EDITORIAL

Antimicrobial management of intra-abdominal infections:
Literature's guidelines

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INTRODUCTION

Intra-abdominal infections (IAIs) encompass a variety of pathological conditions, ranging from uncomplicated appendicitis to fecal peritonitis. Cases of IAI are further subcategorized as being either uncomplicated or complicated.[1]

In the event of an uncomplicated case of IAI, the infection only involves a single organ and does not extend to the peritoneum. Patients with such infections can be treated with either surgical resection or antibiotics. When the infection is effectively resolved by surgical excision, 24-h perioperative prophylaxis is typically sufficient. Patients with IAIs, including acute diverticulitis and certain forms of acute appendicitis, may be treated non-operatively by means of antimicrobial therapy.

In the event of complicated IAI, the infectious process proceeds beyond the organ, causing either localized or diffuse peritonitis. The treatment of patients with complicated IAIs involves both source control and antibiotic therapy.

Antimicrobial therapy plays an integral role in the management of IAIs, especially in critically ill patients who require immediate empirical antibiotic therapy. An insufficient or otherwise inadequate antimicrobial regimen is one of the variables most strongly associated with unfavorable outcomes.[2,3]

Various studies have demonstrated that inappropriate
antimicrobial use is common. Excessive antimicrobial use has contributed to the emergence and spread of drug-resistant microorganisms and has simultaneously increased overall treatment costs. An antimicrobial-based approach to treating IAIs always involves a delicate balance between the optimization of empirical therapy, which has been shown to improve clinical outcomes, and the reduction of excessive antimicrobial use, which has been proven to increase the rate of emergence of antimicrobial-resistant strains.

The threat of antimicrobial resistance has been identified as one of the major challenges in the management of complicated IAIs. In the past few decades, an increased prevalence of infections caused by antibiotic-resistant pathogens, including methicillin-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus species, carbapenem-resistant Pseudomonas aeruginosa, extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae (E. coli) and Klebsiella species, and multidrug-resistant Acinetobacter species, has been observed, especially in IAIs.

To resolve the medical community’s tendency to overuse antibiotics, a set of guidelines outlining the proper use of antimicrobial therapy has been implemented, which contains specific directions for addressing IAIs.

Two different sets of guidelines outlining the clinical management of IAIs were recently published.

In 2010, the Surgical Infection Society (SIS) and the Infectious Diseases Society of America (IDSA) instituted standardized guidelines for the diagnosis and management of complicated IAIs.

The new SIS and IDSA guidelines replace those previously published in 2002 and 2003.

The World Society of Emergency Surgery (WSES) guidelines represent an additional contribution to the debate by specialists worldwide. These guidelines represent the conclusions reached by the consensus conference held in Bologna, Italy, in July 2010, during the first congress of the WSES; in attendance at this event were surgeons, infectious disease specialists, pharmacologists, radiologists and intensivists, all of whom wished to define and streamline a standardized set of recommendations for the early treatment and management of IAIs.

GUIDELINES BY SIS AND IDSA: ANTIMICROBIAL MANAGEMENT FOR COMPLICATED INTRA-ABDOMINAL INFECTIONS

In the SIS and IDSA guidelines, selection of the appropriate antimicrobial regimen is based primarily on the “risk factor” of the potential failure of the treatment in question.

“High risk” describes patients with an increased likelihood of treatment failure and a greater potential severity of infection according to clinical assessment criteria. Such patients include those with anatomically unfavorable infections or health care-related infections.

Clinical factors predicting failure of treatment for IAIs include: (1) delay in the initial stages of intervention (24 h); (2) high severity of illness (Acute Physiology and Chronic Health Evaluation II score > 15); (3) advanced age of patient; (4) comorbidity involving organ dysfunction; (5) low albumin levels; (6) poor nutritional status; (7) peritoneal involvement or diffuse peritonitis; (8) inability to achieve adequate debridement or control of drainage; (9) presence of malignancy; and (10) health care-related infection.

Health care-related infections refer to a spectrum of adult patients treated in acute care hospitals or monitored in chronic care settings. These patients increase their risk of infection due to the emergence of multidrug-resistant bacteria. Health care-related infections have higher risks of complication and mortality than community-acquired disease.

