



Special article

Recommendations in the empiric anti-infective agents of intra-abdominal infection[☆]

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A significant number of patients with abdominal infection develop advanced stages of infection and mortality is still above 20%. Failure is multifactorial and is associated with an increase of bacterial resistance, inappropriate empirical treatment, a higher comorbidity of patients and poor source control of infection. These guidelines discuss each of these problems and propose measures to avoid the failure based on the best current scientific evidence.

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Recomendaciones en el tratamiento antibiótico empírico de la infección intraabdominal

R E S U M E N

Un número importante de pacientes con infección intraabdominal desarrollan estados avanzados de la infección y la mortalidad es todavía superior al 20%. El fracaso es multifactorial y se relaciona con el incremento de resistencias bacterianas, el tratamiento empírico inapropiado, la mayor comorbilidad de los pacientes y el mal control del foco de infección. Estas guías analizan cada uno de estos problemas y proponen medidas para evitar el fracaso, basadas en la mayor evidencia científica actual.

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Consensus justification and philosophy

In spite of the improvement of the understanding of the pathophysiology of serious infections, diagnostic tests, treatment with antibiotics, perioperative care, and surgical technique, there is still a prominent percentage of patients that suffer intra-abdominal infection (IAI) that develop advanced degrees of infection and that need to be admitted to Intensive Care Units (ICU). Within this context, the mortality rate is 23%,¹ mostly in elderly patients, with greater co-morbidities and those diagnosed in the most advanced stages of the infection.

In the 1990's, we were witnesses and participants of the development and consolidation of new antibiotics that improved the prognosis of patients with IAI. In this respect, the association of β -lactam antibiotics with β -lactamase inhibitors such as tazobactam, allowed for the recuperation of the spectrum of the ureidopenicillins for the treatment of mixed infections in seriously ill patients. However, the continued use of broad-spectrum β -lactam antibiotics has favoured the development of resistance, complicating the correct adaptation of empirical antibiotic treatment and compromising the prognosis of patients.

This manuscript reflects the contrasted opinion of an assembly of specialists involved in the treatment of patients with IAI attended to in the emergency rooms and surgery theatres, and that need antibiotic and surgical treatment. These recommendations highlight the fact that successful treatment of IAI is multifactorial, and that the best antibiotic guidelines can fail if the control of the source of the infection is deficient or difficult to obtain. Furthermore, the concept that the adequate antibiotic treatment does not only refer to its activity against the responsible flora of IAI, but also to initiating treatment as early as possible and with the adequate dosage is emphasised. The choice of the antibiotic should be made keeping in mind the best pharmacokinetic-pharmacodynamic profile depending on the haemodynamic situation of the patient and the duration, in order to delay the appearance of resistance and to avoid compromising the treatment of future patients.

The professional responsible for the patient suffering IAI should be capable of identifying the severity of the infection and, depending on the factors of risk of the patient, selecting the best possible treatment. The excessive use of antibiotics in spectrum and duration without taking into account these precepts, may lead us to a health care model that is not sustainable in an environment threatened by the scarcity of research and development of new antimicrobials needed to fight against the appearance of pathogens resistant to the current antimicrobials.²

The board justifies the draft of new recommendations due to the need to create a document that, by means of a greater understanding of the problem, encourages the improvement of the global treatment of IAI and gives credibility to the health care services involved in its management. Furthermore, the document is meant to clarify the field of its application, attending to the diverse degrees of severity and to the different agents involved, in order to be carried out within the health care process and not only as an occasional annotation.

Consensus methodology

The consensus board has considered that the empirical antibiotic treatment of patients with IAI should take into account the following points:

1. Definition of the different types, field and severity of the IAI.
2. Definition of the risk factors of poor evolution that have been classified in:
 - Inadequacy of the empirical antibiotic treatment and risk factors of IAI produced by pathogens resistant to the empirical antibiotic treatment.
 - Factors related to the presence of significant associated co-morbidity of the patient with IAI.
 - Factors related to the inefficient control of source of infection.
3. Basic concepts of pharmacodynamics and pharmacokinetics that are useful in the adaptation of the empirical antibiotic treatment of IAI.
4. Concepts of precociousness, duration and recovery of the antibiotic treatment.

The board has discussed the main points based on the available evidence. In the situations in which controversy has existed, a voting has been carried out based on the criteria of simple majority.

Types of intra-abdominal infections

The term IAI refers to the infectious process that affects either the wall of the hollow viscera or beyond its limits, reaching the peritoneal cavity. In the present recommendations the term "complicated IAI" is disregarded and the severity of the infection is assessed depending on its extension, the systemic repercussions and the risk factors of therapeutic failure. The main types of IAI are peritonitis and intra-abdominal abscesses.

Primary peritonitis

It is defined as a peritoneal infection, generally monomicrobial, in which no macroscopically visible alteration of the integrity of the gastrointestinal tract has been documented. The most frequent form is the spontaneous peritonitis associated with advanced liver disease (infected ascites), followed by infection in patients treated with peritoneal dialysis. In general, the administration of antibiotics is sufficient to treat this type of IAI. In spite of the fact that the patients that suffer episodes, such as that caused by streptococcal peritonitis, can be diagnosed thanks to the exploratory laparotomy, the present recommendations aim is not clarifying the antibiotic treatment of this condition.

Secondary peritonitis

Peritonitis due to the perforation of hollow viscera is the type of IAI that requires surgical intervention most frequently.

The responsible flora is generally mixed (gram-positive cocci, enterobacteria, and anaerobic microorganisms). In this type of IAI, apart from the empirical antibiotic treatment, some kind of intervention should also be carried out (surgical or minimally invasive) to reduce and control the bacterial inoculum (control of the source of the IAI).

Tertiary peritonitis

It is defined like the "post-infection" intra-abdominal infection and it usually affects patients that undergo repeated surgical procedures, admitted to the ICU and in those where there is a co-existence of satellite infections (sepsis by catheter, respiratory and urinary infections). The pathogens that cause the infection are usually nosocomial, predominantly resistant gram-positive cocci (coagulase-negative *Staphylococcus* and *Enterococcus* spp), *Candida* spp and non-fermenting gram-negative bacillus. However, this type of infection, encumbered by a high mortality, should be differentiated from the persistent and/or recurrent infections that are observed in patients treated for IAI in which the control of the source has been insufficient or has failed by inadequacy of the initial empirical antibiotic treatment.

Intra-abdominal abscesses

The disposition and dynamics of the fluids of the peritoneal cavity work to eliminate and enclose the disseminated peritoneal infection. The recognition of the bacterial molecular patterns by the receivers of the peritoneal macrophages initiates the recruitment of leukocytes and monocytes in the peritoneal cavity, favouring the elimination of the bacterial inoculum. The inflammatory response stimulates the coagulation cascade and the formation of fibrin whose mission is, aside from limiting the bacterial contamination, to capture and enclose bacteria. Teleologically, the formation of intra-abdominal abscesses represents the adequate response of the Immunocompetent host, contrary to what occurs in the patient with tertiary peritonitis in which the IAI is poorly located.

Microbiology of the intra-abdominal infection: community-acquired and nosocomial

In the IAI of community-acquired origin, gram-negative bacilli are the most common, with *Escherichia coli* at the head (25%–30%), followed at a distance by *Klebsiella* spp and *Pseudomonas aeruginosa* (3%–6%). The anaerobic microorganisms, fundamentally of the *Bacteroides fragilis* group, occupy the third place in order of frequency of the microbiological cultures (8.6%–14.3%).³⁻⁵ The gram-positive cocci are also prominent in IAI, especially *Streptococcus* spp (16%), *Staphylococcus* spp (5.2%) and less frequently, *Enterococcus* spp. (4.7%), fundamentally *Enterococcus faecalis*.

In the IAI of nosocomial origin, mostly peritonitis and postoperative abscesses, *E. coli* continues being the enterobacteria more often implicated (22%)⁶ next to *Enterobacter* spp (12%).⁷ The frequency of isolation of *B. fragilis*

(5.5%) is lower than in the common IAI and the presence of *Enterococcus* spp is higher (17%)^{6,7} including *Enterococcus faecium*. The prevalence of unfermented gram-positive bacilli (*P. aeruginosa*) is discreetly greater than the community-acquired IAI, however, it presents a greater pattern of resistance.⁸⁻¹⁰

In both community-acquired and nosocomial IAI, the incidence of peritoneal cultures that are positive for methicillin-resistant *Staphylococcus aureus* (MRSA) and *Enterococcus* spp resistant to vancomycin, is anecdotal as of now.¹¹

Regardless of the origin of the IAI, it is important to highlight that one of the determinant factors of the species and the phenotype of antibiotic sensitivity of the responsible flora, depends, among others aspects, on prior antibiotic treatment. Therefore, in patients with postoperative peritonitis (paradigm of nosocomial IAI) that had received prior antibiotic treatment before the re-intervention, it has been observed that they presented positive cultures for microorganisms with a pattern of very high resistance, like *E. coli* and *Klebsiella* spp resistant to β -lactam antibiotics (producers of β -lactamase), MRSA, *Acinetobacter* spp, *E. faecium*, and *Candida* spp, among others.

