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Antimicrobial management in nosocomial peritonitis: microbiota, drug and time

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ABSTRACT

Complicated intra-abdominal infection requires surgical treatment and broad-spectrum empiric antibiotic treatment used early. The rapid spread of multidrug-resistant bacteria has become a serious threat, especially in critical care units. The excessive use of carbapenems has led to carbapenemase-producing Enterobacteriaceae, leaving tigecycline and colistin as therapeutical options. The new antimicrobials, ceftazidime-avibactam and ceftolozane-tazobactam open new horizons in the treatment of multi-drug resistant Enterobacteriaceae. *Candida* peritonitis causes a high mortality in the critical patient. Diagnosis and early treatment are associated with a better prognosis, the administration of an echinocandin being of choice in these patients.

Manejo antimicrobiano en peritonitis nosocomial: microbiota, fármaco y tiempo

RESUMEN

La infección intraabdominal complicada requiere tratamiento quirúrgico y tratamiento antibiótico empírico de amplio espectro utilizado de forma precoz. La rápida diseminación de las bacterias multirresistentes se ha convertido en una grave amenaza en las unidades de cuidados críticos. La excesiva utilización de carbapenémicos ha condicionado la aparición de enterobacterias productoras de carbapenemasas, dejando como opciones terapéuticas a tigeciclina y colistina. Los nuevos antimicrobianos, ceftazidima-avibactam y ceftolozano-tazobactam, abren nuevos horizontes en el tratamiento de enterobacterias multirresistentes. La peritonitis candidiásica condiciona una elevada mortalidad en el paciente crítico. El diagnóstico y el tratamiento precoz están asociados con un mejor pronóstico, siendo de elección en estos pacientes la administración de una equinocandina.

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Intra-abdominal infection (IAI) is a challenge in clinical practice. It is the main cause of postoperative morbidity after abdominal surgery and the most frequent cause of admission into post-surgical critical care units. We understand nosocomial IAI to be an infectious process that occurs over 48 hours after hospital admission, and includes anastomotic leakage, perforation, and abscesses arising as complications of surgery. However, it is estimated that approximately 80% of all intra-abdominal infections are community acquired[1]. More than 21% of nosocomial infections are caused by resistant pathogens[2]. As a consequence, these multi-drug resistant bacteria, which frequently cause intra-abdominal infections, prolong hospital stay (from 6.4 to 12.7 days), increase the number of complications and decrease the efficacy of treatments[3].

In this context, intra-abdominal infection associated with healthcare must also be defined. This term is used to describe infections in those patients who regularly use the healthcare system because of underlying conditions (patients who have had recent hospital admissions, are living in care homes, attending day hospitals, those who have previously taken antibiotics, or are receiving haemodialysis). This definition implies that patients will need initial treatment with broader-spectrum antibiotics than patients with community-acquired infections, due to the presence of microorganisms with a higher degree of resistance to antibiotics.

The so-called core or essential microorganisms of IAIs are Enterobacteriaceae (*Escherichia coli* and *Klebsiella pneumoniae*) and *Bacteroides* spp. (mainly *B. fragilis*), which should always be covered by empiric antibiotic treatment.

Most of the morbimortality produced by multi-drug resistant bacteria is caused by Gram-negative bacteria, which

account for 27% of the most common pathogens in US hospitals[4]. Enterobacteriaceae in particular are primarily responsible for digestive tract infections.

Based on the most recent data from the European antibiotic surveillance reports, the prevalence of resistance to ESBL-type (beta-lactamase-producing enzymes) *E. coli* and *Klebsiella* varies markedly from one country to another. This is probably related to factors such as the availability of drugs, as well as their restriction, waste, water management and general living conditions. In Spain, there has been a notable increase in the prevalence of ESBL-producing Enterobacteriaceae, from 0.5% in 2000 to 4.04% in 2006. In the data obtained from a Study for Monitoring Antimicrobial Resistance Trends (SMART), in which samples including peritoneal fluid, abscesses and bile were collected, the most frequently isolated organism was *E. coli* of nosocomial origin (49.9%). Of the total of Enterobacteriaceae isolated in IAIs, 7.5% were ESBL producers, most frequently *E. coli* (8.7%), followed by *K. pneumoniae* (8.4%), *Klebsiella oxytoca* (4%) and *Proteus mirabilis* (1.6%). In all ESBL-producing microorganisms, the frequency of these enzymes was markedly higher in nosocomial-acquired than in out-of-hospital acquired infections. There was also an increase in isolates with ESBL parallel to that of the patients' age, reaching a frequency higher than 6% in those over 60 years old[5]. Among the risk factors most frequently identified for the appearance of these Enterobacteriaceae capable of expressing ESBL is previous antibiotic treatment. In this regard, rapid enteric colonisation by bacteria resistant to the antibiotic received has been observed in patients receiving third-generation cephalosporins or piperacillin-tazobactam.

