UPDATE IN INTENSIVE CARE

Antibiotic multiresistance in critical care units

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Abstract
The presence of microorganisms with acquired resistance to multiple antibiotics complicates the management and outcome of critically ill patients. The intensivist, in his/her daily activity, is responsible for the prevention and control of the multiresistance and the challenge of prescribing the appropriate treatment in case of an infection by these microorganisms. We have reviewed the literature regarding the definition, important concepts related to transmission, recommendations on general measures of control in the units and treatment options. We also present data on the situation in our country known primarily through the ENVIN-UCI register. Addressing the multiresistance not only requires training but also teamwork with other specialists and adaptation to the local environment.
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Multirresistencia antibiótica en unidades de críticos

Resumen
La presencia de microorganismos con resistencia adquirida a múltiples antibióticos complica el manejo y la evolución de los pacientes críticos. El intensivista, en su actividad diaria, se enfrenta a este problema desde la responsabilidad de la prevención y control y desde el reto de prescribir el tratamiento antibiótico apropiado ante una posible infección. Se realiza una revisión de la bibliografía en lo concerniente a definición, conceptos importantes relacionados con la transmisión, recomendaciones sobre medidas generales de control en las unidades y opciones de tratamiento. Además se presentan datos epidemiológicos sobre la situación en nuestro país obtenidos, fundamentalmente, a través del ENVIN-UCI. El abordaje de la multirresistencia antibiótica requiere formación adecuada, trabajo en equipo con otros profesionales y conocimiento de la epidemiología local.
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Introduction

Is this article necessary?

Patients in Intensive Care Units (ICUs) are particularly vulnerable to colonization or infection by multiresistant microorganisms (MRMs).[1] Such antibiotic resistance in turn has an impact upon the course of the critical patient and on resource utilization within the Units.[2-5] The appearance and spread of antibiotic resistance is conditioned by two fundamental factors: infection control measures and the selective pressure of the antibiotics used.[6]

As intensivists, we have a direct responsibility in the correct application of these two factors, and specific training in these areas is crucial. As a result, these topics are included in the training programs of the specialty.[7] The existing literature with a good level of evidence for recommending intervention guidelines in the critical patient is limited. A PubMed search using the keywords "antibiotics AND resistance AND intensive care" yielded 2293 references, of which only 51 corresponded to randomized clinical trials (all published in the last 10 years), and which predominantly referred to the duration of treatment or to different antibiotic therapy regimens.

The above considerations thus justify an update to help the intensive care professional to take adequate decisions in relation to strategies for the control and treatment of MRMs. For the correct and effective application of these recommendations, it is necessary to adapt them to the reality of each individual hospital, as determined by the local epidemiological and resources characteristics found in the center. In addition, coordinated collaboration is required with other implicated specialists (preventive care, internists-specialists in infectious diseases, microbiologists and hospital pharmacists).

Definition of multiresistance

What do we mean by MRMs?

Epidemiologically, MRMs are defined as those microorganisms that are resistant to one or more classes of antibiotics.[1] There is no universally accepted definition of multiresistant bacteria that can be applied to all of these microorganisms; rather, the concept has different connotations depending on whether the context is clinical, microbiological or epidemiological. From a general perspective, the definition of multiresistance should include at least two conditions: the existence of resistance to more than one family or group of commonly used antimicrobials, and clinical relevance (i.e., implying or potentially implying difficulties for treatment) and epidemiological relevance of the resistance (possibility of epidemic outbreaks, transmission of the resistance mechanism, etc.). Accepting these conditions, the term "multiresistant microorganism" has been used particularly in reference to classically hospital bacteria that have developed resistance to a range of antimicrobials, and which are able to cause outbreaks, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* spp. (VRE), extended spectrum betalactamase (ESBL) producing enterobacteria, and non-fermenting gramnegative bacilli (GNB) such as *Acinetobacter baumannii* or *Pseudomonas aeruginosa* resistant to different groups of antimicrobials. In addition, the term "multiresistant" is usually also applied to bacteria that are intrinsically or naturally resistant to multiple antimicrobials, such as *Stenotrophomonas maltophilia* or *Clostridium difficile.*[8] More specifically, we speak of multiresistant GNB when the latter are resistant to three or more families of antibiotics to which they are usually sensitive - including betalactams (penicillins and cephalosporins), carbapenems, aminoglycosides and quinolones.[9]

To practical epidemiological effects, a number of antimicrobials have been defined that act as multiresistance markers, and which are different for each microorganism.[10] Table 1 shows the resistance frequencies documented by the ENVIN registry and their variations in recent years.

Repercussion of MRMs for patients and the healthcare system

Are MRMs really important?