Severity assessment of the intra-abdominal infection

Clinical severity assessment of the intra-abdominal infection

Early initiation of the adequate antibiotic treatment, depending on the severity of the patient, has been associated to a better prognosis of serious infections.^{12,13} Therefore, sensitive means to evaluate the severity that are easy and fast to obtain are needed so that patients can benefited early on from the most adequate antibiotic treatment.

The scoring systems used in the ICU area, such as the APACHE II and the SOFA are among the most employed scoring systems to evaluate the severity of septic patients. The APACHE II¹⁴ has been validated as a mortality predictor for patients admitted to the ICU or in the postoperative reanimation area. The SOFA permits the graduation of the alteration of 6 organs or systems and the continued evaluation has shown to be useful in the appraisal of the prognosis of surgical patients.¹⁵ However, for the diagnosis of the severity of patients with IAI, the evaluation using easy-to-obtain scores, at the patient's bedside in the emergency room or in the patient's hospital room, seems to be more convenient.

To date, and in spite of the criticisms received, the most useful classification because of their simplicity and easy application has been that of the Systemic Inflammatory Response Syndrome (SIRS).^h The criteria published by Bone et al¹⁶ have shown their utility in the identification of severe sepsis and septic shock, demonstrating a good correlation with the percentage of mortality of the patients with serious infections.¹⁷ In spite of the fact that the classification of the SIRS suffers from a lack of specificity, the ease of obtaining

^hTwo or more criteria of fever $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, heart rate >90 bpm, respiratory rate >20 breaths per minute, leukocyte count $>12\,000$ L/mm³ or <4000 L/mm³ or $>10\%$ of band neutrophils.

and quantifying the main parameters has resisted the onslaught of its main critics. Thus, for example, it has been established that the patient with IAI that presents two or more SIRS criteria, together with a parameter of organic insufficiency (low blood pressure, oliguria or altered mental state), is classified as presenting serious sepsis and this constitutes the cut-off point to initiate treatment by means of a broader-spectrum antibiotic regimen. However, data exist illustrating that the classification of serious sepsis is not sensitive enough to detect all the patients at risk. In this respect, studies on a cohort of patients with serious infections have shown that the mortality of the cases that presented four SIRS criteria (17%) was similar to those classified in the group of serious sepsis (20%).¹⁷ It has also been observed that, given the fast evolution of sepsis, some parameters such as the leukocyte count may not be present when the patient is moving towards leukopenia and, therefore, the severity can be underestimated. Furthermore, initial studies in patients with serious postoperative infections have revealed that tachycardia and tachypnoea are SIRS parameters that are more sensitive in the premature stages of IAI, while the alterations of the leukocyte count and fever do not appear or appear late.¹⁸ As a result, the SIRS classification is still a useful classification system, although more sensitive earlier parameters must be defined to warn the physician that the patient is developing a septic shock and the most appropriate treatment for this situation should be initiated without delays.

Biological markers

The biological markers are substances produced by the inflammatory cells or by-products of the cell metabolism in response to inflammatory, traumatic or septic stimuli. The ideal biological marker for the assessment of the patient with IAI should have an adequate sensitivity/specificity ratio for the detection of serious sepsis, it should be easily quantifiable in plasma and its plasma concentration changes should be sensitive to healing or persistence of the IAI. The markers that have been shown to be useful in clinical situations are the determination of lactic acid, the C-reactive protein (CRP) and procalcitonin (PCT).

Lactic acid

It is an indicator of tissue hypoxia and the presence of concentrations over 4 mmol/L¹² in the context of infection, classifies the patient in the stage of septic shock. Furthermore, it has been observed that high concentrations of lactate (2–4 mmol/L) are correlated with mortality, independent of the haemodynamic state of the patient and, therefore, can detect serious sepsis before the clinical diagnosis of septic shock.¹⁹ The determination of lactic acid is easy to carry out and makes it possible to understand the severity of the patients in a premature manner and to quickly initiate adequate antibiotic treatment.²⁰

C-reactive protein

The CRP is an acute-phase protein that is produced in the liver whose synthesis is stimulated by the IL-6. In spite of the fact

that it has been considered an inflammatory response marker, data exist that indicate its active participation in the innate immune response and in the regulation of the inflammatory response.²¹ The CRP can be detected from the 4th hour since the stimulus, reaching its maximum concentration between 48–72 hours. It has been documented that the concentrations of CRP are higher in patients with infections than in those who present non-septic inflammation.²² Furthermore, it has been observed in patients in critical situations that a significant decrease of the CRP values between the first day of admission and the 4th day foretells a complete recovery with a sensitivity and specificity of 89 and 79%, respectively.²³ The CRP has also shown to be a marker of the response to antibiotic treatment. Therefore, the patients admitted to the ICU that respond to the antibiotic treatment in a satisfactory manner present a faster decrease of the CRP values, while the increase of the CRP values 48 hours after initiating antibiotic treatment foretells therapeutic failure with a sensitivity of 77% and a specificity of 67%.²⁴ As a result, the CRP complies with the criteria to be a useful clinical marker: a biological trial within reach of the average laboratory, reproducible, with an acceptable variability between individuals and with a capacity to predict the severity and response to the treatment employed.

Procalcitonin

The PCT is a precursor polypeptide of calcitonin, whose concentration is practically undetectable in healthy individuals (<0.5 ng/mL). It shows a slight increase with local bacterial and viral infections (0.5–2 ng/mL), it increases moderately in the systemic inflammatory response syndrome of non-infectious origins (5–20 ng/mL) and presents a marked increase in systemic bacterial infections, where it reaches concentrations between 10 and 1000 ng/mL.

The PCT is easy to determine and the changes of its concentration in plasma are early, fast and they remain stable. The PCT is increased and clears quickly in response to treatment (antibiotic and surgical), it is more related with the severity of the sepsis and seems to have, in comparison with the CRP, a better prognostic capacity for the risk of postoperative mortality. Furthermore, clinical studies have observed, as opposed to the CRP, a smaller alteration after surgical interventions.^{25,26} However, discordant data exist that could be the cause of the lack of consolidation in its generalised clinical application. Therefore, it has been seen that the sensitivity for the detection of the persistence or relapse of IAI is lower than that observed with CRP.²⁷ Under these circumstances, the physician needs a highly sensitive marker that warns about the inflammatory process under way. The lack of specificity will be resolved with adequate diagnostic procedures. Furthermore, a recent meta-analysis does not currently support the systematic application of the determination of PCT in the differentiation of inflammation and infection.²⁸ However, a recent study evaluating the changes (quotient) of the PCT concentration has obtained more hopeful results.²⁶

This document has included the SIRS and APACHE scores as well as the venous lactate concentration in the classification of the IAI severity (Table 1). The CRP is recommended as a

marker of evolution, useful in the appraisal of therapeutic failure and in the duration of the antibiotic treatment.

Definition of poor evolution risk factors

Inadequacy of the empirical antibiotic treatment

Among the most important prognostic factors of serious infections, the adaptation^{3,29-34} and precociousness³⁵ of the antibiotic treatment are emphasised. Retrospective studies have shown that the therapeutic window (period of time in which the antibiotic treatment could be effective to control the IAI before the local and systemic progression conditions the bio-availability of the antibiotic and the therapeutic success) in the IAI can be limited. A better evolution has been observed in those patients in whom the empirical treatment was active against the pathogens that grew in the samples of the index intervention. The poor adaptation of the antibiotic treatment in the IAI is found in 13%-16% of cases,^{34,36} showing a rate of therapeutic failure from resistance to empirical treatment of 11% in community-acquired IAI and close to 30% for those of nosocomial origin.³⁷ In these studies, the definition of treatment inadequacy has been established based on the theoretical sensitivities and not on the results of the specific antibiogram of each sample, for which this percentage could be even greater. Other weak points of the studies on the adaptation of the empirical antibiotic treatment include the lack of stratification of the severity and the absence of information relating to the time in which the culture and antibiogram were available.³⁸

In special circumstances and with an adequate control of the initial source of infection, it is possible that the persistence of the IAI due to the failure of the initial antibiotic treatment can be solved with an early change of the antibiotic treatment, based on the epidemiological context of the patient, the results of the Gram stain and the presumption of the main causes of infection (recovery of the antibiotic treatment).