The main species of *Enterococcus* spp. participating in the IAI are *Enterococcus feacalis* (80%) and to a lesser extent, *Enterococcus faecium*. They have a natural resistance to many antibiotics, can be selected and proliferate in weakened patients or recipients of a solid organ transplant. In a previous study of secondary peritonitis, the isolation of a high inoculum of this microorganism was associated with nosocomial origin, a higher score in the Charlson Index and APACHE II, or with a poor outcome[6]. Its presence is also very common in tertiary peritonitis.

Pseudomonas aeruginosa has a greater impact on patients with low responsiveness or those who have undergone invasive treatment such as peritoneal dialysis in the form of primary peritonitis. Among the most relevant risk factors for *P. aeruginosa* bacteraemia, nosocomial acquisition, history of invasive procedures in the preceding 72 hours, immunosuppression, neutropenia and hospital stay > 30 days were identified. Another risk factor for *P. aeruginosa* colonisation/infection in critical patients is previous antibiotic treatment. A relationship between this fact and treatment over the last 12 months has been observed with 3rd-generation cephalosporins, quinolones and imipenem. *P. aeruginosa* is the third most prevalent Gram-negative bacillus (9-13%) but remains far behind *E. coli* Its importance is anecdotal in community infection (3%)[7].

Due to its special pathogenicity and opportunistic yeast condition, the participation and causality of *Candida* spp. in IAI has been widely debated. *Candida* spp. colonises the surgical patient with high frequency (72%) and appears more frequently in IAI cultures of nosocomial origin. The isolation of *Candida* spp. in the peritoneal cavity is observed in 20-30% of secondary peritonitis and its presence could imply a poor prognosis.

The prevalence of invasive fungal infections in patients undergoing gastrointestinal surgery has increased in recent years. There are numerous risk factors associated with *Candida* peritonitis, the main ones being those that promote *Candida* colonisation and impaired host immunity. Among the most relevant factors are the following: the origin of the peritonitis (perforation of upper gastrointestinal tract), the type of peritonitis (tertiary peritonitis in patients with multiple reinterventions), severe acute pancreatitis, high degree of severity (APACHE> 25 points, septic shock), prolonged paralytic ileus, total parenteral nutrition, prolonged antibiotic treatment, prolonged stay in intensive care unit, presence of catheters and/or drainage systems, and administration of gastric therapy (proton pump inhibitors, anti-H2)[8].

EARLINESS, DURATION AND ANTIBIOTIC TREATMENT

Antibiotic treatment is more effective when started early, as well as when it is adapted to the sensitivity of the IAI pathogens. Cohort studies in patients with severe sepsis have shown that for every hour that the initiation of appropriate antibiotic treatment is delayed, mortality increases by 7.6%[9].

The choice of an effective empiric treatment for IAI remains a challenge. Ineffective empiric therapy is associated with higher rates of therapeutic failure, surgical wound infections, surgical reintervention, and higher mortality rates. The choice of antibiotic requires consideration of the source of the infection, safety or toxicity of the antibiotic, interaction with other drugs, administration guidelines, as well as the microbiological variability and patterns of intrinsic resistance of each hospital or critical care unit. Due the polymicrobial nature of secondary peritonitis, empiric treatment inevitably requires combined treatment to achieve the necessary coverage of both habitual pathogens and unexpected pathogens.