Nosocomial infections caused by MRMs are associated with a delay in the start of adequate therapy and with treatment

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Table 1 Resistance markers. Evolution. ENVIN-ICU

	2005	2006	2007	2008	2009
Staphylococcus aureus R methicillin	37.1	42.2	24.4	25.0	27.4
Staphylococcus aureus R vancomycin	0.6	0	0	0	0.8
Staphylococcus epidermidis R methicillin	85.2	83.6	80.9	84.1	87.5
Staphylococcus epidermidis R vancomycin	0	0	0.7	1.9	0
Escherichia coli R ciprofloxacin	32.1	34.4	34.4	32.4	36.9
Escherichia coli R cefotaxime	10.0	13.1	16.8	13.2	14.9
Acinetobacter spp. R imipenem	58.3	54.6	76.4	66.3	85.6
Pseudomonas aeruginosa R amikacin	11.4	13.0	12.9	17.7	9.8
Pseudomonas aeruginosa R ceftazidime	29.0	27.9	27.2	26.3	32.1
Pseudomonas aeruginosa R ciprofloxacin	30.2	33.1	35.2	38.0	40.3
Pseudomonas aeruginosa R imipenem	28.6	36.3	32.0	34.6	41.8
Pseudomonas aeruginosa R piper/tazo	22.4	18.7	18.9	14.5	19.3
Enterococcus spp. R vancomycin	1.0	0	0	0	1.03

failure. As a result, they prolong hospital stay and increase the costs and patient mortality.

Scientific information is available on the implication of MRMs in inadequate empirical antibiotic treatment[11-13] and in the delay in starting adequate therapy - a situation which may double patient mortality.[13] These considerations are valid for the great majority of MRMs, whether grampositive cocci (GPC) or GNB.[14-21]

In most cases, the appearance of MRMs implies patient contact isolation, even when only colonization is involved, with the purpose of avoiding epidemic outbreaks or situations of endemia due to cross-transmission. Such situations of endemia make it necessary to prescribe empirical broad-spectrum treatments[22] which in turn can contribute to generate more resistances and increase the costs. Control policies generate additional costs derived from the material resources needed to implement them.[23,24] Moreover, isolation can cause patients to suffer loneliness, poorer care,[23] more adverse effects[25] and a delay in hospital discharge.[26] All this in turn can lead to high ICU occupancy rates.

A recent report of the European Center for Disease Prevention and Control (ECDC) and the European Medicines Agency (EMEA) entitled: "The bacterial challenge: time to react", describes the human and economical repercussions of what are regarded as the principal MRMs, given their frequency and importance as the cause of bacteremia.[27] Data are analyzed corresponding to the period 2002-2007 and originating from the European Antimicrobial Resistance Surveillance System (EARSS), with participation of the European Union (EU) member states and also Iceland and Norway.

The report concludes that, in general terms, antibiotic resistance in the EU, Iceland and Norway is high; in some cases may be increasing; and that the human and economical consequences are serious. Taking the current tendencies into account, the report considers that an evolution towards greater resistance among GNB is to be expected, particularly enterobacteria resistant to third-generation cephalosporins, and non-fermenting GNB resistant to carbapenems.

Compared with infection caused by a sensitive organism, infection due to a MRM increases the costs by between 5000 and 25,000 €.[28] In the United States, quantification has been made of both the annual extra cost (between 4000 and 5000 million USD) and of direct mortality (19,000 deaths a year) attributable to these microorganisms.[29] The most frequent MRMs are implicated in a prolongation of hospital stay and increased costs.[15,16] There are also other costs that have not been adequately quantified, and which derive from an increase in work burden in the microbiology laboratories, costs associated with educational programs, and the delay in patient return to work. Other repercussions that have not been well evaluated refer to MRM contribution to the scarcity of antibiotics that are active against the main etiological agents; the spread of these microorganisms within the community; and the impact upon the credibility of the healthcare system as a result of media pressures or an increase in lawsuits due to the contagion of nosocomial infections - particularly those caused by MRMs.

Table 2 Percentage isolates of the different species in the total nosocomial infections registered, with the different percentage resistances

	ENVIN (2009)	EPINE	NHSN
P. aeruginosa	12 (2)	10.32 (2)	7.9 (5)
R IMP	41.81	3.53[a]	11.8[a]
R CIP	40.34	11.22[b]	15.9
R piper/tazo	19.3	–	7.9
S. aureus	8.76 (4)	11.1 (3)	14.5 (2)
R oxa	27.4	46.2	49.2
Coagulase-negative staphylococcus	12.43 (1)	9.96 (4)	15.3 (1)
R methi	87.5	–	
A. baumanii	7.53 (5)	4.1	2.7
R IMP	85.6	38.53[a]	30.6[a]
K. pneumoniae	5.08	4.4 (5)	5.8
E. coli	10.66 (3)	15.43 (1)	9.6 (4)
R CIP	36.94	17.23[b]	22.7[b]
E. faecalis	5.45	5.2	3.5
R ampi	2.41		4.1
R van	0		4.7
E. faecium	1.29	2.33	5.6
R ampi			71
R vanco			56.5
Enterococcus spp.	0.8	0.85	
R ampi	0		10.9
R van	0		6.7
Enterococcus			(3)
R ampi		12.59	
R van		0.71	19.7

The order of frequency of the isolates is shown in parentheses. ampi: ampicillin; CIP: ciprofloxacin; IMP: imipenem; oxa: oxacillin; piper/tazo: piperacillin-tazobactam; R: resistant; van: vancomycin.
[a]IMP or mero = meropenem.
[b]Quinolones (non-specified).

Resistance to antibiotics in Spanish ICUs

Is the problem frequent in our setting?