The majority of the recommendations or guides on the treatment of IAI coincide on the need for treatment with broad-spectrum antibiotics when there is risk of therapeutic failure, as occurs with the patients with serious infections, those previously treated with antibiotics³⁹ and those with

important co-morbidity.⁴⁰ Although in previous guidelines to the use of β -lactam antibiotics associated with β -lactamase inhibitors (for example: the combinations of 3rd generation cephalosporins and metronidazole) therapeutic failure was associated to infections by *E faecalis*⁴¹ or *Pseudomonas* spp, currently the causes of persistence or relapse of IAI (as opposed to the nosocomial bacteraemias, in which the failures are related to the presence of *Enterococcus* spp resistant to vancomycin, *Candida* spp, or MRSA³²) lie in infections by gram-negative resistant bacteria, *Enterococcus* spp resistant to the β -lactam antibiotics and/or to fungus infections.

Subsequently, the importance of the main pathogens involved in the inadequacy of the empirical antibiotic treatment is discussed.

Enterobacteriae that produce broad-spectrum or AmpC β -lactamases

The extended spectrum β -lactamases (ESBL) derive from the mutations of the TEM and SHV genes and affect the main pathogens of the IAI such as *E coli* and *K pneumoniae*. They inactivate the cephalosporins, amoxycillin-clavulanic acid, and, to some degree, piperacillin-tazobactam, sufficiently, however, to disqualify this combination for the empirical antibiotic treatment of IAI with the risk of being produced by enterobacteriae that produce ESBL. Furthermore, the ESBL disable aztreonam, a monobactam antibiotic used in the antibiotic combinations in patients allergic to β -lactam antibiotics.⁴² Some aminoglycosides (amikacin), carbapenem antibiotics, and tigecycline are active against enterobacteriae that produce ESBL.

The prevalence of type AmpC β -lactamases increases after exposition to antibiotics such as amoxycillin, cephalosporins, and ureidopenicillins, and they affect species like *Enterobacter* spp, *Serratia* spp, *Citrobacter* spp, *Morganella morganii*, and *P aeruginosa*. They confer resistance to the β -lactam antibiotics associated with β -lactamase inhibitors and to the 3rd generation cephalosporins, while cefepime, aminoglycosides (above all amikacin), carbapenems, and tigecycline maintain their activity.

Multi-centred studies have documented a constant increase in the participation of ESBL producing enterobacteriae in IAI. Therefore, the frequency of isolations of *E coli* and *Klebsiella* spp in IAI (community-acquired and nosocomial) has gone from 7% and 13% in 2002 to 12% and 18% in 2005, respectively.^{8,43}

Table 1 – Evaluation of the severity of the intra-abdominal infection

Mild-moderate intra-abdominal infection	Severe intra-abdominal infection
SIRS ^a with venous lactate ≤ 2 mmol/L ^b	Presence of 4 SIRS criteria or SIRS with failure of an organ (serious sepsis), low blood pressure that requires the use of vasoactive drugs (septic shock) or venous lactate > 2 mmol/L
^a SIRS: systemic inflammatory response syndrome, characterised by the presence of 2 or more of the following criteria: fever $> 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$, heart rate > 90 bpm, respiratory rate > 20 breaths per minute, leukocyte count $> 12\,000$ L/mm ³ or < 4000 L/mm ³ or $> 10\%$ of band neutrophils. ^b The determination of lactate is not indispensable if there are no other criteria of severity. The APACHE classification can also be utilised to classify the IAI in mild-moderate (APACHE < 15) or severe (APACHE ≥ 15).	

Table 2 – Factors of risk of poor evolution in the intra-abdominal infection

Related to the inadequacy of the antibiotic treatment	Risk of infection by ESBL-producing enterobacteriae, <i>Pseudomonas</i> spp, <i>Enterococcus</i> spp, or <i>Candida</i> spp (see Table 3 and 4 and Figure 1)
In relation to the severity of the infection	Septic shock
In relation to the existence of co-morbidity	Immunosuppression Malnutrition Diabetes Chronic renal failure COPD Liver cirrhosis
In relation to age	>65 years old
In relation to the type of intra-abdominal infection	Faecal peritonitis or with a difficult control of focus

However, these data represent the average of a very uneven prevalence by continents. Thus for example, a frequency of *E coli* has been observed with ESBL in 2004 of 6%, 3%, 12%, and 20% for Europe, United States, Latin America, and Asia, respectively.⁸⁻¹⁰ In Europe, the highest frequency is found in the southern and eastern countries.⁴⁴ In Spain, the frequency of ESBL is around 6%, 8%, and 5% for *E coli*, *Klebsiella* spp, and *Enterobacter* spp, respectively.⁴⁵

If, until recently, the ESBL positive enterobacteriae, particularly by *Klebsiella* spp SHV and TEM type β -lactamase producers, were observed in nosocomial infections, an increase of infections from a community-acquired origin has recently been documented (above all in southern countries and those of eastern Europe) produced by *E. coli* with expression of CTX-M type β -lactamases,^{44,46,47} due to the transmission of mobile gene elements (plasmids) that codify the resistances.⁴⁸ If the therapeutic arsenal that is currently available for the empirical treatment of IAI caused by ESBL producing enterobacteriae is already limited, data exists on the appearance of carbapenemases that can compromise the utility of the carbapenems in the future.^{49,50}

The increase of the enterobacteriae capable of expressing ESBL in infections from the community-acquired, complicates even more the design of effective antibiotic treatment protocols for IAI. The prevalence of the illness and the scarce therapeutic arsenal threatened by the expression of new elements of resistance related to the extensive use of broad-spectrum antibiotics,⁵⁰ makes it necessary to identify those patients that present factors of risk of IAI produced by resistant enterobacteriae and that can be the cause of the inadequacy of the empirical antibiotic treatment and therapeutic failure. Most of the tests of these factors of risk stem from studies carried out in patients with bacteraemia,⁵¹⁻⁵⁴ serious urinary infections,⁵⁵ infection of the surgical wound⁵⁶ and specific studies of pathogens resistant to antibiotic treatment in IAI.⁵⁷ Among the factors of risk most frequently identified is previous antibiotic treatment. In this respect, a fast enteric colonization by bacteria resistant to the antibiotic received has been observed in patients being treated with 3rd generation cephalosporins or piperacillin-tazobactam, either during treatment (piperacillin-tazobactam group) or even 15 days

after finishing treatment (ceftazidime group).⁵⁸ These facts reinforce the concept that the enteric colonization by resistant pathogens can precede IAI and be the cause of inadequacy of the empirical antibiotic treatment.⁵⁹ In Table 3 the risk factors of colonization by ESBL-producing enterobacteriae are shown.

The emergency of resistant enterobacteriae adds an additional factor of severity to the antibiotic treatment of IAI. Retrospective studies have shown an increase in mortality of those patients with bacteraemia from an abdominal source of infection, in which gram-negative bacilli grew, that were resistant to the empirical treatment.⁶⁰ Likewise, studies on patients admitted to the ICU have shown that inadequate antibiotic treatment was more frequent in the cases of nosocomial infection after community-acquired infection (45% of inadequate treatments), with a mortality rate of 42%. It must be emphasised that a high percentage of inadequate treatments were related to the presence of resistant gram-negative bacilli (25% of cases).³⁰ Along the same lines, a greater mortality rate has been observed in patients in critical conditions infected by *E coli* and *Klebsiella* spp resistant to the usual antibiotic treatment.⁶¹

The increase of the resistance of the species of enterobacteriae⁸⁻¹⁰ to β -lactam antibiotics (especially to AmpC or ESBL type β -lactamases in *E coli* and *K pneumoniae*, and *Enterobacter* spp) should warn physicians when treating those patients that do not follow the expected evolution or that develop a severe infection.¹ Thus, it has been documented that the therapeutic failures observed in serious IAI in patients that were being treated with a combination of amoxycillin-clavulanic acid, were related to enterobacteriae such as *Enterobacter* spp, *Morganella* spp, or *Klebsiella* spp.⁶² In this sense, a rate of resistance to amoxycillin-clavulanic acid has been detected for *E coli* of peritoneal origin of up to 25%.⁶³ Given the increment of infections by β -lactamase producer bacteriae, it is precise to identify those ESBL infection risk patients. Case-control studies have shown a greater incidence of infections

¹Infection that includes ≥ 2 SIRS criteria with low blood pressure, oliguria, or septic shock.