The duration of antibiotic treatment in peritonitis has been extensively debated, without a consensus having been reached. There is evidence that, in the patient with an appropriate immune response and after adequate focus control, the residual inoculum may respond to a shorter antibiotic treatment. Recent studies have demonstrated the usefulness of biological markers in evaluating the response to antibiotic treatment. In a recent multicentre study involving 121 patients using procalcitonin (PCT) as a guide to terminating antibiotic treatment, it was demonstrated that antibiotic treatment can safely be withdrawn on day 5, even in severe patients, provided that the focus is controlled, showing a 50% reduction in the duration of antibiotic treatment[10].

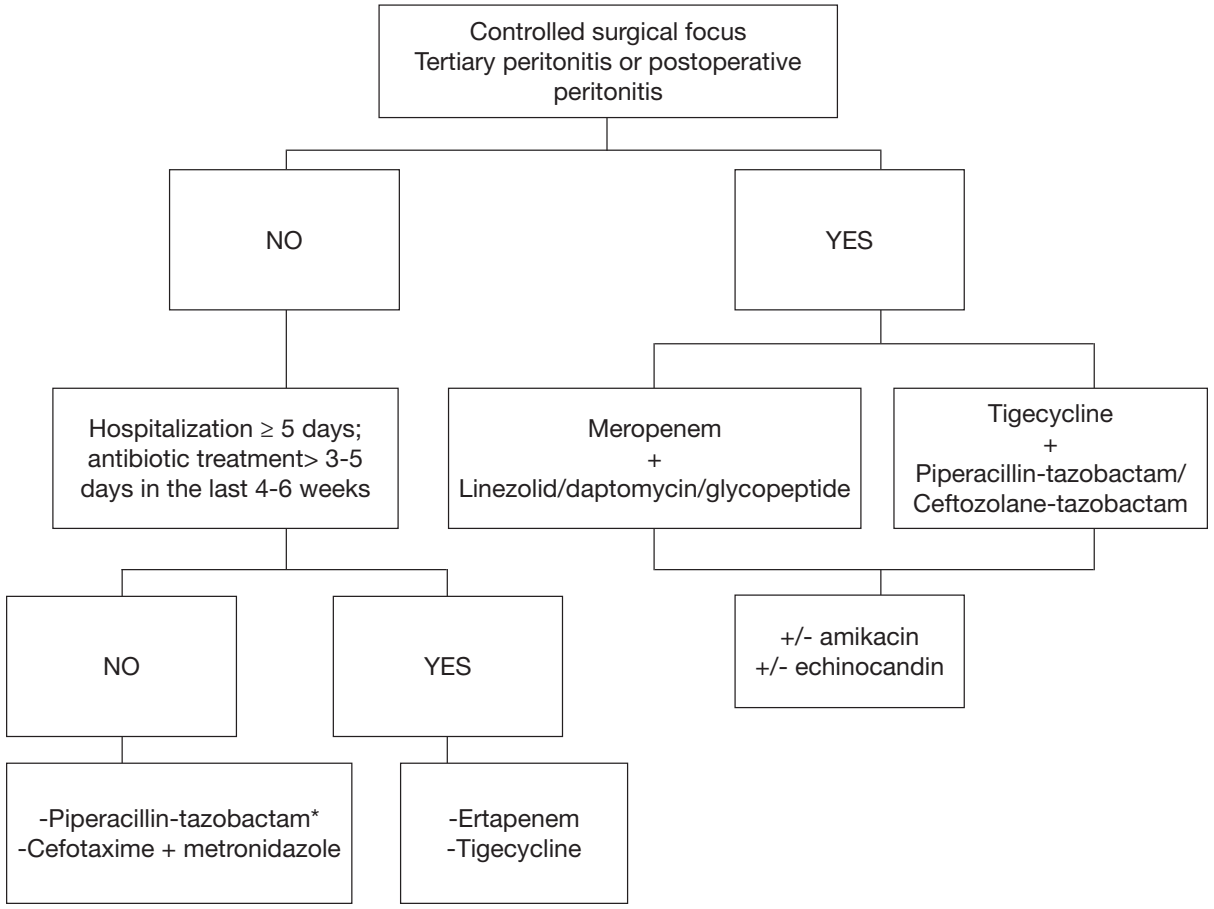

Figure 1 | **Secundary peritonitis. Empirical treatment**

Regarding empirical treatment (figure 1), we must bear in mind that any proposed antibiotic treatment regimen should cover anaerobic microorganisms. A standard treatment regimen is the combination of beta-lactams with beta-lactamase inhibitors, as is the case with piperacillin/tazobactam, which shows activity against *P. aeruginosa*. However, ESBL-producing strains show rates of resistance to piperacillin/tazobactam (according to EUCAST cut-off points) of 27.4% for *E. coli* , of 38.1% for *K. pneumoniae*[11] and 8% for *P. aeruginosa*[12]. New combinations of beta-lactams/ beta-lactamase inhibitors, such as ceftozolane/tazobactam[13] or ceftazidime /avibactam[14] have been developed. Currently available data on the efficacy of these new antibiotics in the treatment of IAI (both administered with metronidazole) are relatively limited, although they show promising data in the treatment of secondary peritonitis (where *P. aeruginosa* may be involved), as part of combined guidelines that include an antimicrobial with activity against anaerobes and against enterococci and/or methicillin-resistant *Staphylococcus aureus* (MRSA) when necessary.

Carbapenems have been recommended as the antibiotics of choice in the empiric treatment of infections caused by multi-drug resistant pathogens, being the first choice when an infection is suspected to be produced by ESBL-producing Enterobacteriaceae or AmpC hyperproducers. However, the excessive use of carbapenems has led to the appearance of carbapenemase-producing *Enterobacteriaceae* (EPC), leaving tigecycline (with activity against multi-drug resistant bacteria) and colistin as therapeutic options. Tigecycline (in high doses) has been included in combined antibiotic regimens for the treatment of secondary peritonitis in critically ill patients, with favourable clinical outcomes[15]. Combined antibiotic treatment guidelines that include tigecycline are an alternative to carbapenems, not only because of their activity but also to avoid the spread of carbapenemases that may compromise the future activity of carbapenems.