The incidence of MRMs varies both geographically and over time. Such variation is observed not only between countries but also between different units belonging to one same hospital.[30]

The truly important information is the incidence within a given unit and at a given time. Table 2 compares the resistance rates of the main etiological agents, according to publications from different vigilance systems in Spain and the United States.[8,31,32]

It is clear that there are important differences, such as the high prevalence of vancomycin-resistant *Enterococcus*
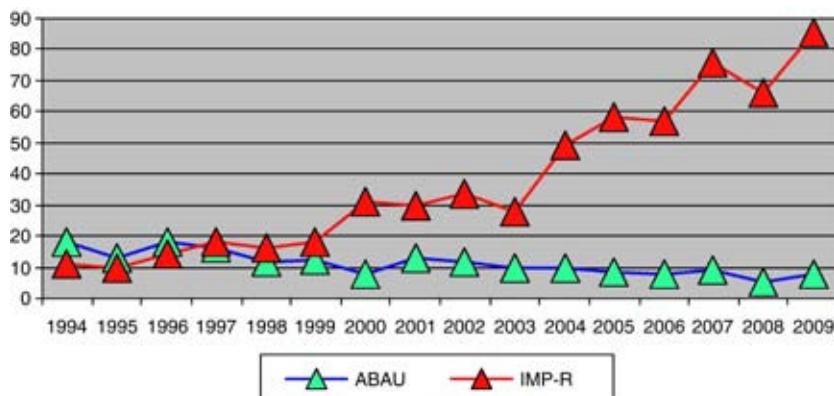
Figure 1 Evolution of the frequency of isolates in ICU infections corresponding to A. baumanii (ABAU), and percentage of resistances to imipenem (IMP-R). ENVIN-ICU.

spp. (VRE) in the United States and the higher incidence of *A. baumannii* in Spain. In Europe.[33,34] differences are also seen between countries in the prevalence of MRSA, which ranges from less than 5% in Sweden to over 90% in turkey. The intermediate figures found in Austria (38.8%) are similar to those recorded in Spain. Specifically in reference to ICUs, the data of the HELICS study show *S aureus* to account for 12.8% of the global isolates in ICU infections, versus 20.4% in Spain.[33] These disparities are repeated in Spain with sometimes important differences between different Autonomous Communities (ENVIN-ICU, data not published), and depend on the methodology used (incidence or prevalence), the referred infections, the study setting (critical care units only, or the entire hospital), and the antibiotic policies used. Whether one cause or the other is involved, the key consideration is the local ecology.

The data of use in daily work are those obtained from incidence studies quantifying the infections related to the exposure to risk factors. In our setting the ideal instrument is the ENVIN-ICU, which meets the criteria and offers global data on occasion of the annual Congress of the SEMICYUC,[35] which moreover can be accessed on the registry website.[9]

Figures 1-3 and table 1 show the evolution of the different resistance markers of the main MRMs in Spain, obtained from the ENVIN-ICU. Based fundamentally on these data, it can be concluded that our problems in multiresistance are the following:
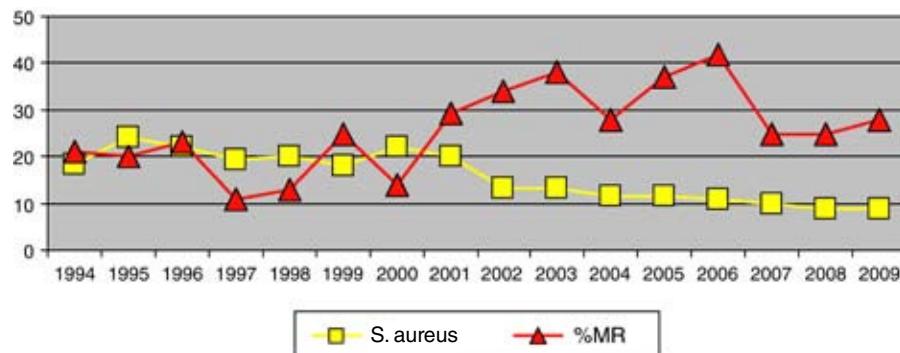
Grampositive organisms

– High incidence of MRSA, though the levels have dropped in recent years.
– The great majority of *S epidermidis* isolates are resistant to oxacillin.
– There have been point reports in ICUs of different countries (including Spain) of the appearance of some *S aureus* and *S epidermidis* strains resistant to linezolid.[36-40] In both cases this situation appears to be related to a local increase in the prescription of linezolid, with posterior clonal spread.

The section corresponding to treatment discusses the management problems posed by the recently observed

AMK: amikacin; CFTZ: ceftazidime; IMP: imipenem; CIPR: ciprofloxacin
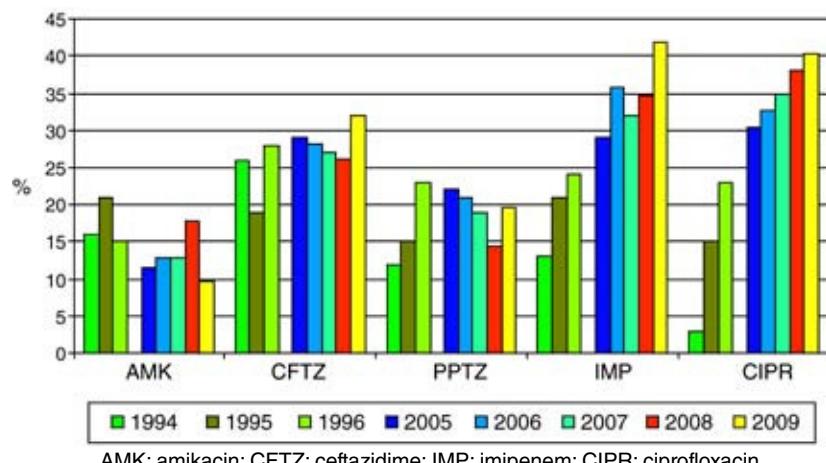
Figure 2 Evolution of resistance markers corresponding to Pseudomonas aeruginosa. ENVIN. AMK: amikacin; CFTZ: ceftazidime; CIPR: ciprofloxacin; IMP: imipenem; PPTZ: piperacillin-tazobactam.

