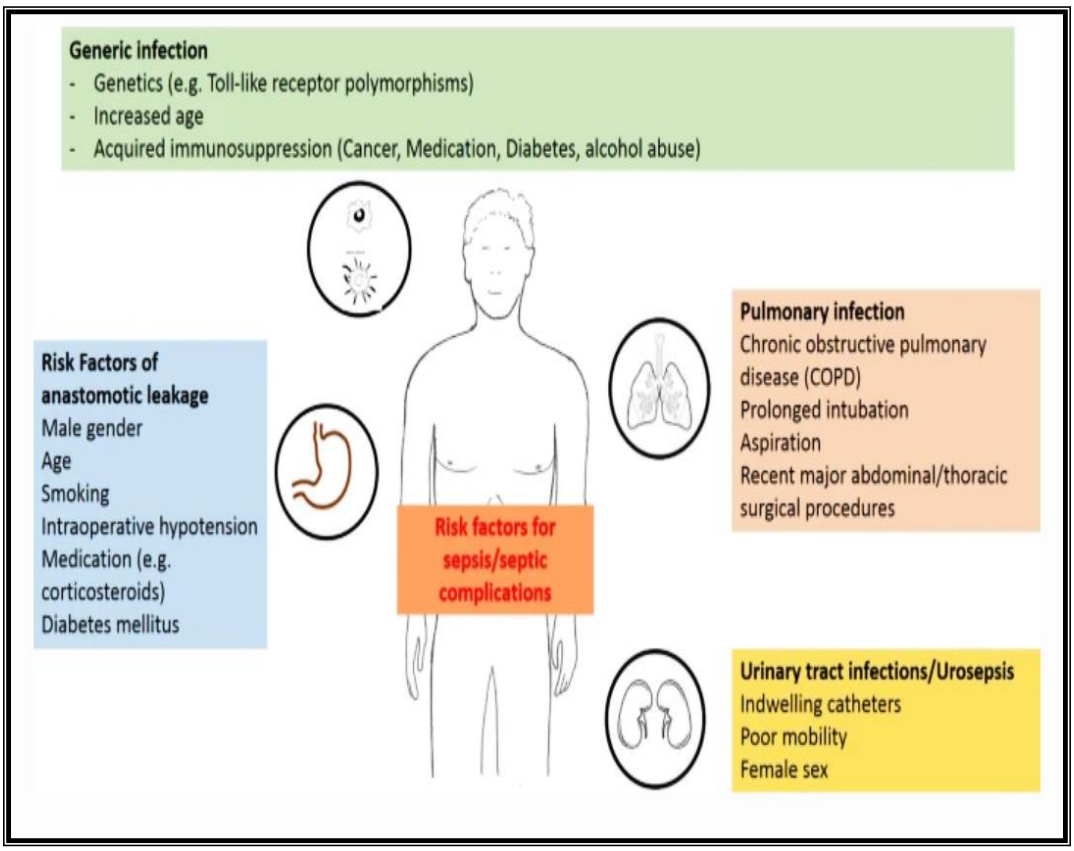

Figure 2: Simplified summary of risk factors for intra-abdominal sepsis development (10).

Microbiology:

A. Bacterial infection

- **Community-acquired infections:** such as appendicitis or cholecystitis often start as obstructive disease that eventually become superinfected by GI flora. Pathogens that eventually cause peritonitis vary depending on the area of perforation. **De Ruiter** et al analyzed peritoneal fluid of 221 patients with abdominal sepsis due to perforated hollow organs at time of the first operation. Gram-negative bacteria were most commonly found in colonic and appendicular perforations. Gram-positive bacteria were mostly observed in colorectal disease **(6)**.
- **Nosocomial infections:** differ for many reasons. Causative organisms are less susceptible to antibiotic regimens or may be multi-resistant. Colonization of high-risk patients with organisms such as Candida spp, Enterococcus faecalis, Staphylococcus epidermidis, and Pseudomonas aeruginosa has been significantly associated with a higher risk of infection and multi-organ failure **(11)**

B. Fungal infection:

Also represents a challenge in the ICU, as it is related to higher length of stay and mortality. Patients susceptible to fungal infections typically have health care association, may have a recent infection, including peritonitis, for which they have been treated with a number of different antibiotics **(12)**.