Table 3 – Infection risk factors by ESBL-producing enterobacteriae

Healthcare environment	Hospital stay (>15 days) Coming from a public health centre
Co-morbidity/base disease	Renal transplant-chronic renal failure Advanced liver disease Diabetes mellitus Recurrent urinary infection Biliary obstruction Treatment with corticosteroids
Procedures	Invasive (nasogastric intubation, therapeutic endoscopy)
Prior antibiotic treatment (during the last 3 months)	3rd generation cephalosporins Aminoglycosides Quinolones Carbapenems β -lactams + β -lactamase inhibitor

by ESBL in patients previously treated with aminoglycoside antibiotics and quinolones, and those with a hospital stay longer than 15 days.⁵¹

Under these circumstances, the treatment with carbapenems (imipenem, meropenem, or ertapenem) could be the safest option.³⁰ However, the indiscriminate use of these could increase the resistance of *P. aeruginosa*^{64,65} or it could also induce infections by ESBL producing bacteria.⁵² As a result, other families of antibiotics must be used, such as the glycolcyclines (tigecycline) with different mechanisms of action and resistances, that allow for the diversification of the empirical antibiotic treatment of IAI.^{66,67}

Enterococcus spp

The main species of enterococci that participate in IAI are *E. faecalis* (80%) and less frequently, *E. faecium*.⁶⁸ Experimental studies on the pathophysiology of IAI have shown that *Enterococcus* spp, as opposed to the enterobacteriae and the anaerobic microorganisms, seems to act on a "second level."⁶⁹ In contrast with *S. aureus* or *Streptococcus pyogenes*, *Enterococcus* spp does not secrete exo-toxins nor does it produce superantigens. However, it has been observed that in certain circumstances it may have its own pathogenic capacity. The cell surface products that favour the adhesion to the heart valves and to the urinary epithelium, and a group of serine-proteins, may increase the virulence of this bacteria.⁷⁰ Furthermore, given their natural resistance to many antibiotics, they can be selected and proliferate in weakened patients or those that receive solid organ transplants.⁷¹ This characteristic could be the cause of the apparition of super-infections in patients with IAI that have received antibiotic treatment with a deficient control of the source of the infection. Therefore, a greater frequency has been observed of the isolation of *Enterococcus* spp in IAI of nosocomial origin⁷ in comparison with the community-acquired form.³ Furthermore, the enterococcal infection is the cause of therapeutic failure in the form of an incisional infection or of an organ or space, after the surgical treatment

of IAI with a source of infection in the colon, above all when the initial empirical antibiotic treatment is not active against *Enterococcus* spp (for example: cefotaxime with metronidazole).⁴¹

Randomised studies, where therapeutic guidelines with different activity against the enterococci have been compared, have shown different results. In patients with moderately severe IAI, positive cultures for enterococci and treatment with antibiotics with/and without enterococcal activity, a clinical rate of response and similar microbiologic eradication have been observed.^{72,73} This paradoxical effect, could be due to the fact that the antibacterial action of the antibiotic on the main pathogens of IAI would also complicate the growth of other less sensitive pathogens such as the enterococci in patients with an adequate immune system.⁷⁴ Other studies, on the other hand, have shown a smaller clinical response in those patients with positive cultures for enterococci and that did not receive specific treatment (63.5% compared to 88.9% in the group of ertapenem and piperacillin-tazobactam, respectively).⁷⁵ In studies comparing antibiotics with limited enterococcal activity, a high incidence of gram-positive cocci was observed related to therapeutic failure.⁷⁶ In the area of antibiotic prophylaxis, although based on different pathophysiological, a predominance of gram-positive cocci has been seen in the postoperative infection of the colon with the employment of antibiotics without enterococcal activity.⁷⁷ While waiting for new studies and given the worst prognosis of patients with IAI where enterococci have been isolated,¹¹ the antibiotic treatment active against *Enterococcus* spp should be administered to patients with the factors of risk mentioned in Table 4.

In severe IAI, with the consolidation of treatment using piperacillin-tazobactam and other β -lactam antibiotics (that provide good cover for *E. faecalis*), the role of *E. faecium* as the pathogen implied in the therapeutic failure is now even more relevant. *E. faecium* expresses an intrinsic resistance to antibiotics such as ampicillin, carbapenems, and quinolones.⁷⁸

Only vancomycin, linezolid, tigecycline, and daptomycin are active against *E. faecium*. When treating a mixed infection using mono-therapy, only tigecycline stays active against the majority of *E. faecium*.^{79,80} These antibiotics are also effective in infections produced by vancomycin-resistant *Enterococcus* spp that are not frequent yet in our area¹¹.

Candida spp

In practice, the isolation of *Candida* spp in the peritoneum (positive culture in a cavity or sterile organ) should be considered a severe candidiasis, although it is not yet clear if its presence in a peritonitis secondary to gastrointestinal perforation constitutes a contamination or an infection and, therefore, needing antifungal treatment. *Candida albicans* is the most frequently isolated species (63%), followed by *C. Parapsilosis* (17%),⁸¹ *C. tropicalis* (17%), *C. glabrata*, and *C. krusei* (the last 2 less than 10%).⁸²

Because of its special pathogenic capacity and condition of opportunistic yeast, the participation and causality of *Candida* spp in the IAI has been extensively debated. *Candida* spp colonizes surgical patients with a high frequency (72%)⁸³ and has been found in 3%–8% of IAI, more frequently in cultures of IAI of nosocomial origin.^{3,6,7,84} *Candida* spp is the fifth most-frequently isolated pathogen in the ICU⁸⁵ and it has been identified as a causal agent of infection of surgical wounds with a frequency of 7%, lower only to that produced by coagulase-negative *Staphylococcus* and *Enterococcus* spp.⁸⁶ Furthermore, *Candida* spp has been detected in postoperative intra-abdominal abscesses (10% of the isolations),⁸⁷ showing a greater difficulty in the control of the source of infection.⁸⁸ Studies in the ICU have documented an incidence of candida infection of 5.8%,⁸⁴ and a greater mortality in patients that suffer a fungal infection acquired in the hospital.⁸⁹ Furthermore, a relationship has been observed between mortality and the colonization-infection by *Candida* spp (for example: twenty-eight percent in the unifocal colonization, 51% in the multifocal, and 58% in the demonstrated candida infection).⁸⁴

Observational prospective studies have shown the importance and severity of the peritoneal candidiasis. In

patients with candidaemia, the initial focus was peritoneal in 17% of the cases,⁸² of them, 24% presented gastrointestinal perforation, and 11% were being treated for a severe pancreatitis.

Case-control studies have identified a good useful number of risk factors that are useful to detect in patients with IAI with a relevant presence of *Candida* spp, and therefore, are indicated to receive empirical antifungal treatment. Among the factors most often implicated are the prolonged antibiotic treatment, the difficulty to control the focus of the IAI and its nosocomial acquisition.^{6,57,81,84,85} Experimental studies have shown that the administration of antibiotics that are active against anaerobic microorganisms (piperacillin-tazobactam, metronidazole, and clindamycin) promotes intestinal colonization by *Candida* spp.⁹⁰

A relationship has been observed between the type and control of the focus of the IAI and the mortality rate of patients infected by *Candida* spp. A high percentage of therapeutic failure related to the gastroduodenal focus (above all in postoperative nosocomial IAI) has been documented and the presence of peritoneal *Candida* not covered by the initial empirical antibiotic treatment.^{57,89} This effect could be due to the presence of *Candida* in the stomach of the patient submitted to gastric surgery and that he/she presents an anastomotic dehiscence with a focus that is difficult to control.

Recent observational studies have designed an easy-to-use and useful scoring system to determine the proper empirical anti-fungal treatment in patients with serious sepsis.⁸⁴ A score of ≥ 3 points, obtained in a formula that combines total intravenous nutrition, serious sepsis, surgery when admitted to the ICU and multifocal colonization by *Candida* spp, has a sensitivity of 81% in the detection of patients with confirmed serious candidiasis that can benefit from early empirical anti-fungal treatment. Another factor associated to the poor prognosis of patients with serious candidiasis is the delay of the start of anti-fungal treatment, given that in most cases it is carried out depending on the growth of *Candida* in the cultures taken, or as therapeutic recovery in a patient that does not evolve satisfactorily.^{82,89}

Table 4 – Indications for antibiotic treatment against *Enterococcus* spp and/or *Pseudomonas aeruginosa* in the intra-abdominal infection

<i>Enterococcus</i> spp	<i>Pseudomonas aeruginosa</i>
Immunosuppressed patients/receivers of a solid organ transplant	Nosocomial intra-abdominal infection and prior antibiotic treatment
Recovery treatment of the intra-abdominal infection (above all in patients that have received treatment with cephalosporins)	Neutropaenia
Patients with valvular heart disease or other factors of risk of endocarditis	Source of infection with biliary-pancreatic origin. History of ERCP/DRAINAGE of the biliary tract
Severe intra-abdominal infection with a colonic or postoperative origin	