Figure 3 Evolution of the frequency of isolates in ICU infections corresponding to S. aureus and the percentage of MRSA (%MR). ENVIN.

increase in the minimum inhibitory concentration (MIC) of vancomycin for *S aureus*.

Gramnegative organisms

– *A. baumannii*, with high rates and an increase in resistance to carbapenems, added to the already existing resistance to betalactams, quinolones and aminoglycosides. Resistances to colistin are merely anecdotal in the ENVIN registry. The local differences can be important.
– *P. aeruginosa,* with variable but increasing resistances to carbapenems and ciprofloxacin.
– Extended spectrum betalactamase (ESBL) producing gramnegative bacilli (GNB): These data are not prospectively contained in the ENVIN-ICU up to recent dates, though there is abundant information on the situation in Spain. Before the year 2000, mention of ESBL was fundamentally referred to in-hospital outbreaks of *K. pneumoniae*.[41] At present there is an important increase in bacteremias, urinary tract infections and abdominal infections, either of an out-hospital nature or associated to healthcare.[42] *E. coli* is more related to urinary infections in non-hospitalized patients, while *Klebsiella* spp. are preferentially of hospital origin and are related to respiratory infections and the ICU.[43-45]

Some important concepts in MRM transmission

What do we need to know?

Once a given MRM appears in a healthcare center, transmission and persistence of the resistant strain are tied to the existence of vulnerable patients, selective antibiotic pressure, colonization pressure[46,47] (taken to be the percentage of colonized or infected patients), and the impact of adherence to the preventive measures adopted.

Vulnerability to MRMs is greatest among the most critical subjects, with defenses impaired by underlying medical conditions, and with greater intrinsic[31] as well as extrinsic risk factors (intubation, venous catheters, bladder catheters, etc.). To one degree or other, these factors are common to the different MRMs,[48] and are frequent in critically ill patients.

According to different studies, there is a time relationship between a reduction in the pressure of a point antibiotic and the reduction in the incidence of a given MRM - particularly GNB.[1,49-53] Appropriate use, in dose and time, of more reduced spectrum antibiotics has also been associated to a decrease in MRM colonization.[54]

The relationship between colonization pressure and MRM acquisition has been studied particularly in relation to VRE and MRSA.[46,47]

There is extensive epidemiological evidence of the transmission of MRM between patients through contamination of the hands of healthcare personnel, via contact with the patient or the surrounding environment.[55-58]

General recommendations

What should we do?

The strategies for reducing the incidence of MRM infection or colonization must contemplate the following:

1. The development of educational programs to optimize antibiotic use (this being the subject of another article in this same series).
2. Reduction of the duration of exposure to the main risk factors (mechanical ventilation, intravenous and urinary catheterization).
3. Improved epidemiological and microbiological vigilance programs. Such improvement includes the introduction of active vigilance systems to secure the early detection of patients colonized or infected with germs of special relevance. Active vigilance is based on systematic microbiological evaluation at the time of admission, and posteriorly on a regular basis. The periodicity of such evaluation depends on the actual problem found in each unit, and on the capacity of the microbiology services. Perhaps the most widespread strategy is the obtainment of screening samples upon admission, and then with weekly periodicity.
4. Introduction of control measures to reduce cross-transmission within the unit. These measures include both the optimization of hygiene of the hands and

Table 3 Orientations on the qualitative interest of different clinical samples for the investigation of multiresistant pathogens with epidemiological purposes. L. Martinez

Organism	Stools/Rectal	Perineal	Pharynx	Clinical samples	
				Nasal	Others
Methicillin-resistant *Staphylococcus aureus* (MRSA)	+[a]	+++	+++	++++	++[b]
Glycopeptide-resistant *Enterococcus* spp.	++++	++++	(+)	-	++
ESBL-producing enterobacteria	++++	++++	+	-	++
Multiresistant *Acinetobacter baumannii*	++++	++	++++[c]	-	+++[d,e]
Pseudomonas aeruginosa resistant to carbapenems due to the production of metallo-betalactamase (MBL)	+	+++	++++[c]	-	+++[d]

Epidemiological vigilance cultures of antimicrobial-resistant bacteria of nosocomial interest 66. Recommendations of the Spanish Society of Infectious Diseases and Clinical Microbiology.
[a]Does not appear of interest for its systematic study, though some studies do contemplate this application.
[b]Bronchial aspirate in patients subjected to mechanical ventilation (++), chronic ulcers (+++), urine in catheterized patients (++).
[c]Most common: sputum, tracheostomy exudate, etc., instead of pharyngeal samples.
[d]Particularly wound exudate samples (+++).
[e]Perineal sample (++++).

isolation (generally referred to contact) when these microorganisms appear.

