

Sparing Anti-pseudomonas Antibiotics in Intraabdominal Infections

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Rezumat

Cruțarea activității antibioticelor antipseudomonazice în infecțiile intraabdominale

Progresele diagnosticului chirurgical al infecțiilor intraabdominale au îmbunătățit controlul precoce al sursei, iar noile antibiotice cu spectru larg au permis punerea la punct a schemelor terapeutice. Aceste motive au condus la reducerea importantă a morbidității și a mortalității datorate acestei patologii în ultimii o sută de ani. Totuși, infecțiile intraabdominale rămân o problemă de tratament pentru chirurghi, internişti, infecţionişti şi pentru microbiologi. Rezistenţele bacteriene progresive şi răspândirea lor în unităţile sanitare limitează evoluţia favorabilă a pacienţilor. Acest articol dezbate motivele pentru care în tratamentul iniţial empiric s-ar putea reduce utilizarea antibioticelor antipseudomonazice atunci când nu sunt necesare şi subliniază tratamentele disponibile pentru infecţiile intra-abdominale.

Cuvinte cheie: infecții intraabdominale, microorganisme multirezistente, antibiotice antipseudomonazice

Abstract

The progress of surgery allowed the timely source control of the intraabdominal infections (IAIs); the availability and use of the

broad-spectrum antibiotics resulted in an important reduction of the morbidity and mortality over the last century. Nevertheless, this pathology remains a major challenge for surgeons, internists, infectious diseases and microbiology specialists. The increased bacterial resistance and its spread within institutions limits the antibiotic treatment options and patients' outcome. This phenomenon is more obvious in Gram-negative bacilli which are the main cause of the IAIs. This paper brings into discussion the criteria which would help reducing the use of anti-pseudomonas antibiotics in the initial empirical treatment when they are not necessary, and also outlines the available therapies for these infections.

Key words: Intraabdominal infections, anti-pseudomonas antibiotics, anaerobes, multidrug resistant organisms

Introduction

IAIs comprise various conditions; their common feature is the inflamed or perforated viscus and the presence of infecting microorganisms in normally sterile sites (peritoneum or retroperitoneal areas). Virtually, most IAIs can evolve to high severity and determine substantial morbidity and mortality (second most common cause of sepsis in ICU). This type of outcome is the result of the inflammatory cascade triggered by the pathogenic strains of Gram-negative bacilli which determine hemorrhagic shock, sepsis and death by multiple organ dysfunction syndrome (MODS) (1). These organisms multiresistant; the spread of the resistance determinants within the hospital and the community limits the choice of the drugs. The adequacy of the initial antibiotic therapy determines the patients' outcome. Since the available antibiotics are becoming

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increasingly restrained, the choice of the schemes should be appropriate to the suspected etiology and local epidemiologic data, avoiding unnecessary long-term use of broad spectrum agents (2). The disruption of the balance between the macro-organism and its commensal flora by the use of unnecessary broad-spectrum antibiotics results in the colonization with pathologic, more resistant species. The New England Journal of Medicine pointed the support offered by the antibiotics in Thomas F. O'Brien's, Editorial "What Has Kept the Antibiotic Miracle Alive?" (N Engl J Med 2011;365:953-955 September 8, 2011). Bacteria respond whenever they are challenged and the administration of ATBs produces the selection of multidrug resistant (MDRO) species (*Bacteroides fragilis*, *Clostridium difficile*, Gram-negative bacilli: Enterobacteriaceae and *Pseudomonas aeruginosa*).

The two cornerstones of the IAIs are the timely source control and the initial appropriate antibiotic regimen.

Epidemiology

The IAIs represent the second most common cause of severe sepsis and septic shock in the ICU and have a poor prognosis. As a result of the progress of surgery (3), nursing and antibiotic regimens the mortality rates have dropped from approximately 90% in 1900 to 23% in 2002 (3-5). This outcome depends upon the level of the perforation (Table 1) and the host and risk factors.

The high rate of mortality is related to MODS which is a direct consequence of the poorly controlled infection. The risk assessment for the development of a complicated IAI or the treatment failure regards the severity of the case at admission, the previous maneuvers, the immunocompromised status and the prior antibiotic regimens. The host factors and the risk factors related to a higher risk for a poor outcome and failure of source control, including those with higher scores on the Acute Physiology and Chronic Health Evaluation (APACHE II) classification are listed in Table 2 (6).