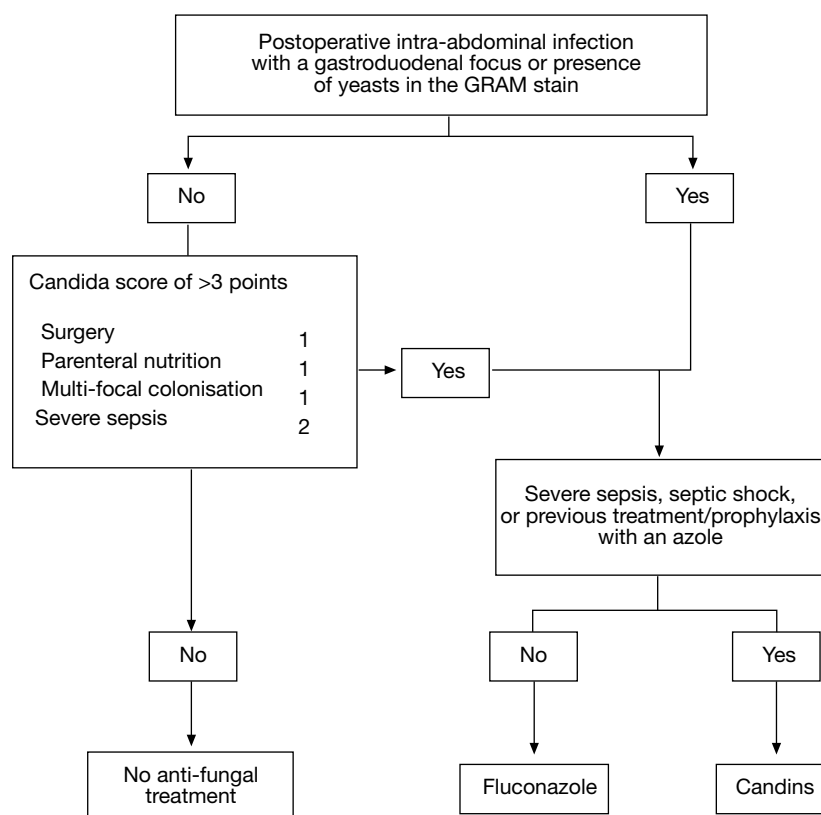


Figure 1 – Decision tree for the empirical anti-fungal treatment in intra-abdominal infections.

In spite of these tests, the lack of randomised studies has impeded the consolidation of empirical anti-fungal treatment in patients of risk with IAI. However, there are guides where empirical anti-fungal treatment is recommended in patients with IAI where forms that are compatible with yeasts are found in the Gram stain of the peritoneal liquid.⁹¹ The availability of mildly toxic drugs (azoles and echinocandins) and the possibility to suspend treatment if the culture does not confirm the candida infection, justifies early empirical anti-fungal treatment without the necessary compliance of the strict criteria of an invasive infection⁹² (Figure 1).

The majority of *C. albicans* are sensitive to fluconazole, however, prophylaxis or previous anti-fungal treatment may determine the presence of species of resistant *Candida* (*C. krusei*, *C. glabrata*), and lead to therapeutic failure from inadequate treatment.⁹³

Pseudomonas aeruginosa

P. aeruginosa is a gram-negative bacteria that does not ferment carbohydrates and grows in aerobic mediums. This bacteria has been implicated in processes such as bacteraemias, pneumonia, osteo-articular infections, urinary infections, and serious infections of soft tissues (above all in burn patients).⁹⁴ It is usually nosocomial and is more frequent in patients with

a low immune response capacity or those undergoing invasive treatments such as peritoneal dialysis for primary peritonitis. Among the most prominent factors of risk of bacteraemia by *P. aeruginosa*, the nosocomial acquisition has been identified along with a history of invasive procedures in the last 72 hours, immunosuppression, neutropaenia, and hospital stays longer than 30 days⁹⁵ (Table 4).

The antibiotic treatment of infections where *P. aeruginosa* is involved may be a challenge during the next few years. During the 1990's, treatment was ensured using 3rd generation cephalosporins, aminoglycosides, ureidopenicillins, and carbapenems; however, the appearance and transmission of various mechanisms of resistance have greatly decreased the antibiotics available that are useful in these cases. This warns about the need, in the first place, to adapt the treatment against *P. aeruginosa* in a selective manner to avoid over-treating and the indiscriminate use of antibiotics, effective until now, lead to the loss of activity and to induce resistances; and in second place, the need of greater investment in the development of new active molecules that are well tolerated against resistant species.

P. aeruginosa has also been identified in the peritoneal cultures of patients with IAI; however, the coverage of this pathogen should be selective. *P. aeruginosa* is the third most

prevalent gram-negative bacillus (9%–13%), but it remains far from the prevalence of *E. coli*. Its importance is anecdotal in community-acquired infections (3%)⁴ and more prominent in nosocomial infections.^{6,7,11} The severity of the patient also influences the presence of this microorganism. In a series in which 29.3% of the hospitalised patients suffered from IAI, it was observed that *P. aeruginosa* represented 5.9% of the bacteria isolated in the cases of septic shock admitted to the ICU.¹³ These data indicate that patients with IAI meeting septic shock criteria should receive specific anti-pseudomonic treatment. Observational studies have shown that the sources of infection that are most frequently associated to serious infections by *P. aeruginosa* (bacteraemia) are those of biliary-pancreatic (including those that require biliary drainage), pulmonary (above all in the environment of the ICU), urinary and soft tissue origins. A primary peritoneal focus has only been documented in 4% of bacteraemias by this microorganism.⁹⁵ It is not infrequent to observe that patients admitted to the ICU with IAI present a co-infection with a pulmonary focus. In these cases, the persistence or relapse of the septic process will also require specific treatment against *P. aeruginosa*.

Another risk factor of colonization-infection by *P. aeruginosa* in the severe patient is previous antibiotic treatment. A relationship has been observed between this fact and treatment during the last 12 months with 3rd generation cephalosporins, quinolones, and imipenems.⁹⁶

The decision to employ active treatment against *P. aeruginosa* should take into account the severity and origin of the IAI. Studies in patients with moderately severe community-acquired IAI (APACHE average of 6), in which the effect of imipenem has been compared against tigecycline (that is not active against this bacteria), did not show differences in the rate of clinical and microbiological recuperation in the group of patients where *P. aeruginosa*⁶⁶ was isolated. However, in studies where patients with postoperative IAI were included (nosocomial origin and more serious), the group with specific treatment against *P. aeruginosa* (piperacillin-tazobactam) presented a rate of clinical recuperation slightly greater than the group that received treatment without antipseudomonic activity (ertapenem), 88.5% compared with 73.1%, respectively.⁷³ Table 4 shows the primary indications for active antibiotic treatment against *P. aeruginosa* in IAI.

Factors of risk of the host: age and co-morbidity

The effects that IAI produces on the host depend on the pathogenesis of the infection (fundamentally primary focus and responsible pathogens), on the prior state of the patient and on his/her capacity to respond to the infection.

The age of the patient and his/her co-morbidity, that have been shown as factors of risk of poor evolution in prior analysis, have been validated in extensive sample studies and they are part of, currently, the two severity scoring systems most employed in the stratification of patients in studies of IAI: the APACHE II and the Mannheim Peritonitis Index (MPI). The 2 scores have been correlated satisfactorily with the mortality observed,^{97,98} without revealing differences in their predictive capacity.⁹⁹

Age

Studies by Wachta et al, concerning the MPI, have shown that the mortality rate of patients was significantly greater for the age range above 50-years-old (from here, ages older than 50 years already score on the MPI).⁹⁸ The APACHE II also gives larger scores for patients older than 65 years.

Age has also been related as a risk factor of infection by pathogens resistant to antibiotic treatment and consequently, to a worse prognosis. Therefore, a relationship has been observed between age over 60 years and colonization⁵⁹ or infection by ESBL,⁵⁵ infection by *Pseudomonas* spp⁹⁶ and infection by enterococci.⁶⁸

Another factor to keep in mind is the prevalence of serious IAI by age ranges. There is a peak of high incidence between 70 and 80 years, reaching 17% in people older than 80.¹⁰⁰ In spite of the fact that recent studies in patients with IAI have shown a higher mortality rate from the range of 70-years-old, the board of this document considers ages over 65 years as a factor of risk, above all in the elderly considered to be "fragile."

Co-morbidity

Immunosuppression or immunodeficiency. Patients that receive organs or undergo chemotherapy treatment and/or treatment with corticosteroids in an active manner, present a greater risk of suffering infections by multi-resistant gram-positive cocci and *P. aeruginosa*.¹⁰¹

Malnutrition. The majority of nutritional appraisal indexes include biochemical parameters (albumin) that are difficult to obtain in the situation of the patient suffering a serious IAI. Therefore, the application of the subjective appraisal of the nutritious state is advised (Subjective Global Assessment, SGA) of easier application in urgent situations. The SGA includes a history of caloric consumption and the ponderated loss (loss of 10% in the last 6 months), the state of the fat compartment and the current metabolic stress. This exploration serves to classify the patient as well nourished, moderately nourished or poorly nourished. Therefore, the malnutrition risk factor would be applied in those patients with moderate or severe malnutrition according to the SGA.