The importance of active vigilance is to secure the early identification of patient colonization or infection, in order to:

1. More rapidly implement the control measures needed to minimize spread to other patients. This policy allows drastic reduction of the so-called blind period, i.e., the interval between colonization or infection of the patient, and its identification.
2. Improve adequate antibiotic treatment in relation to the empirical management of infections within the ICU. There is evidence that the adequate empirical antibiotic treatment rate in MRM-induced bacteremias and pneumonias associated to mechanical ventilation increases when the prior colonization state is known.[59-62]

The introduction of molecular techniques with real-time PCR (RT-PCR), or the more economical use of chromogenic culture media, allows rapid identification (between 2-24 hours). This strategy allows the prompt adoption of preventive and decolonizing measures, thereby reducing spread and the infection rates.[63] This approach has been shown to be effective and profitable from the economical perspective, in different endemic situations.[64]

In practical terms and in our country, active vigilance in the ICU of all patients would be justified, regardless of the identification method used. This recommendation is warranted by the majority of both national and international scientific societies.[1,65]

The sampling to be carried out depends on the microorganism we aim to identify. Table 3 provides some indications relating to the qualitative interest of different clinical samples for preparing epidemiological vigilance cultures of antimicrobial-resistant bacteria of nosocomial interest, published by the website of the SEIMC.[66]

To summarize, it is advisable to conduct active vigilance in the ICU, evaluating (with the implicated Departments:

Microbiology, Preventive Medicine, etc.) the problem microorganisms in the Unit and the available resources for defining the periodicity and samples to be collected, with a view to ensuring the fastest possible isolation and adoption of other measures (decolonization in the case of MRSA, etc.).

In the event of suspected infection in a patient in the ICU, we should address the following aspects: possible focus, MRM carrier status of the patient in question and of the patients in the vicinity, with the aim of optimizing empirical treatment and contributing as little as possible to the development of resistances, on the basis of the options detailed below.

Treatment of multiresistant germ infections

Gramnegative bacilli

In this case the therapeutic problems center mainly on the following pathogens: *P. aeruginosa, A. baumannii,* ESBL-producing GNB and *S. maltophilia*.

Pseudomonas aeruginosa
Unfortunately, no new antibiotics have been introduced in clinical practice offering activity against this GNB. In this context we have only witnessed the marketing of doripenem, a new carbapenem which *in vitro* is twice as active as imipenem-cilastatin or meropenem against *P. aeruginosa*.[67] A recent randomized, open-label multicenter clinical trial has evaluated the efficacy of doripenem versus imipenem-cilastatin in the treatment of mechanical ventilation associated pneumonia. Clinical healing proved similar in both arms, though the patients with *P. aeruginosa* showed a nonsignificant tendency towards greater clinical healing among those administered doripenem (80% vs 42.9%). Resistance to doripenem was less frequent than resistance to imipenem-cilastatin: 5 out of 28 strains of *P. aeruginosa* in the doripenem arm and 14 of the 25 strains in the imipenem-cilastatin arm were resistant at the start or

developed resistance during treatment (p<0.05).[68] New and well designed studies are needed to confirm these results in patients with serious infections due to *P. aeruginosa*.

The other antimicrobial requiring mention in this section is colistin. Most of the studies that have evaluated this antimicrobial in recent years include infections caused by *P. aeruginosa and A. baumannii*. Accordingly, they will be described in the section on infections produced by *A. baumannii*. However, mention will be made here of a recent Spanish study involving 121 non-critical patients with infections produced exclusively by multiresistant *P. aeruginosa* strains. The clinical healing rate varied between 62.5% in the case of bacteremia and 84.6% in the case of urinary infections.[69]

An aspect that has been widely debated is the advisability of combined antibiotic treatment versus monotherapy in serious *P. aeruginosa* infections. The following advantages of combination therapy have been postulated: 1) an increased probability that the pathogen will be sensitive to at least one of the prescribed antibiotics; 2) prevention of the development of resistances; and 3) the additive or synergic effect of the drug combination. However, the potential disadvantages of combination therapy comprise an increased risk of toxicity, cost increments, and possible superinfection. The *in vitro* synergism of certain antibiotics in combination against *P. aeruginosa* is well known, particularly as refers to synergism between betalactams and aminoglycosides. There is less evidence of synergism between the quinolones and other groups of antibiotics.[70] Two research studies have attempted to clarify this subject. Chamot et al.[71] compared the course of 115 patients with bacteremia due to *P. aeruginosa* and subjected to anti-pseudomonas treatment, considering whether the empirical and definitive therapies were adequate, in both monotherapy and in combination. It was seen that mortality between the day on which the results of the antibiogram were obtained and up until the first 30 days was greater among the patients administered adequate empirical monotherapy (OR 3.7; 95%CI 1.0-14.1) and in those who had received inadequate treatment (OR 5.0; 95%CI 1.2-20.4) than in those administered adequate empirical combination therapy. However, on analyzing the definitive treatment, combination therapy was not found to offer benefit in terms of mortality after 30 days with respect to monotherapy.