The source of infection governs the mortality but the host factors and risk factors are better predictors of outcomes than either the source or the type of infection (e.g., community acquired or nosocomial) (5, 6). These factors are not specifically related to IAI; they are encountered in many types of infections, bacterial and fungal, with localized or systemic manifestations. Studies have shown that the presence of MDRO is associated with higher rates of treatment failure (8-11). (Table 3)

Etiology and classification

IAIs occur as a result of the perforation or inflammation of a viscus or as a result of bacterial translocation. While uncomplicated IAIs involve a single viscus and have little/no peritoneal inflammation, complicated IAIs involve the inflammation of the peritoneum in various degrees. Community acquired IAIs (CA-IAIs) are generally produced by wild bacterial phenotypes (which do not have acquired resistance mechanisms), but MDRO can also be encountered; the presence of the *P. aeruginosa* is unlikely.

Table 1. The mortality ranges depending upon the level of the perforation

Source of the infection	Mortality rate
Appendix	0.25%
Stomach/duodenum	21%
Small bowel	38%
Large bowel	45%
Biliary tract	50%
Secondary peritonitis with sepsis and septic shock	30%

Table 2.

Host factor	Risk factor
Poornutritional status	Unsuccessful surgical attempts to control the local infection
Hypoalbuminemia < 2 g/dL	Prior broad-spectrum antibiotics
Significant organ disease (cardiovascular, respiratory, liver)	Hospital acquired infection/ transfer from another institution
Diabetes	
Immunocompromised status (chemo/ radiotherapy, neutropenia)	ICU stay (5)
Corticosteroid use (4)	Mechanical ventilation (5)
Organ transplantation	
Duodenal source	
Age >= 65 yrs	
Delay in the initial intervention (> 24 h)	
Prior antibiotic administration (cephalosporins broad spectrum, quinolones, antipseudomonal drugs) (5, 7)	

Table 3. Risk factors for MDR (8), modified by (9-11)

Risk factors for multi drug resistance
- High APACHE II score
- Longer preoperative hospitalization
- Health care associated peritonitis
- Prior antibiotic treatment
- Longer postoperative antibiotic treatment
- Postoperative changes in antibiotic treatment
- Longer postoperative hospitalization

Health acquired IAIs (HA-IAIs), occur in patients from hospital or long-term care facilities; they have increased mortality both because of underlying patient health status and increased likelihood of an infection caused by MDRO and *P. aeruginosa* (13). The most severe IAI is the peritonitis. Primary bacterial peritonitis is the result of bacterial translocation which produces spontaneous peritoneal inflammation in the absence of the disruption of anatomical barriers. It occurs in children and in patients with cirrhosis or in immunocompromised hosts. Secondary bacterial peritonitis results from the disruption of the gut wall or from infected viscera. The organisms present in the gastrointestinal tract

Table 4.

Microorganism	Comments	Type of infection
Aerobes/facultative anaerobes		
<i>Escherichia coli</i> (<i>K. pneumoniae</i> , <i>Enterobacter</i> spp)	Most common, pathogenic, MDRO	Community acquired
Faecal streptococci and enterococci*	Common, implicated mostly in secondary intraabdominal abscesses Pathogenicity remains controversial <i>E. faecium</i> may be MDRO	Community acquired
Anaerobes		
<i>Bacteroides fragilis</i>	Most common MDRO	Community acquired
<i>Clostridium difficile</i>	Less common MDRO	HAI
Aerobes		
<i>Pseudomonas aeruginosa</i>	Specific risk factors, severe clinic aspect	HAI
<i>Acinetobacter</i> species	Pathogenic MDRO	Almost never in CAI

*The role of enterococci in intra-abdominal infections remains controversial, but treatment failure attributable to these organisms appears to be common in high-risk patients. When enterococci are isolated, *Enterococcus faecalis* and *Enterococcus faecium* account for 90% and 10% of episodes, respectively (14).

proliferate in the peritoneum. It may be community-acquired or health care-associated. Tertiary peritonitis is characterized by persistent or recurrent infection that occurs at least 48 hours after primary or secondary peritonitis; it is associated with treatment failure. Patients have significant comorbidities and are immunocompromised.