Guidelines developed by the SIS and the IDSA have recommended various single-agent and combination regimens for patients with different levels of risk.

Extra-biliary community-acquired intra-abdominal infections

In the treatment of patients with community-acquired IAIs, empiric antimicrobial therapy should protect against common gram-negative and anaerobic enteric bacteria. The SIS and IDSA guidelines classify community-acquired IAIs as being mild, moderate, or severe on the basis of the patient’s assessed risk factors.

For high severity infections, those cases for which adequate empirical therapy helps reduce the rate of mortality, regimens having a broader spectrum of antimicrobial activity are recommended.

For adult patients with mild-to-moderate community-acquired infections, the SIS-IDSA guidelines recommend the use of ticarcillin-clavulanate, cefoxitin, ertapenem, moxifloxacin, or tigecycline as single-agent therapies; the guidelines also advocate combinations of metronidazole with cefazolin, cefuroxime, ceftriaxone, cefotaxime, or levofloxacin, as opposed to single agents featuring broader antimicrobial activity.

The empiric use of antimicrobial regimens with broad-spectrum activity against gram-negative organisms, which include meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam as single-agent therapies, or ciprofloxacin, levofloxacin cefazidime, cefepime each combined with metronidazole, is recommended by the SIS-IDSA guidelines for treating high-severity community-acquired IAIs.

(Due to the increasing resistance of E. coli to fluoroquinolones, local population susceptibility profiles and, if available, isolate susceptibilities should be reviewed).

The SIS-IDSA guidelines do not recommend the routine use of agents effective against enterococci in community-acquired infections, even if infections caused by these organisms may be associated with poorer clinical outcomes.

Additionally, antifungal protection is not required for community-acquired infections.
According to the guidelines, Amynoglicosides should be reserved for patients allergic to \( \beta \)-lactam agents and, even in these cases, they are “last resort” options that should be used only when quinolone-based regimens are unavailable. That said, depending on the local susceptibility patterns of nosocomial gram-negative bacilli, Aminoglycosides may be a reasonable choice for the empiric or definitive treatment of certain patients with health care-related IAI.

**Health care-associated intra-abdominal infections**

Health care-related infections are commonly caused by more resistant strains, which may include the non-fermenting gram-negative *P. aeruginosa, Acinetobacter species*, *E. coli, Enterobacter species, Proteus species, methicillin resistant Staphylococcus aureus*, enterococci, *Candida species*, and extended spectrum \( \beta \)-lactamase-producing Klebsiella. For these infections, given that adequate empiric therapy appears to be a crucial factor affecting postoperative complications and mortality rates, complex multidrug regimens are recommended.

According to the SIS-IDSA guidelines, antibiotic selection should always be tailored to address the nosocomial microorganisms known to be present at the facilities in which the patient developed the infection.

**Biliary intra-abdominal infections**

For patients with complicated biliary IAI, selection of a specific antimicrobial therapy should be based on the origin of the infection (community versus health care), on the severity of illness, and on the presence or absence of a biliary-enteric anastomosis.

For biliary infections, anaerobic therapy is not recommended unless a biliary-enteric anastomosis is present.

Regarding community-acquired biliary infections, antimicrobial activity against enterococci is not required because such strains have not proven to be pathogenic. For certain immunosuppressed patients, however, particularly for those who have undergone extensive hepatic-related procedures or liver transplants, enterococcal infections can be clinically significant and may require treatment.

For community-acquired acute cholecystitis of mild-to-moderate severity, the SIS and IDSA guidelines recommend treatment regimens of cefazolin, cefuroxime, or ceftriaxone. On the other hand, for community-acquired acute cholecystitis causing severe physiologic disturbance, advanced age, and/or immunocompromise, the IDSA guidelines recommend Imipenem-cilastatin, meropenem, doripenem, piperacillin-tazobactam as single-agent therapies, or ciprofloxacin, levofloxacin, cefepime, each in combination with metronidazole. Contrastingly, for acute cholangitis of any severity grade following biliary-enteric anastomosis, the SIS-IDSA guidelines recommend Imipenem-cilastatin, meropenem, doripenem, piperacillin-tazobactam as single-agent therapies, or ciprofloxacin, levofloxacin, cefepime, each in combination with metronidazole. For health care-related biliary infection of any severity grade, the IDSA guidelines recommend Imipenem-cilastatin, meropenem, doripenem, piperacillin-tazobactam, or ciprofloxacin, levofloxacin, cefepime, each in combination with metronidazole, supplementing them with vancomycin.