A retrospective study was published in 2005, analyzing 305 patients (55% in the ICU) with monomicrobial bacteremia caused by *P. aeruginosa*.[72] Forty percent of the episodes were of unknown origin, followed by pulmonary foci in a little under 20% of the cases. The analysis of the results confirmed inappropriate empirical antibiotic treatment (OR 2.04) as an independent mortality factor, together with respiratory failure (OR 5.18) and shock (OR 4). Adequate empirical antibiotic treatment was more often administered to patients who received combination therapy than to those who received monotherapy (79.4% vs 65.5%; p=0.011).

A retrospective study carried out in 5 Spanish ICUs evaluated the prognosis of 153 monomicrobial episodes of mechanical ventilation-associated pneumonia produced by *P. aeruginosa*. The initial use of combination therapy significantly reduced the risk of inadequate treatment, which was associated to an increased mortality risk.

However, the use of monotherapy or combination therapy in effective empirical treatment (only antibiotics with *in vitro* activity) or in guided treatment yielded similar results in terms of mortality, duration of stay and recurrences.[73] We therefore can conclude that although empirically combination therapy should be used to increase the chances for adequate treatment, once the sensitivity profile of *P. aeruginosa* has been established, treatment with a single antimicrobial is indicated.

Acinetobacter baumannii

The sensitivity patterns can vary according to environmental factors, the evolutive duration of the endemic or epidemic outbreak, and the different antibiotic prescription policies applied in the hospitals. At present, in endemic settings, most *A. baumannii* strains are resistant to aminoglycosides, ureidopenicillins, third- and fourth-generation cephalosporins and fluoroquinolones, and these drugs have no indication in the empirical management of such infections. Empirical treatment sometimes poses a serious problem due to the frequent and changing appearance of resistances. Classically, carbapenems have been the empirical treatment of choice, imipenem-cilastatin being comparatively more active than the rest of the drugs belonging to this group. In a murine model of pneumonia due to *A. baumannii*, imipenem-cilastatin has been shown to exert a prolonged post-antibiotic effect at pulmonary level, with the preservation of tissue concentrations above the MIC.[74] In addition, imipenem-cilastatin has been shown to be more effective in animal models,[75] and is regarded as the treatment of choice for these infections - with the possible exception of central nervous system infections, in which meropenem should be used in view of its lesser association to seizures. Doripenem is less effective against *A. baumannii* than imipenem-cilastatin.[67]

Another option can be sulbactam, which has been found to be an effective alternative for treating serious infections produced by multiresistant *A. baumannii* strains.[76] A retrospective study showed sulbactam to be as effective as imipenem-cilastatin in the treatment of mechanical ventilation-associated pneumonia caused by *A. baumannii*.[77] Likewise, and despite its scant meningeal penetration, sulbactam has been shown to be a valid option for treating nosocomial meningitis caused by *A. baumannii*.[78] The current problem is that according to data from the ENVIN registry, almost 80% of all *A. baumannii* strains isolated in Spanish ICUs are resistant to sulbactam.

At present, colistin (polymyxin E) is the antimicrobial with the greatest activity against *A. baumannii*. This is a polypeptidic antimicrobial with bactericidal action against different GNB, though the genera *Proteus, Providencia* and *Serratia* are resistant.

The drug was used in the 1970s and 1980s via the systemic route, but was abandoned because of its important toxicity particularly at renal level and in the peripheral nervous system, where it caused generalized weakness secondary to neuromuscular conduction block. In the late 1990s colistin was again introduced in view of its excellent activity against certain multiresistant gramnegative organisms such as *P. aeruginosa* and *A. baumannii*. A retrospective study revealed

a 58% healing rate in serious infections produced by these two pathogens - the poorest results being obtained in the case of pneumonia (clinical healing rate 25%). Twenty-seven percent of the patients with normal kidney function developed reversible renal dysfunction, in the same way as 58% of the patients who already presented altered kidney function from the start - though renal failure was not a cause of treatment suspension in any case.[79] In theory, due to the large size of the molecule, colistin penetration of the lung parenchyma is poor - and this might explain the results obtained. In this context, in a murine model of *A. baumannii* pneumonia, colistin exhibited a lesser antibacterial capacity than any of the other antimicrobials used.[80]

A prospective study.[81] compared 21 episodes of mechanical ventilation-associated pneumonia produced by *A. baumannii* sensitive only to colistin, and which were treated with the latter drug via the intravenous route, versus 14 episodes treated with imipenem-cilastatin and involving strains sensitive to the latter. The healing rate was similar in both groups, as was the incidence of renal failure - the latter being better explained in the context of septic shock with secondary renal dysfunction. In none of the evaluated cases was neuromuscular block detected, and the percentage of critical patient polyneuropathy proved similar in both groups. Different posterior studies have confirmed efficacy in serious infections in different locations caused by *P. aeruginosa* and *A. baumannii*,[82,83] or specifically in mechanical ventilation-associated pneumonia.[84,85]

Colistin has also been successfully used in nebulized form for the treatment of lung infections in patients with cystic fibrosis, and its use has been described in cases of pneumonia produced by multiresistant GNB.[86,87] Recently, a retrospective comparative study has been published in which the clinical healing rate was significantly greater in patients administered intravenous colistin plus inhalatory colistin (62/78; 79.5%) than in those who only received intravenous treatment (26/43; 60.5%) (p=0.025), though there were no differences in terms of mortality.[87] In any case, nebulized colistin always must be combined with systemic therapy, and at present its systemic use cannot be recommended in critical patients with pneumonia, due to the lack of conclusive clinical information and the acceptable results obtained when the drug is administered via the intravenous route.