Bacteriology

The microbial etiology of the IAIs has the central role in the pathogenesis (13-15). The local gastrointestinal (GI) flora has an important role in the defense and homeostatic mechanisms of the peritoneal cavity. The GI microorganisms make-up a system with a stable composition. Most of them have not yet been described, much less isolated from IAIs. Stability of the GI flora is maintained by factors like the competition for nutrients and mucosal binding sites, gut motility, local pH, bile flow, and the production of antimicrobial substances by the gut epithelium and other luminal organisms. Normal flora plays a crucial role in the maintenance of normal metabolic and immunologic homeostasis. Anaerobes greatly outnumber aerobes within the colon, but the disruption of the anaerobic flora by the injudicious use of broad-spectrum antibiotics promotes pathologic gut colonization by resistant species (16).

The IAIs are generally polymicrobial. However, not all the microorganisms cultivated from IAIs need to be targeted with antibiotics as they have low virulence (Table 4).

To assess the global European prevalence of different pathogens in IAIs two types of studies were examined: the ECDC¹ data collected from ten countries between 2008-2009 (17) on the Surgical Site Infection (SSI) and the SMART² studies. The SSI comprise nosocomial infections as well as community acquired and were collected from cholecystectomy

Table 5.

Isolated pathogens	Cholecistectomy n= 400	Colorectal surgery n=2888
Enterobacteriaceae (%)	49.8	46.2
• <i>E. coli</i> (%)	25.3	28.9
<i>P. aeruginosa</i> (%)	2.8	7.3
<i>Acinetobacter</i> spp (%)	0.5	0.4
Anaerobes (%)	4.5	6.3

Table 6.

Isolated pathogens	(%)	ESBL producers (%)
Enterobacteriaceae	83.7	
• <i>E. coli</i>	46.4	7.6
• <i>Klebsiella pneumoniae</i>	17.5	41.2
Other bacteria (Anaerobes, gram-positive cocci and other Gram-negative bacilli)	17.3	

and colorectal surgery, which produce the most complications. The prevalence of the *P. aeruginosa* does not exceed 7.3%. The SSIs data are presented in Table 5.

The European SMART study (2004-2009) showed that the Enterobacteriaceae represented are the most prevalent and the ESBLs producers are more frequent in *K. pneumoniae* strains (18) (Table 6).

The type and site of infection and acquisition mode predicts likely pathogens. (Table 7)

The MDRO can be encountered if previous broad-spectrum antibiotic treatment was administered (e.g.: MDRO Enterobacteriaceae in CAI after treatment with betalactamines).

¹ECDC – European Centre for Disease Prevention and Control

²SMART – Study for Monitoring Antimicrobial Resistance Trends

Table 7.

The site/ type of infection	Microorganisms likely to be found	Mode of infection
Primary (spontaneous) bacterial peritonitis	Monomicrobial (eg, streptococci, E coli, staphylococci)	CAI
Secondary and tertiary peritonitis	Polymicrobial mixtures of aerobic and anaerobic bacteria P. aeruginosa, Acinetobacterspp MDRO Enterobacteriaceae occasionally fungi: Candida albicans	CAI HAI
Infections Derived from the stomach, duodenum, biliary system (cholecystitis), And proximal small bowel	- Gram-negative aerobic and facultative anaerobic bacteria (Enterobacteriaceae: E. coli, Klebsiellaspp and enterococci) - Anaerobes	CAI
Secondary Intraabdominal abscesses	Anaerobes (Bacteroides) and enterococci	CAI /HAI

Pathogenicity and selection of MDRO

Although normally present in low concentration, *E. coli* becomes the dominant aerobe bacterium recovered in infection. In contrast, although anaerobic organisms predominate in the bacterial population of the normal bowel, their implication in infection is in the formation of secondary intra-abdominal abscesses. The main pathogenic mechanism is the endotoxin of the Gram-negative bacilli. It is responsible for hemorrhagic shock, sepsis and death.