Other factors. Liver cirrhosis, diabetes mellitus, chronic renal failure, heart failure, severe COPD, and active cancer are risk factors of therapeutic failure. The cause of this association is multi-factorial and they share a greater predisposition to infection by resistant pathogens, a high frequency of previous antibiotic treatments and a state of immunosuppression from coadjuvant treatments and malnutrition.¹¹

Factors related to the inefficient control of the source of infection

The control of the focus of the IAI consists of the elimination of the source of infection and the contention of the contamination and decrease of the inoculum, with the maximum possible functional and anatomical restoration. Although, in general, this type of control has been associated to surgery, it can be carried out adequately by means of percutaneous drainage, guided by imaging techniques. The intervention type will depend on the cause of the intra-abdominal sepsis, the local conditions of the peritoneal cavity and the state of the patient.

When dealing with a diffuse peritonitis and an established septic syndrome (serious systemic repercussion), the best option is to practice an abbreviated laparotomy to achieve an adequate drainage of the septic focus, avoiding surgical interventions, such as new intestinal anastomoses, that prolong the intervention and compromise the postoperative evolution of the patient. This procedure allows for the elimination of most of the sources of contamination with the least possible additional stress for the patient, the main objective of this stage of the surgical treatment. Once the severe IAI is solved, other definitive treatments can be considered.

In these recommendations, it is considered that the inadequate control of the focus is a factor of additional severity of the IAI and it is associated with a worse evolution. Thus, for example, faecal peritonitis has been associated to a worse prognosis and has a higher score in the Mannheim peritonitis index. At this location, the inoculum can affect the effectiveness of the antibiotic treatment used, increasing the values of minimum inhibitory concentration (MIC) for certain beta-lactam antibiotics (3rd generation cephalosporins). Furthermore, the persistence of the bacterial inoculum can favour the selection of resistant pathogens and cause a recurring persistence of the IAI.

Concepts of the antibiotic treatment

Indications of antibiotic treatment in the intra-abdominal infection

The American Surgical Infection Society (SIS-A) identifies those infections in which antibiotic treatment is not justified aside from for perioperative prophylaxis.¹⁰² Table 5 shows that principle surgical processes in which the patient does not need conventional antibiotic treatment aside from antibiotic prophylaxis, depending on the infection type and, above all, on the control of the primary source of infection (early and effective intervention).

Precociousness of the antibiotic treatment

The antibiotic treatment is more effective when, along with the adaptation to the sensitivity of the pathogens of the IAI, it

is initiated in a premature manner. Cohort studies in patients with severe sepsis have shown that for each hour that the initiation of the adequate antibiotic treatment is delayed, the mortality rate increases by 7.6%.¹³ Therefore, the early initiation of antibiotic treatment for severe infections^{12,35} can improve the prognosis of patients with IAI.

Duration of the antibiotic treatment

The normalization of the leukocyte count, apyrexia, and the recovery of intestinal functioning, have been the parameters classically used to decide when to terminate the antibiotic treatment of IAI. In spite of the knowledge of these recommendations, the average duration of the antibiotic treatment in patients that present good evolution usually exceeds 7 days.¹⁰³ Furthermore, classical studies have shown that the biological and clinical parameters present a limited negative predictive value (clinical recuperation in absence of fever or leukocytosis).¹⁰⁴ There is evidence of the possible response of residual inoculum to a shorter antibiotic treatment in patients with an appropriate immune response and after an adequate control of the focus. Under these favourable circumstances, the extension of the antibiotic treatment may only "treat" the inflammation, and not the infection, aside from favouring the selection of resistant pathogens. On the other hand, it is probable that in the patient that does not respond, the extension of the antibiotic treatment does not avoid therapeutic failure.

Retrospective studies have shown that patients with IAI that received treatment during 5 days only presented an incidence of postoperative infection of 5%, which is not very different than that observed in previous series. However, the culture of "short" treatments has not been consolidated and the majority of surgeons consider that 7 days is the minimum duration of treatment that patients with IAI should receive.¹⁰⁵

The Shein group studied the optimum duration of antibiotic treatment in a prospective manner, establishing strict guidelines depending on the type of IAI. The patients with severe IAI received antibiotics during a maximum of 5 days, with or without fever. In the 28 patients that followed these guidelines, only the presence of a sub-hepatic abscess and three wound infections¹⁰⁶ were observed. Antibiotic

Table 5 – Recommendations on the duration of the antibiotic treatment in the intra-abdominal infection

24 hours

- Intestinal wound by penetrating trauma of <12 h of evolution
- Gastroduodenal or proximal jejunal perforation, in absence of antacid treatment or chemotherapy, of less than 24 h of evolution
- Appendicitis or cholecystitis without signs of gangrene, perforation or abscess with effective and premature intervention

3 days

- Mild-moderate infection, without factors of risk of poor evolution and adequate control of focus

5 days

- Severe Infection in patients without septic shock, adequate control of focus, recovery of intestinal function and decrease of the CRP by ≥50% regarding the values of the day the focus was controlled

treatment with a fixed duration would make sense if it could be demonstrated that therapeutic failure is avoidable in spite of the extension of treatment for longer than 5 days. In this respect, randomised studies in patients with moderately severe IAI, in which the efficacy of the treatment during 3 or 5 days has been compared, have not shown differences in the rate of clinical recovery.¹⁰⁷

Recent studies have shown the utility of the biological markers in the evaluation of the response to the antibiotic treatment. It has been observed that the patients in whom the suspension of the antibiotic was carried out depending on the concentration of the CRP, had a shorter course of treatment than those in whom the classical criteria of recuperation was applied.¹⁰⁸ It is reasonable to consider that in mild to moderate IAI, in the immunocompetent patient with an adequate control of the focus, the antibiotic treatment that lasts 3 days is sufficient. In any another situation, antibiotic treatment can be discontinued on the 5th day in stable patients, with recovered intestinal functioning and with a notable decrease of the inflammatory response (decrease of more than 50% of the CRP values around 48 hours after controlling the focus) (Table 5).

To conclude, if the surgeon believes in the new tendency of using the minimum effective treatment and he/she carries

out an adequate control of the focus, the possibility of super-infections by selected resistant pathogens will diminish and the adverse effects of the prolonged antibiotic treatment will be reduced¹⁰⁹ (Table 7).

Useful parameters of pharmacokinetics/pharmacodynamics

The most prominent compartmental changes during severe sepsis are the obtention of energy by means of the increase of lipolysis and proteolysis, as well as the hypoalbuminaemia and expansion of extracellular water.¹¹⁰ These changes can influence the pharmacokinetic and pharmacodynamic parameters of the antibiotics administered. Therefore, the effectiveness of hydrophilic antibiotics (aminoglycosides, glycopeptides) can be limited in the serious patient with the increase of extracellular water.¹¹¹ However, antibiotics like tigecycline or linezolid with a higher volume of distribution (more than 10 L/kg and 0.7 L/kg, respectively) are hardly modified by the expansion of the extracellular volume. The antibiotics with a high protein fixation (ertapenem) can also have their half-life modified and they may require a greater frequency of administration in those situations of severity that are accompanied by extreme hypoalbuminaemia or in obese patients.¹¹²

Table 6 – Recommendations on the duration of the antibiotic treatment in the intra-abdominal infection

ORIGIN	COMMUNITY-ACQUIRED		NOSOCOMIAL	
Type	Mild-moderate ^a	Severe ^a	Postoperative (includes therapeutic endoscopy)	Recurring-persistent (tertiary peritonitis)
WITHOUT FACTORS OF RISK OF POOR EVOLUTION ^b	Amoxycillin-clavulanic acid or 3rd generation cephalosporins + metronidazole or Ertapenem	Piperacillin-tazobactam ^c ± Fluconazole ^d Tigecycline ^c ± Fluconazole ^d	Meropenem or imipenem ^c + Linezolid or daptomycin or glycopeptides + Fluconazole or candin ^d or Tigecycline ^{c-e} + Ceftacide or amikacin + Fluconazole or candin ^d	
	Gentamycin or aztreonam + metronidazole			
WITH FACTORS OF RISK OF POOR EVOLUTION ^b	Ertapenem Tigecycline	Imipenem ^c or Meropenem or Tigecycline ^{c-e} ± Fluconazole or candin ^d		

The sign ± indicates the possibility of treatment beyond the different antibiotic guidelines previously cited. The characters in italics correspond to the alternative antibiotic treatment when the patient presents hypersensitivity to β-lactam antibiotics.

^aSeverity of the IAI (see Table 1).

^bFactors of risk of poor evolution (see Table 2).