Since colistin has problems crossing the blood-brain barrier, it has been administered via the intrathecal route for the treatment of nosocomial meningitis produced by multiresistant *A. baumannii* strains.[88] However, there have also been reports of successful treatment of *A. baumannii* meningitis using intravenous colistin - and the cerebrospinal fluid drug concentrations moreover reached bactericidal levels.[89]

Lastly, it should be mentioned that there are studies in critical patients evaluating colistin associated to rifampicin.[90,91] However, these are short and non-comparative series that do not allow the drawing of firm conclusions.

Tigecycline, a modified derivative of minocycline, is the first representative of a new class of antibiotics: the glyclcyclines. This drug is administered via the parenteral route, and it offers a very broad spectrum of activity. Tigecycline is active against grampositive and gramnegative pathogens (except *P. aeruginosa, Proteus* spp., *Providencia* and *Morganella*), anaerobes and atypical strains - including microorganisms resistant to multiple antibiotics. Tigecycline

has been approved for the treatment of moderate to serious infections of the skin and soft tissues, and complicated intraabdominal infections - but not pneumonias.

Tigecycline is active against *A. baumannii*, including strains resistant to carbapenems and colistin.[92] As a result, in some cases it represents the only treatment option. A number of series involving a moderate number of patients have evaluated tigecycline in infections produced by *A. baumannii* in different body locations, with clinical healing rates in the order of 60-70%.[93-95] It therefore can be affirmed that tigecycline is an adequate option in relation to the approved indications for treating multiresistant *A. baumannii* infections, though it must be noted that the development of resistances has been reported during treatment.[94]

Extended spectrum betalactamase (ESBL) producing gramnegative bacilli

The treatment options for infections caused by these microorganisms are very limited, for in addition to conferring resistance to all the betalactams except the cephamycins and carbapenems, the plasmids encoded for by ESBL often contain other resistance genes against different antimicrobials such as the aminoglycosides, tetracyclines and cotrimoxazole.[96] In addition, for reasons that are not clear, ESBL strains are more often resistant to quinolones than non-ESBL strains. On the other hand, there have been reports of treatment failure in patients treated with third-generation cephalosporins, in relation to strains exhibiting intermediate *in vitro* sensitivity to these drugs, or even sensitive to these antimicrobials. The failure rate in this context can exceed 50%.[97] This behavior has been related to the inoculum effect, whereby the antimicrobial MIC can increase 10- to 100-fold simply in the presence of a large bacterial burden.[98] This phenomenon has also been observed with the fourth-generation cephalosporins, despite the fact that these compounds are structurally more stable against hydrolysis. For this reason, once ESBL production has been confirmed, and independently of the *in vitro* MIC values, the strain in question must be regarded as resistant to all betalactams except, in principle, to the carbapenems and cephamycins. In turn, the cephamycins, which include cefoxitin, cefotetan and cefamandole, are not recommended, due to the risk of resistances developing during therapy, secondary to porin modifications that lead to a decrease in permeability. Another cephamycins resistance mechanism has been described, attributable to the AmpC betalactamases. It is therefore essential to take into account that the cephamycins likewise cannot be regarded as first choice treatment for infections of this kind.

At present, the carbapenems are the treatment of choice for serious infections caused by ESBL-producing GNB, since they are very stable against betalactamase-mediated hydrolysis and appear to be the only drugs capable of maintaining bactericidal activity for 24 hours against large ESBL strain inocula.[96-99] Paterson et al. analyzed patients with serious infections caused by ESBL-producing GNB and found that those subjects administered carbapenems showed lesser mortality after 14 days than those patients who received non-carbapenem active antibiotic treatment (4.8% vs 27.6%; p<0.05).[97] The choice of carbapenem is difficult, since all of them (meropenem, imipenem, ertapenem and doripenem)

offer excellent *in vitro* activity. In any case, there are a series of particularities that should be considered when making a choice: 1) the published clinical experience is greater for imipenem and meropenem; 2) ertapenem is not active against *P. aeruginosa* and *Acinetobacter spp.*,[100] and resistances have been reported *in vitro* and *in vivo* for *E. coli* and ESBL-producing *K. pneumoniae* - as a result of which it must be used with caution;[101] and 3) there is little clinical experience with doripenem - further studies being needed to clarify its role in these situations.

Lastly, studies are being made on the usefulness of the combination of antimicrobials with cefepime or ceftazidime and sulbactam, among others, in those patients who cannot be treated with carbapenems - the results obtained being contradictory.[99,102] New studies are needed to assess the utility of possible drug combinations in relation to this therapeutic indication.