Antibiotics

The antibiotics are among the very few life-saving drugs, but this armamentarium is coming to an end; this is more prominent against Gram-negative bacilli. Their unquestionable reliability defines them, both for the patient and the doctor, in terms of infection and psychological confidence. This can be so strong that it makes us lose sight of mild signs and symptoms and neglect lab information. Since the ultimate treatment goals are to avoid sepsis/bacteremia, local destructive effects of infection, and death, broad spectrum drugs are largely used. The selection of initial empiric antimicrobial therapy is likely to influence the clinical outcome. The use of broad-spectrum antibiotics should target the presumable organisms implicated in the pathogenic process. In CAI, especially uncomplicated appendicitis, cultures are rarely necessary. In other types of IAIs, especially HAIs, cultures are mandatory (19). The bacterial resistance is an increasing phenomenon and it represents the major challenge in the treatment of the complicated IAIs. The management of the antibiotic regimens in IAIs must not include antibiotics that are last resource drugs for the MDRO, particularly the *P. aeruginosa*. This is an ubiquitous micro-organism; it has a rich enzymatic equipment and is able to survive in most media. The particular hospital environment offers suitable conditions for its proliferation and spread. The patients having special host and risk factors represent predilection receivers for the MDRO strains, and the unnecessary contact of the *P. aeruginosa* strains with small quantities of broad-spectrum antibiotics would kill the susceptible cells. The naturally resistant ones will survive and will acquire new resistance mechanisms that are transferable to the same species but also to other Gram-

negative bacilli like the Enterobacteriaceae. The resistant clones spread around in a setting and in the community. This way, our last resource drugs can be rendered inactive in a short interval (20, 21). The right antibiotic regimens must represent a balance between optimizing empirical therapy, which has been shown to improve outcomes, and reducing unnecessary antimicrobial use. The important MDRO are the Enterobacteriaceae (with resistance to third generation fluoroquinolones and cephalosporins and ESBL producers which can be encountered both in CAI and HAI) and the HAI (peritonitis or secondary abscesses) produced by MRSA and methicillin resistant coagulase-negative staphylococci, MDRO *E. faecium*, clindamycin resistant anaerobes, but only rarely resistant to metronidazole. Resistance in *C. albicans* is rare, but the MICs³ can get higher (> 8 µg/mL) if the patient had previous fluconazol treatments.

Despite increasing antimicrobial resistance and multi-drug resistance in clinical isolates, there are few novel antimicrobial agents in development. Some broad spectrum agents maintain still satisfactory profiles of safety and efficacy in treatment of multi-drug resistant bacteria in complicated intra-abdominal infections but they must be used judiciously to preserve their effectiveness.

A number of regimens are available, and are all of essentially comparable effectiveness (17). The IDSA⁴ guidelines are centered on the severity of the case. There are two schemes of antibiotic treatment for high severity and mild to moderate severity cases. Each scheme contains one antibiotic regimen or two antibiotic regimens. But only the schemes for the high severity target the *P. aeruginosa* (22) (see Table 8).

The microbiological results are generally available in 24-48 hrs. and the antibiotic regimens (24) can be adjusted to narrow its spectrum on evidence-based principles, aiming to optimize the outcome and sparing the unnecessary anti *Pseudomonas* drugs. There are no studies to support the necessity to specifically treat the Enterococci or *Candida* isolated from a polymicrobial IAI (25) although the isolation of either species is associated with a higher risk of mortality. The optimal duration of antibiotic therapy is

³MIC – Minimum Inhibitory concentration

⁴IDSA - Infectious Diseases Society of America.

Table 8. *Therapeutical recommendations*

Recommendations for single-agent therapy		Recommendations for combination regimens	
Mild-to-moderate severity* (<i>P. aeruginosa</i> sparing drugs)	High risk or severity** (<i>P. aeruginosa</i> active drugs)	Mild-to moderate severity* (<i>P. aeruginosa</i> sparing drugs)	High risk or severity** (<i>P. aeruginosa</i> active drugs)
Cefoxitin	Imipenem/cilastatin	Cefazolin, cefuroxime, ceftriaxone, cefotaxime, ciprofloxacin, or levofloxacin, each in combination with metronidazole	Cefepime, ceftazidime, ciprofloxacin, or levofloxacin, each in combination with metronidazole
Ertapenem	Meropenem		
Moxifloxacin	Doripenem		
Tigecycline	Piperacillin / tazobactam		
Ticarcillin/clavulanic acid			