Diagnosis:

Early detection and adequate treatment is essential to minimize complications in the patient with acute abdomen. A physical examination combined with abdominal ultrasonography (US) represents the initial investigation in patients with acute abdominal pain. Systemic manifestations in complicated IAI are SIRS manifestations: body temperature > 38 °C or < 36 °C, heart rate > 90 beats per minute, respiratory rate > 20 breaths per minute (not ventilated) or PaCO2 < 32 mm Hg (ventilated), WBC > 12,000, < 4,000. Procalcitonin (PCT) appeared to be a parameter for early detection of progressing sepsis and valuable aid in deciding if further re-laparotomies were necessary after initial operative treatment of an intra-abdominal septic focus **(13).**

Computerized tomography (CT) is the imaging of choice for most intra-abdominal processes in hemodynamically stable patient and diagnostic laparoscopy should be considered in patients without a specific diagnosis after appropriate imaging and as an alternative to active clinical observation which is the current practice in patients with non-specific abdominal pain **(14).**

Management:

Management of IAI requires resuscitation, source control, and antibacterial treatment. The most important of these factors is source control, which "encompasses all measures undertaken to eliminate the source of infection and to control ongoing contamination" **(15).**

There are three key components of source control:

Drainage, debridement, and definitive management

- ***Drainage***

Hospital mortality associated with IAI varies between settings and disease entities, but is generally high at 23–38% .Drainage is the treatment of choice for intra-abdominal abscesses and can be achieved via open surgery or percutaneous drainage with ultrasound or CT guidance. To minimize trauma, the percutaneous approach is usually preferred in the critically ill patient, leaving surgery as second option if percutaneous drainage is inadequate or not technically feasible. Percutaneous drainage of intra-abdominal abscesses is a safe procedure and has been reported to have low mortality, morbidity, and risk of recurrent disease **(15).**

- ***Debridement.***

Debridement is indicated in the case of intra-abdominal necrosis at high risk of super infection such as ischemic bowel or necrotic pancreas tissue. The extent of debridement remains controversial. Some surgeons prefer a minimally invasive approach while others favor high-volume abdominal lavage and the removal of all fibrin adhesive to the abdominal organs and the peritoneum, despite the higher risk of iatrogenic bowel injury. To save the patient from unnecessary stress of the operation and to wait for demarcation of necrotic tissue, debridement procedures may be delayed for several days, if adequate control of GI bacteria has already been established through drainage or repair. In these cases, it may be wise to schedule a second-look procedure **(16).**

Principles of antibiotic management

Antibiotics should be used after a treatable infection has been recognized or if there is a high degree of suspicion of an infection **(Figure 3).** The prolonged and inappropriate use of antibiotics appears a key factor in the rapid rise of antimicrobial resistance worldwide over the past decade. In the setting of uncomplicated IAIs, such as uncomplicated appendicitis or cholecystitis, single doses have the same impact as multiple doses and post-operative antimicrobial therapy is not necessary if source control is adequate **(17).**

In the setting of complicated IAIs**,** a short course of antibiotic therapy after adequate source control is a reasonable option. The recent prospective trial by **Sawyer et al.** demonstrated that in patients with complicated IAIs undergoing an adequate source control, the outcomes after approximately 4 days of fixed-duration antibiotic therapy were similar to those after a longer course of antibiotics that extended until after the resolution of physiological abnormalities **(18).**

In patients with evidence of an ongoing infection**,** an individualized approach should be mandatory and the patient's inflammatory response should be monitored regularly and decisions to continue, narrow, or stop antibiotic therapy must be made on the basis of clinician judgment and laboratory (such as CRP or PCT levels) investigations, Patients who have ongoing signs of infection or systemic illness beyond 5–7 days of Antibiotic treatment should undergo a diagnostic investigation to determine whether additional surgical intervention or percutaneous drainage is necessary to address an ongoing uncontrolled source of infection or antibiotic treatment failure **(17)**.