(Due to the increasing resistance of *E. coli* to fluoroquinolones, local population susceptibility profiles and, if available, isolate susceptibilities should be assessed and systematically reviewed).

**GUIDELINES BY WSES: ANTIMICROBIAL MANAGEMENT FOR INTRA-ABDOMINAL INFECTIONS**

Patients with IAI are classified by SIS-IDSA guidelines into low risk and high risk.

However the definition of “risk” in IAI remains too vague. Dividing patients with IAI into lower and higher risk categories may be not easy, and attempting to assess a patient’s risk of treatment failure may be not sufficient to optimize an antimicrobial treatment plan.

In order to stratify the patients with IAI, WSES guidelines stratify patients with IAI according to the specific risk for antimicrobial resistant bacteria and to the clinical patient’s severity.

In order to better identify the pathogens present and evaluate the associated resistance patterns, infections are classified as being either community- or hospital-acquired.

In the past two decades, the incidence rate of hospital-acquired infections caused by resistant microorganisms has risen significantly, a finding that is probably correlated with higher levels of antibiotic exposure and an increasing number of patients with one or more predisposing conditions such as recent exposure to antibiotics, high severity of illness, advanced age, comorbidity, degree of organ dysfunction, low albumin level, poor nutritional status, immunocompromise, and the presence of malignancy.

In the last years, the level of resistance has become significant also in the community acquired infections. The main resistance problem in IAI is represented by ESBL producers Enterobacteriaceae, even today frequently found in community acquired infections\(^{[12,13]}\).

The available therapeutic options for the treatment of ESBL-associated infections are limited by drug resistance conferred by the ESBLs\(^{[14,15]}\).

The third generation cephalosporins, recommended by SIS-IDSA for high risk patients in association with metronidazole, should not be used to treat suspected infections with ESBL producing organisms because clinical outcome is poor even in the presence of apparent susceptibility\(^{[14]}\).

Also cefepime should not be used as the first line therapy against ESBL-producing organisms\(^{[14]}\).

Piperacillin-tazobactam, recommended by SIS-IDSA guidelines for high risk patients, is not regarded as suitable first line therapy for serious infections caused by ESBL producer\(^{[14]}\).
Ciprofloxacin has been a potential antimicrobial option for the treatment of infections caused by ESBL-producing enterobacteriaceae; however, in recent years, the usage of ciprofloxacin has risen, and ESBL-producing isolates resistant to fluoroquinolones has increased over time also in E. coli.[16]

For two decades Carbapenems have been the antibiotics of first choice for ESBLs. The increased carbapenem consumption has been associated to increasing of carbapenem-resistant bacterial species.[13]

The rapid spread of carbapenemases in Klebsiella pneumoniae (K. pneumoniae) emphasizes the concept that the usage of carbapenems should be optimized in terms of indication and exposure.

Therefore, group 2 carbapenems should be used in community acquired IAIs only in critically ill patients where inadequate antimicrobial therapy may have a significant impact on the patients mortality, independently by the site of infection.

The choice of the antimicrobial regimen poses serious problems for the management of critically ill patients. In patients with severe sepsis or septic shock an early correct empirical antimicrobial therapy has a significant impact on the outcome, independently by the site of infection.

It is confirmed by a recent prospective observational study, involving 180 consecutive patients with secondary generalized peritonitis, by Riché et al.[17] that demonstrated, a significantly higher mortality rate in septic shock (35% vs 8% for patients without shock).

Recently published international guidelines outlining the proper management of severe sepsis and septic shock (Surviving Sepsis Campaign)[18] recommend the intravenous administration of antibiotics within the first hour following diagnosis; the use of broad-spectrum agents that can effectively penetrate the presumed site of infection; and the daily reassessment of the antimicrobial regimen in order to optimize treatment efficacy, prevent the development of drug resistance, avoid drug-induced toxicity, and minimize the overall cost of hospitalization.