^cIn patients with risk of infection by *P. aeruginosa* or in those that present septic shock a specific anti-pseudomonic drug must be added such as amikacin, ceftazidime, or cefepime. The administration of colistin should be considered in those patients previously treated with an antibiotic with anti-pseudomonic activity and those that present persistence or relapse of the intra-abdominal infection.

^dIn patients at risk of intra-abdominal infection in which *Candida* spp may be involved, an anti-fungal should be added to the treatment (fluconazole or a candin). The candins are indicated in those patients that present severe sepsis or septic shock and in those that have previously received fluconazole.

^eGuideline of choice in patients allergic to β-lactam antibiotics.

Table 7 – Critical points of the antibiotic treatment in the intra-abdominal infection

<ul style="list-style-type: none"> • Premature detection of patients with intra-abdominal infection that are evolving toward a severe infection • Start of the antibiotic processing within the first hour of suspicion or diagnosis of intra-abdominal infection • In case of severe infection, the spectrum of the antibiotic active against enterobacteriae should be as extensive as possible
<ul style="list-style-type: none"> • In patients in shock or that need an important perfusion of liquids, effective antibiotics should be administered with the greatest volume of distribution and an efficacy not only depending on concentration
<ul style="list-style-type: none"> • The findings in surgery can reveal a greater severity of that initially considered based on the clinical data and they may require a change of the empirical antibiotic treatment • The duration of the antibiotic treatment should be adapted to the severity, to the clinical response and to the evolution of the inflammatory response markers • Treatment must be evaluated 72 hours after initiation to recognise any patient that does not show a satisfactory evolution and adapt treatment respectively (see Figure 2)

Empirical antibiotic treatment plan in the intra-abdominal infection

The plan of the empirical antibiotic treatment (Table 6 and 7) takes into account the origin of the IAI, either community-acquired or nosocomial, the severity regarding the SIRS, APACHE and venous lactate parameters (Table 1) and the factors of risk of poor evolution (Table 2). In the nosocomial IAI, the postoperative infection has been differentiated, also including the IAI that is originated after a therapeutic endoscopy, from the persistent or recurring IAI, in which the predominant factor of risk of poor evolution and of therapeutic failure is prior antibiotic treatment.

Community-acquired mild-moderate intra-abdominal infection without factors of risk of poor evolution

In this type of infection few days of antibiotic treatment are needed when the focus is controlled and/or the peritonitis is not faecal. The scarce residual inoculum can be eliminated with the use of amoxycillin-clavulanic acid or the combination of a 3rd generation cephalosporin with metronidazole. Ertapenem (1 g/24 h) is a treatment option for outpatients as it is active in mixed infections and has a long half life (Table 6).

Community-acquired mild-moderate intra-abdominal infection with factors of risk of poor evolution

The patients included in this section have a risk of infection by ESBL and AmpC producing enterobacteriae for which in this situation, ertapenem (1 g/24 h) is considered to be a good therapeutic option (Table 6).

Community-acquired and postoperative severe intra-abdominal infection without factors of risk of poor evolution

In this group of patients the antibiotic guidelines of choice should be active against the main pathogens (enterobacteriae, anaerobials, and gram-positive cocci). Furthermore, it should cover *Enterococcus* spp in the infections originating in the colon and in postoperative infections. The profile of the pathogens involved in the postoperative IAI (that normally

occurs a few days after hospital admission and without intra-hospital antibiotic treatment) does not differ too much from those affected by community-acquired severe IAI. This group may respond to piperacillin-tazobactam for the necessary enterococcal coverage in these more serious patients and/or those with postoperative infections. Ertapenem 1 g/12 h can be an alternative in the cases of IAI with a low risk of enterococcal infection (Table 8).

In patients with a biliary-pancreatic focus or with a recent intervention of the biliary tract (endoscopic retrograde cholangiography), the treatment should be active against *P. aeruginosa*. An anti-pseudomonic betalactam antibiotic can be used (ceftazidime, cefepime, piperacillin-tazobactam, meropenem, or imipenem), associated or not to amikacin or tobramycin. In the postoperative IAI with a gastroduodenal focus or with any other focus, when *Candida* is found in the Gram stain of the intra-abdominal liquid, fluconazole, or a candidin in the most severe cases, should be added (Figure 1).

Community-acquired and postoperative severe intra-abdominal infection with factors of risk of poor evolution

The antibiotic treatment should be active against the main pathogens, enterococci and the beta-lactamase producing enterobacteriae of the AmpC or ESBL type. The use of a carbapenem (meropenem or imipenem) or tigecycline is recommended. In the cases of serious sepsis or septic shock, or if the patient presents risk factors of infection by *P. aeruginosa* (Table 4), associating tigecycline, amikacin, ceftazidime, or cefepime is recommended. In the event that a carbapenem is used, amikacin can be associated.

Patients with IAI with a gastroduodenal focus or if yeasts have been observed in the Gram stain, fluconazole must be administered, and in the cases of established septic shock, a candidin must be administered given that they provide a greater anti-fungal spectrum and a better fungicide activity (Figure 1).

Persistent or recurring intra-abdominal infection (tertiary peritonitis)

Most of these patients present prior administration of antibiotics in the same hospital stay, the control of a repeated focus and the scarce inflammatory response and respective

Table 8 – Dosage of the main antibiotics used in the empirical treatment of the intra-abdominal infection

Antibiotic	IV dose, adult	IV dose, paediatric
Amikacin	15–20 mg/kg/d (1 dose)	15–22 mg/kg/d (1, 2, or 3 doses)
Amoxycillin-clavulanic acid	1–2 g (200 mg clavulanic acid) /6–8 h	100 mg/kg/d (4 doses)
Aztreonam	1–2 g/8 h	100–150 mg/kg/d (3–4 doses)
Cefotaxime	1–2 g/6–8 h	100–150 mg/kg/d (3–4 doses)
Ceftriaxone	1–2 g/12–24 h	50–100 mg/kg/d (1–2 doses)
Colistin	2–3 MU/8 h (in 30 min)	50 000 U/kg/d
Daptomycin	4–6 mg/kg/d	NA
Ertapenem	1 g/12–24 h ^a	NA
Gentamycin	5–7 mg/kg/d (1 dose)	3–7.5 mg/kg/d (1–3 doses)
Imipenem ^b	0.5 g/6–8 h	40–60 mg/kg/d (4 dose)
Linezolid	600 mg/12 h	10 mg/kg/12 h
Meropenem ^c	0.5–1 g/6–8 h	10–20 mg/6–8 h
Metronidazole	250–750 mg/8–12 h	15–25 mg/kg/d (3 dose)
Piperacillin tazobactam	4 g (500 mg tazobactam)/6–8 h	100 mg (12.5 mg tazobactam)/6–8 h
Tigecycline	100 mg at start and 50 mg/12	NA

Anti-fungal treatment	IV dose, adult	IV dose, paediatric
Fluconazole (Azole)	400–800 mg/d	3–12 mg/kg/d
Caspofungin (Candin)	70 mg 1st day and 50 mg/d	50 mg/m ²
Anidulafungin (Candin)	200 mg 1st day and then 100 mg/d	3 mg/kg/1st day and then 1.5 mg/kg

^aThe dosage of ertapenem every 12 hours is indicated in overweight patients and those with severe infections in which the volume of distribution can be raised.

^bImipenem is marketed together with cilastatin, an inhibitor of the renal dihydropeptidase that can produce neurological toxicity (convulsions). In renal failure, the half-life of the cilastatin is extended more than that of imipenem.

^cMeropenem can be administered in bolus, it is not associated with cilastatin and has a slightly milder activity against enterococci with a better anti-pseudomonic activity.

immunosuppression as the principal factors of risk of a poor evolution. Aside from the main pathogens of mixed infections, resistant enterobacteriae (ESBL), gram-positive cocci resistant to β -lactam antibiotics (such as *E faecium*), *P aeruginosa*, and *Candida* spp must also be considered.

The recommended combinations are:

1. The association of a carbapenem (meropenem or imipenem) with an active antibiotic against resistant gram-positive cocci (linezolid, daptomycin, or a glycopeptide) and fluconazole or a candidin. For the coverage of gram-positive cocci, the administration of vancomycin can be useful. However, therapeutic failure has been observed in those cases of severe infections by *S aureus* with a CMI of vancomycin $>1 \mu\text{g/mL}$ and when the situation of the patient does not guarantee an $\text{ABC}_{24\text{h}}/\text{CMI}^{\text{J}}$ ratio over 400 with the usual dose, similar to what happens in those patients with an increase of the extracellular volume.¹¹⁴
2. The association of tigecycline (active against resistant grampositive cocci) with amikacin, ceftazidime or cefepime and fluconazole or a candidin. The combined treatment with cefepime or amikacin is also useful to treat some isolated strains of *Enterobacter* spp with a decreased sensitivity to tigecycline.¹¹³

In the case of serious sepsis or septic shock and in patients with risk factors of infection by *P aeruginosa*, one must consider

^J $\text{ABC}_{24\text{h}}/\text{CMI}$: area under the concentration curve of the antibiotic relating to the minimum inhibitory concentration.

the reinforcement of the antipseudomonic coverage. If the patient receives a carbapenem (increment of the resistance to imipenem by *P aeruginosa*), a colistin or amikacin can be added. The choice of the antipseudomonic antibiotic that must be added to tigecycline should be evaluated individually keeping in mind the presence of renal failure (avoid aminoglycosides) and the best pharmacokinetic-pharmacodynamic profile (ceftazidime or cefepime are better than amikacin).