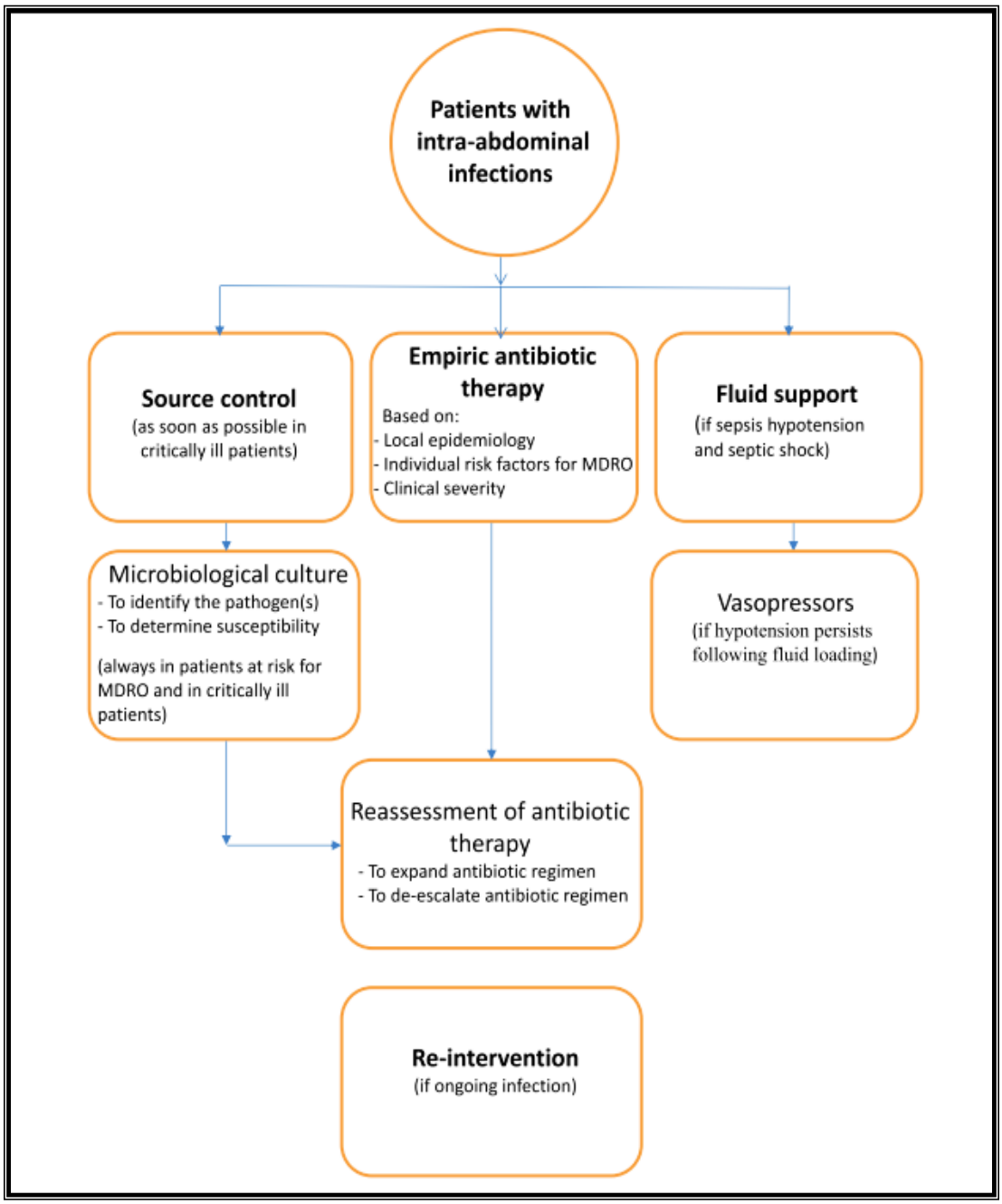

Figure 3:Principles management of IAIs (17).

The choice of empiric antibiotic regimens in patients with IAI should be based on the local resistance epidemiology, the individual risk for infection by resistant pathogens, and the clinical condition of the patients, also Empiric antibiotic therapy for patients with IAI should include agents with activity against aerobic Gram-negative bacteria (e.g., Enterobacteriaceae), aerobic streptococci, and obligate enteric anaerobic

organisms found in the gastrointestinal tract, although coverage of the latter may not be absolutely essential in patients with an upper gastrointestinal source of infection **(**

Table 2) (17).

In the last two decades, antimicrobial resistance has become a global threat to public health systems and some of the most common causes of misuse of antibiotics, and poor prevention and control with respect to infections, In the context of IAIs, the main resistance problem is posed by extended-spectrum beta-lactamases (ESBL) roducing Enterobacteriaceae, which are alarmingly prevalent in nosocomial infections and frequently observed in community-acquired infections, albeit to a lesser extent **(19)**.

ESBL are enzymes capable of hydrolyzing and inactivating a wide variety of beta-lactams, including third-generation cephalosporins, penicillins, and aztreonam **(20)**.

Polymyxins are an old class of cyclic polypeptide antibiotics discovered in 1947. Of the five chemical compounds, polymyxin B and polymyxin E (colistin) are the two that have been used in clinical practice. the main difference in clinical practice is that colistin is administered intravenously as the prodrug colistimethate sodium (CMS), whereas intravenous polymyxin B is administered as the active form, its sulfate salt, directly in the systematic circulation One milligram of polymyxin B and CMS is equivalent to 10,000 International Units (IU) and 12,500 IU, respectively **(21)**.