For years, antibiotics have typically been used as single-agent therapies; only once microbiological cultures and susceptibility tests had been performed were more potent compounds then administered. The traditional approach, however, may no longer be appropriate for critically ill patients in the current context of increasing antibiotic resistance.

Increasing rates of antibiotic resistance and a better understanding of the inflammatory process together prompted the medical community to begin advocating the use of broad-spectrum regimens initially when treating critically ill patients.

This two-stage approach, consisting of aggressive initial therapy followed by a less intense follow-up treatment, allows for the immediate and effective treatment of serious infections while simultaneously avoiding the overdose of antibiotics, potential microbial resistance, and excessive hospitalization costs.

**Community-acquired intra-abdominal infections**

Empirical antibiotic treatment of community-acquired IAIs should be conducted in accordance with the most frequently isolated germs and the local trends of antibiotic resistance. The major pathogens involved in community-acquired IAIs are enterobacteriaceae, streptococci, and anaerobes. The primary problems with resistance stem from ESBL-producing enterobacteriaceae, which are frequently found in community-acquired infections.[13,18]

Many factors can increase the risk of ESBL selection, but prior exposure to antibiotics (mainly third generation cephalosporins) and comorbidities that continuously require antibiotic treatment regimens, are among the most significant predisposing criteria.[18]

In the event of community-acquired IAIs, antimicrobial therapy for enterococci should be considered on a patient-by-patient basis, mainly for critically ill and immunocompromised patients as well as patients with valvular heart disease or prosthetic implants.

Community-acquired IAIs may be treated with either single or multiple antimicrobial regimens depending on the patient's condition as well as the predominant risk factors for specific microorganisms and resistance patterns. For stable, non-critical patients presenting with no ESBL-associated risk factors, amoxicillin/clavulanate and ciprofloxacin plus metronidazole regimens are recommended. Contrastingly, for critically ill patients presenting with no ESBL-associated risk factors, treatments of piperacillin/tazobactam are recommended.

On the other hand, for stable, non-critical patients presenting with ESBL-associated risk factors, ertapenem or tigecycline treatments are recommended. Contrastingly, for critically ill patients presenting with ESBL-associated risk factors, meropenem or imipenem plus fluconazole regimens (the latter in the event of risk factors for Candida) are recommended.

Antimicrobial regimens recommended by WSES[11] for treating extra-biliary community-acquired IAIs was summarized in Table 1.

**Biliary intra-abdominal infections**

Antibiotics are always recommended when treating complicated cholecystitis and advanced uncomplicated cholecystitis.

The most important factors for antimicrobial drug selection in biliary infections are the following: antimicrobial activity against causative bacteria, the clinical condition of the patient in question, and the biliary levels of the antimicrobial agents.

An antibiotic's in-bile efficacy as well as the manner in which it is ultimately secreted into the bile are also important selection criteria when choosing an appropriate drug regimen.

The microorganisms that are most often isolated in biliary infections are the gram-negative aerobes, E. coli and K. pneumoniae, and several anaerobes, especially Bacteroides fragilis. Activity against enterococci is not typically required since their pathogenicity in biliary tract infections remains unclear.
The efficacy of antibiotics in treating biliary infections depends largely on the drugs’ resulting biliary concentrations.\(^{21-23}\)

However, there are no clinical or experimental data available from which to infer the antimicrobial dosage that would safely maximize biliary duct penetration, and as such, no standardized recommendations have been established.

For stable, non-critical patients presenting with no ESBL-associated risk factors, amoxicillin/clavulanate, ciprofloxacin plus metronidazole regimens are recommended.

For stable, non-critical patients presenting with ESBL-associated risk factors, Tigecycline is recommended.

For critically ill patients presenting with no ESBL-associated risk factors, Piperacillin/tazobactam is recommended.

For critically ill patients presenting with ESBL-associated risk factors, Tigecycline plus piperacillin (plus fluconazole in the event of risk factors for *Candida*) is the recommended drug regimen.

Antimicrobial regimens recommended by WSES\(^{11}\) for treating biliary IAI were summarized in Table 2.