Empiric treatment against MRSA is recommended in hospitalised patients or those in long-term healthcare facilities colonised by MRSA, or those at risk of infection due to prior

antibiotic exposure. MRSA is also frequently isolated in difficult-to-treat infections with poor outcome and should be covered in patients with tertiary peritonitis[16]. Vancomycin shows activity against enterococci and MRSA, but it is necessary to consider the tolerance of these microorganisms against the antibiotic, mainly *E. faecium*. These facts compromise the effectiveness of vancomycin, making necessary the use of other antibiotics with activity against Gram-positives such as daptomycin or linezolid and that are recommended in the different clinical guidelines.

Mortality rates for *Candida* peritonitis are very high. The control of the infectious focus, together with the establishment of an early and appropriate antifungal treatment are determinant factors in this. There is sufficient evidence in the literature to support the use of empiric antifungal therapy in patients with secondary peritonitis of nosocomial origin and tertiary peritonitis, since the prognosis of these patients worsens with the isolation of *Candida* in peritoneal fluid[17].

The antifungal treatment of choice in critically ill patients with *Candida* peritonitis should be established by the administration of an echinocandin in the following cases: presence of haemodynamic instability, previous treatment with azoles, existence of fluconazole-resistant *Candida* isolate (peritoneal fluid) or need of renal replacement therapy. Echinocandins should be de-escalated to azoles in those patients in whom antifungal treatment was initiated early, azoles-susceptible strains were isolated and have clinically improved after surgery[17].

CONCLUSIONS

The choice of an appropriate empiric therapy for IAI is vital. It requires knowledge of the intrinsic microbiological variability of each hospital or critical care unit, as well as the source of infection, safety or toxicity of the antibiotic, interaction with other drugs, the dosage guidelines and the presence of risk factors. The use of any antimicrobial carries with it the potential development of tolerance or resistance from the first moment that it is used. Antibiotic resistance in Gram-negative bacteria is increasing exponentially worldwide. There are few clinical trials available that provide us with information on decision making. While we wait for new antibiotic combinations to become available in our centres, optimisation of antibiotic treatment as well as a rational use of it is required.

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