Antibiotic treatment of the intra-abdominal infection in patients with hypersensitivity to betalactam antibiotics (in Table 6, paragraphs in italics)

1. **Community-acquired mild-moderate IAI without factors of risk.** Alternative treatment may consist of gentamycin or aztreonam (crossed sensitivity of less than 1%) with metronidazole.
2. **Community-acquired mild-moderate IAI with factors of risk.** In these patients, tigecycline as a single treatment can be sufficient to cover the patients with risks of IAI by ESBL-producing or AmpC type enterobacteriae.
3. **Community-acquired and postoperative mild-moderate IAI with or without factors of risk.** The β -lactam antibiotics can be substituted by tigecycline associated with amikacin or aztreonam if the patient presents septic shock or is at risk of infection by *P aeruginosa* (Table 4).
4. **Persistent or recurring intra-abdominal infection (tertiary peritonitis).** In these cases, the association of tigecycline with amikacin or colistin is necessary for coverage against *P aeruginosa*.

Recovery of the empirical antibiotic treatment of the intra-abdominal infection

The progressive appearance of resistant pathogens that cause IAI and the shortage of available effective antibiotics requires the systematic and premature evaluation of the empirical antibiotic treatment initiated and in the case of unfavourable clinical evolution, to consider modifying said treatment ("recovery") without waiting for the results of the culture obtained the day of the surgery (Figure 2).

In the health care conditions of the average hospital, the results of the antibiogram are available in around 4-5 days, a period of time that is excessive for the change of the antibiotic treatment to be effective.³ In a multi-centred study in the ICUs of our country, it was observed that in 44% of the cases a change of antibiotics was made during the treatment of the infection. In 62% of the cases, the change was carried out based on the results of the antibiogram, and only in 32% it was related to the poor clinical evolution.²⁹ Observational studies in patients with peritonitis have shown a similar mortality

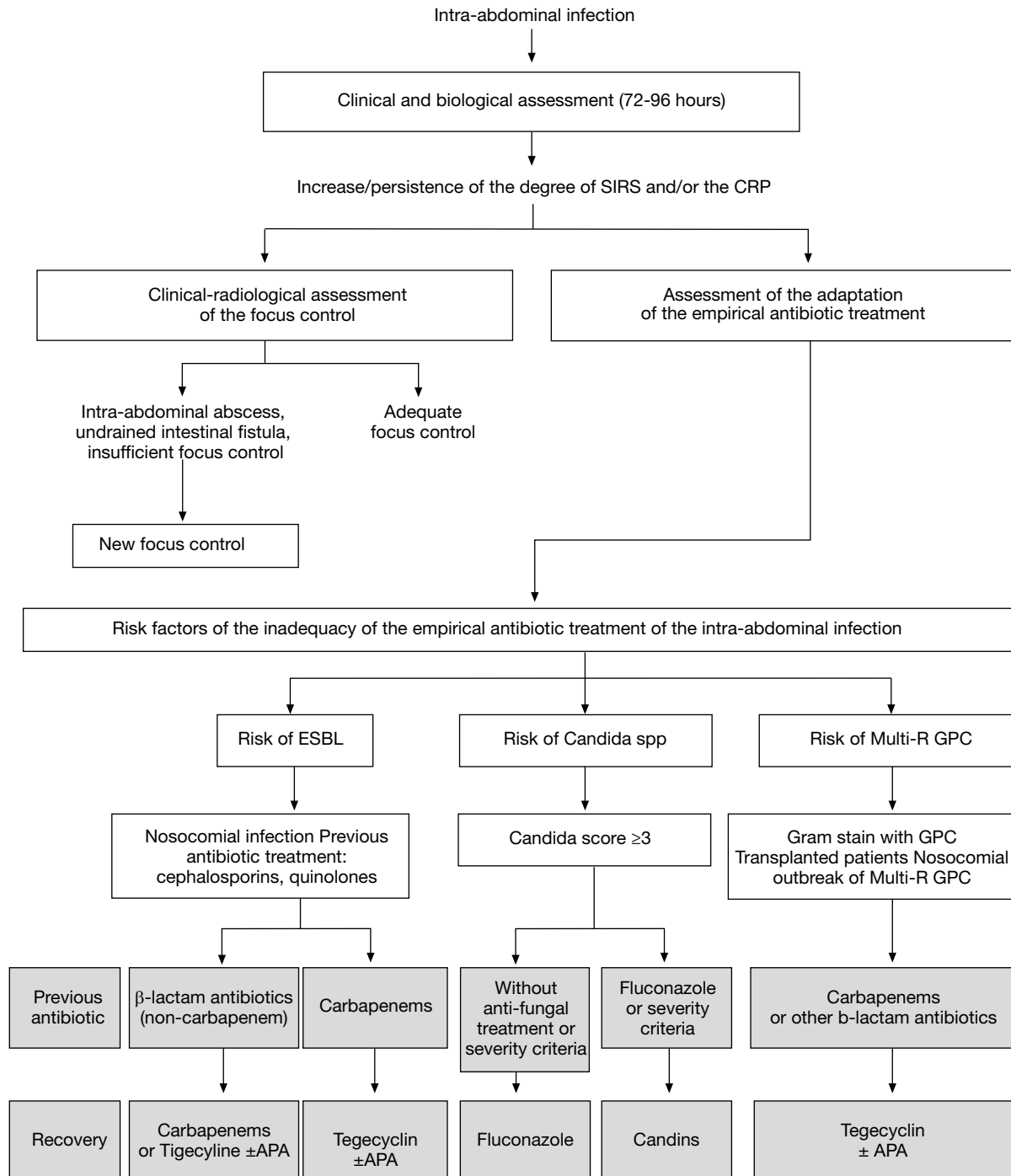


Figure 2 – Decision tree for the recovery empirical antibiotic treatment in intra-abdominal infections APA indicates anti-pseudomonic antibiotic; CRP, C-reactive protein; ESBL, extended spectrum b-lactamases; GPC, gram-positive cocci.

rates in patients who had their antibiotic treatment adapted to the results of the cultures and antibiograms (22% without changes compared to 26% with changes). However, no patients with changed antibiotic treatments in an empirical manner regarding their clinical evolution ("empirical recovery") passed away.⁶³ In spite of these tests, observational studies have shown that only 30% of the intensive doctors would consider changing the antibiotic treatment taking into account the clinical deterioration, and 27% would add an antifungal treatment to the initial treatment.¹¹⁵

Besides the resistance of the enterobacteriae to the broad spectrum β -lactam antibiotics, another cause of possible therapeutic failure is found in the persistence or superinfection by *Candida* in those serious patients that must be admitted to the intensive care unit. Poor evolution, the presence of mixed flora (gram-negative bacilli and gram-positive cocci) in the Gram stain of the intra-abdominal liquid of the primary intervention and the existence of a high *Candida* score, should warn the physician to improve the antibacterial spectrum and add an anti-fungal to the treatment (fluconazole or a candin). If the β -lactam antibiotic previously administered was not a carbapenem, the antibiotic regimen can be substituted by meropenem or imipenem¹¹⁵ adding an anti-fungal if a *Candida* score greater of 3 is reached. Another possible strategy would be to change the treatment to tigecycline with an antibiotic with antipseudomonic activity (aztreonam, amikacin, or colistin) if there is a risk of infection by *P aeruginosa*, reducing the association according to the antibiogram, above all if the employed antibiotic was an aminoglycoside, so that possible nephrotoxicity could be avoided (Figure 2).

Conclusions

To improve the prognosis of patients with severe IAI, the concepts that have shown to be effective for the treatment of severe sepsis must be applied, including early detection and antibiotic treatment. Furthermore, the bacterial inoculum must be controlled and diminished in the most effective manner, depending on the type of IAI and the patient's condition. The application of these basic principles should also be accompanied by the adaptation of the antibiotic treatment depending on the severity and the rate of resistances suspected in the area in which the IAI started. The antibiotic treatment will not be completely adequate if its duration is not taken into account, in order to stop the apparition of new resistances.

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