**Hospital-acquired intra-abdominal infections**

Hospital-acquired IAI are, by definition, infections that were not present upon hospital admission but become evident at least 48 h following admission in patients hospitalized for a reason other than IAI.

The threat of antimicrobial resistance has been identified as one of the major challenges in the management of complicated IAI.

Hospital-acquired infections are commonly caused by more resistant strains, and for these infections, complex multi-drug regimens are usually recommended.

The use of anti-enterococcal drugs in empirical antibiotic regimens to treat nosocomial IAI is always warranted if directed against *Enterococcus faecalis.*

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**Table 1** Antimicrobial regimens recommended by the World Society of Emergency Surgery recommendations for treating extra-biliary community-acquired intra-abdominal infections

| Antimicrobial agents | Dosage |
|----------------------|--------|
| **In stable, non-critical patients** | |
| **With no ESBL-associated risk factors** | Amoxicillin/clavulanate 2.2 g every 6 h (2-h infusion time) + Ciprofloxacin 400 mg every 8 h (80-min infusion time) + Metronidazole 500 mg every 6 h (1-h infusion time) |
| **With ESBL-associated risk factors** | Ertapenem 1 g every 24 h (2-h infusion time) + Tigecycline 100 mg LD then 50 mg every 12 h (2-h infusion time) |
| **In critically ill patients presenting** | |
| **With no ESBL-associated risk factors** | Piperacillin/tazobactam 9 g LD then 18 g per day via continuous infusion or 4.5 g every 6 h (4-h infusion time) |
| **With ESBL-associated risk factors** | Meropenem 500 mg every 6 h (6-h infusion time) or Imipenem 500 mg every 4 h (3-h infusion time) + Fluconazole 600 mg LD then 400 mg every 24 h (2-h infusion time) |

ESBL: Extended-spectrum β-lactamase; LD: Loading dose.

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**Table 2** Antimicrobial regimens recommended by the World Society of Emergency Surgery recommendations for treating biliary intra-abdominal infections

| Antimicrobial agents | Dosage |
|----------------------|--------|
| **In stable, non-critical patients** | |
| **With no ESBL-associated risk factors** | Amoxicillin/clavulanate 2.2 g every 6 h (2-h infusion time) + Ciprofloxacin 400 mg every 8 h (80-min infusion time) + Metronidazole 500 mg every 6 h (1-h infusion time) |
| **With ESBL-associated risk factors** | Ertapenem 1 g every 24 h (2-h infusion time) + Tigecycline 100 mg LD then 50 mg every 12 h (2-h infusion time) |
| **In critically ill patients** | |
| **With no ESBL-associated risk factors** | Piperacillin/tazobactam 9 g LD then 18 g per day via continuous infusion or 4.5 g every 6 h (4-h infusion time) |
| **With ESBL-associated risk factors** | Piperacillin 8 g LD then 16 g/d via continuous infusion or 4 every 6 h (4-h infusion time) + Tigecycline 100 mg LD then 50 mg every 12 h (2-h infusion time) + Fluconazole 600 mg LD then 400 mg every 24 h (2-h infusion time) |

ESBL: Extended-spectrum β-lactamase; LD: Loading dose.
The recently published IDSA guidelines for the treatment of invasive candidiasis don't explicitly address candidal peritonitis\(^6\). However, the use of echinocandins is generally favored as a first-line empirical therapy in treating critically ill patients, while fluconazole is typically used for patients with less severe conditions. Consequently, by applying these trends to the context of IAIIs one might suggest the prescription of echinocandins as a first-line treatment for cases of severe nosocomial IAIIs.

For stable, non-critical patients presenting with risk factors for multidrug-resistant pathogens, fluconazole and tigecycline plus piperacillin are recommended. In critically ill patients presenting with risk factors presenting for multidrug-resistant pathogens meropenem, imipenem/cilastatin, and doripenem (plus an echinocandin and Teicoplanin) or Tigecycline (plus an Echinocandin and Piperacillin) are recommended.

Antimicrobial regimens recommended by WSES\(^7\) for hospital-acquired IAIIs was summarized in Table 3.

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S- Editor Sun H  L- Editor Stewart GJ  E- Editor Xiong L