*including perforated or abscessed appendicitis

unknown, and when antibiotics are used in association with adequate source control, the duration of therapy can be short and certainly no longer than 5–7 days. For empirical treatment, the combination therapy is preferred especially in institutions with a greater prevalence of multidrug-resistant organisms. Moreover, the patient's outcome can be monitored using the procalcitonin test (26). The antibiotics selected for the combination, however, need to be adapted to local susceptibility data, because the benefits can be lost in the presence of high cross-resistance, such as to fluoroquinolones and third-generation cephalosporins. As soon as the microbiology report defines the susceptibilities of the infecting organism(s), monotherapy is preferable; combination therapy does not improve the outcome or the risk of emergence of MDRO. *P. aeruginosa* can be targeted with monotherapy aminoglycosides, which is inferior to any other monotherapy. However, monotherapies should reflect local organisms' prevalence and their susceptibilities (cumulative antibiogram) (27–29). This is a general agreement. Combination therapy for the empirical treatment of serious HAI Gram-negative infection should be followed by de-escalation to monotherapy with the right beta-lactam, based on the microbiological report, in spite of the clinicians' preference for double antibiotic regimens. This is applicable both to *P. aeruginosa* infections and Enterobacteriaceae (19). The microscopic examination of the pus and peritoneal fluid can also provide important information on the nature of the infecting microorganisms (30).

Conclusions

- The source control and the antibiotic regimens are the cornerstones of the management of the IAIs.
- It is the surgeon's decision to operate or to treat, but the antibiotic scheme should be approached in a multidisciplinary team. This evidence based medicine aims to reduce mortality and morbidity.
- Repeated surgery, hemodynamic instability and the administration of combinations of various broad-spectrum antibiotics able to select MDRO can be prevented. However, antibiotics cannot supply the effective source control, the control of aseptic maneuvers and of the sterilization process; they are important as adjuvant therapy when source control can be

accomplished.

- Antibiotics are first choice therapy in the case of primary peritonitis and percutaneous drainage of abscesses.
- The mortality and morbidity of HAI IAIs remains high, but it reflects mainly the biologic terrain of the patients afflicted.
- The empiric antibiotic therapy must reflect the severity of the case, the specific host and risk factors and the hospital specific resistance rates aiming to avoid the unnecessary use of anti-pseudomonas drugs. De-escalation to the susceptibility of the infecting microorganisms should be a part of the quality system. Timely initial antibiotic therapy includes high dose of broad spectrum drugs, regardless of the expenses.
 - In patients with community-acquired secondary peritonitis antibiotic therapy should cover Enterobacteriaceae and anaerobes. In patients with post-operative IAIs the more resistant species have to be targeted, including Gram-negative and Gram-positive species with MDR (ESBL, VRE, MRSA). The highest risk for infections with MDR pathogens exists in immunocompromised patients with organ dysfunctions, a recent surgical history or prior broad spectrum antibiotic therapy (Carmeli score 3).
 - Studies do not provide information upon the necessity of treating enterococci and *C. albicans* in polymicrobial IAIs (24).
 - Empiric initial antibiotic treatment procedures should be revised at least yearly according to the cumulative antibiograms. The set-up of a regular report information of the local phenotypes (the hospital specific surveillance data) as a part of the quality assurance system keeps the personnel up to date with the prevalence of the MDRO and the susceptibilities; it is a reliable tool for the choice of the empiric antibiotic regimens. The use of the Carmeli score provides helpful information.
 - De-escalation and the use of the drugs with differently acting mechanisms reduces the selection pressure among pathogens; avoid prolonged antibiotic exposure.
 - Doctors should restore and preserve the antibiotic molecules available and reconsider therapies on

evidence based medicine.

- The pharmaceutical industry should make efforts for the development of new antibiotics especially against Gram-negative bacilli.

The global management of the infections in the third millennium relies very much on the preservation of the balance of our relationship with the microorganisms. The prevention of the colonization of normally sterile sites by the use of aseptic maneuvers and the control of contamination and of sterilization methods can avoid the unnecessary antibiotic regimens; non-pathogenic microorganisms should not be targeted and unnecessary broad-spectrum antibiotics regimens should be avoided. The therapeutic means should be adapted to the nature and susceptibility of the infecting microorganism(s).

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