Intravenous colistin has been used in a few countries, especially in hospitals for patients with MDR Gram-negative bacterial infections. In the USA, Brazil, Malaysia and Singapore, both colistin and polymyxin B are available for intravenous administration. Of note, in some countries, such as Japan and South Africa, neither colistin nor polymyxin B are available . The potential pharmacokinetic benefits of intravenous polymyxin B compared with intravenous colistin, coupled with the advancing morbidity and mortality associated with MDR Gram-negative infections, make the critical evaluation of the evolving global literature related to clinical use of intravenous polymyxin B a contemporary issue **(22)**

Table 2: Antibiotics for treating patients with IAIs based upon susceptibility (17).

Antibiotic	Anaerobic coverage	*Pseudomonas* coverage	Non-resistant enterococci coverage	Enterobacteriaceae coverage	ESBL coverage
Amikacin	–	+	–	+	+/–
Amoxicillin/ clavulanate	+	–	+	+/–[a]	–
Ceftazidime/ avibactam	–	+[b]	–	+[c]	+
Ceftolozane/ tazobactam	–	+[b]	–	+	+
Cefotaxime	–	–	–	+	–
Ceftazidime	–	+	–	+	–
Ceftriaxone	–	–	–	+	–
Ciprofloxacin	–	+	–	+/–[a]	–
Eravacycline	+	–	+	+[e]	+
Ertapenem	+	–	+/–	+	+
Imipenem-cilastatin	+	+	+[d]	+	+
Meropenem	+	+	+/–	+	+
Metronidazole	+	–	–	–	–
Piperacillin/ tazobactam	+	+	+	+	+/–
Tigecycline	+	–	+	+[e]	+

a. Increasing rates of antimicrobial resistance among Enterobacteriaceae worldwide

b. Active against MDR Pseudomonas aeruginosa except metallo-beta-lactamases (MBL)-producing Pseudomonas aeruginosa

c. Active against carbapenemase-producing Klebsiella pneumoniae except MBL-producing Enterobacteriaceae

d. Imipenem/cilastatin is more active against ampicillin-susceptible enterococci than ertapenem, meropenem, and doripenem

e. Not active against Proteus, Morganella, and Providencia.

IAIs may be managed by either single or multiple antibiotic regimens. Beta-lactam/beta-lactamase inhibitor combinations, including, amoxicillin/clavulanate, ticarcillin/clavulanate, piperacillin/tazobactam, have an in vitro activity against Gram-positive, Gram-negative and anaerobic bacteria. Increasing rates of antimicrobial resistance to amoxicillin/clavulanate among E. coli and other Enterobacteriaceae worldwide, during

the last decade, has compromised the clinical utility of this agent for empiric therapy of serious Gram-negative infections and therefore should be used based on local rates of resistance . Broad-spectrum activity of piperacillin/tazobactam, including anti-pseudomonal and anaerobic coverage, still make it an attractive option in the management of severe IAIs **(23)**.

1. The source of infection should always be identified and controlled as soon as possible.
2. Antibiotic empiric therapy should be initiated after a treatable surgical infection has been recognized, because microbiologic data (culture and susceptibility results) may not be available for up to 48–72 h to guide targeted therapy.
3. In critically ill patients, empiric broad-spectrum therapy to cover the most likely pathogens should be initiated as soon as possible after a surgical infection has been recognized. Empiric antimicrobial therapy should be narrowed once culture and susceptibility results are available and adequate clinical improvement is noted.
4. Empiric therapy should be chosen on the basis of local epidemiology, individual patient risk factors for MDR bacteria and Candida spp., clinical severity, and infection source.
5. Specimens for microbiologic evaluation from the site of infection are always recommended for patients with hospital-acquired or with community-acquired infections at risk for resistant pathogens (e.g., previous antimicrobial therapy, previous infection or colonization with a multiple drug resistant (MDR), extensively drug resistant (XDR), and pan drug resistant (PDR) pathogen) and in critically ill patients. Blood cultures should be performed before the administration of antibiotic agents in critically ill patients.
6. The antibiotic dose should be optimized to ensure that Pharmacokinetics and Pharmacodynamics targets are achieved. This involves prescribing an adequate dose, according to the most appropriate and right method and schedule to maximize the probability of target attainment.
7. The appropriateness and need for antimicrobial treatment should be re-assessed daily.
8. Once source control is established, short courses of antibiotic therapy are as effective as longer courses regardless of signs of inflammation.
9. Intra-abdominal infection-4 days are as effective as 8 days in moderately ill patients
10. Blood stream infection-5 to 7 days are as effective as 7 to 21 days for most patients
11. Ventilator-associated pneumonia—8 days are as effective as 15 days.
12. Failure of antibiotic therapy in patients having continued evidence of active infection may require a reoperation for a second source control intervention.

Biomarkers such as procalcitonin may be useful to guide the duration and cessation of antibiotic therapy in critically ill patients.

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