Lastly, tigecycline is a good alternative for infections caused by ESBL-producing organisms, without forming part of the co-resistance phenomenon. This drug is one of the few existing options with *in vitro* activity against metallo-betalactamases produced by gramnegative species, and especially in the case of carbapenemases produced by *K. pneumonia.*[103] A phase II clinical trial has described the efficacy of tigecycline in 7 out of 9 patients with complicated intraabdominal infections associated to ESBL-producing *E. coli* and in 5 out of 6 patients with infections associated to *K. pneumonia.*[104] It therefore can be affirmed that tigecycline is an adequate option in relation to the approved indications for treating infections caused by ESBL-producing GNB, though further studies are needed to confirm these results.

Stenotrophomonas maltophilia

Stenotrophomonas maltophilia is a scantly virulent pathogen that causes infections in weakened patients, and which is resistant to carbapenems. The classical treatment option is trimethoprim - sulfamethoxazole at high doses, as in pneumonia produced by *Pneumocystis jirovecii*. The resistance rate of *S. maltophilia* for cotrimoxazole is about 5%,[105] though higher rates have been reported in Spain.[106] Other options are the fluorquinolones or ticarcillin - clavulanate, but not piperacillin - tazobactam, for which the resistances rates are close to 90%.[107] Tigecycline could be an option, since it offers excellent activity against *S. maltophilia*, though the clinical experience gained to date is limited.[105]

Grampositive cocci

In this case the treatment problems are almost exclusively referred to methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* spp. (VRE). Fortunately, the incidence of VRE is very low in Spain. A review is offered below of the treatment options available for infections produced by these microorganisms.

Vancomycin

Vancomycin is the treatment of choice for infections caused by MRSA. However, its inconveniences are poor diffusion in tissues

such as the lungs, and tolerability problems. In recent years, *S. aureus* has been associated with an increase in MIC for this antibiotic, though the values remain within the sensitivity range (MIC ≤2 mg/l). This increase in MIC has been related to treatment failures in patients with bacteremia or pneumonia produced by MRSA.[108,109] Soriano et al., in a study of 414 episodes of MRSA bacteremia treated with vancomycin in which vancomycin trough values of >10 mg/l had been attempted, found inadequate empirical treatment and a vancomycin MIC of 2 mg/l to be independent mortality risk factors.[110]

The studies that have analyzed the relationship between the pharmacokinetic characteristics of vancomycin and the clinical course of MRSA infection show a ratio between the area under the antibiotic concentration curve (AUC) over 24 hours and a MIC of the infection-causing strain (AUC24h/MIC) of over 400 to be associated to an increased probability of clinical healing.[111] Accordingly, dose elevation is recommended in order to maintain serum vancomycin concentrations between 15-20 mg/l, or alternatively continuous perfusion of the drug is indicated. In application to strains with MIC 2 mg/l, reaching the same ratio would require maintaining the serum vancomycin concentration during 24 hours at least between 30-40 mg//l. Such higher doses have been associated with an increased renal failure rate.[109,112] Therefore, vancomycin should not be used to treat MRSA infections with MIC >1 mg/l, and other treatment options should be considered in such situations.[113,114]

Linezolid

Linezolid is an oxazolidinone antibiotic with activity against grampositive cocci, approved for the treatment of nosocomial pneumonia, community-acquired pneumonia and skin and soft tissue infections. It reaches high concentrations in tissues, including the lungs. The efficacy of linezolid has been compared with that of vancomycin in pneumonia patients.[115,116] Survival was found to be greater in the linezolid group than in the patients treated with vancomycin at discontinuous doses, in the global series of patients with MRSA pneumonia (80% vs 63.5%; p=0.03)[115] and in those with mechanical ventilation-associated pneumonia produced by MRSA[116] (84.1% vs. 61.7%; p=0.02). This was confirmed by a multivariate analysis in which linezolid proved to be an independent hospital survival factor (OR 2.6; 95%CI 1.3-5.1; p=0.006). Accordingly, linezolid is presently regarded as the option of choice in the case of MRSA pneumonia, and treatment can be modified to use vancomycin only if the MRSA exhibits MIC ≤0.5 mg/l.[113]

In the treatment of skin and soft tissue infections produced by MRSA, linezolid has been shown to be clinically more effective than vancomycin,[117] and has more often been able to eradicate *S. aureus* from infected wounds. Linezolid therefore has been regarded as the treatment to be used in soft tissue infections produced by MRSA, instead of vancomycin, though as we will see, we can also prescribe daptomycin or tigecycline.

Daptomycin

Daptomycin is a lipopeptide antibiotic with rapid bactericidal action that has been approved for treating skin and soft

tissue infections, as well as bacteremias and right-side endocarditis produced by MRSA. Its administration in pneumonia has been ruled out, however, since its effect is inhibited by lung surfactant. Following its authorization in application to bacteremias and right-side endocarditis due to *S aureus*, other studies have been published based on a prospective registry in which the bacteremia healing rate was 89% (43% of patients admitted to the ICU), while the endocarditis healing or improvement rate was 63%.[118,119] Although the dose approved for these infections is 6 mg/kg, doses of ≥8 mg/kg offer an 89% healing rate in the case of bacteremia, without adverse effects.[120]

Tigecycline

Tigecycline is a broad spectrum antibiotic active also against grampositive cocci - including multiresistant MRSA and *Enterococcus* spp. It reaches high levels in tissues and is quickly cleared from the bloodstream; as a result, it cannot be recommended in cases of bacteremia. Tigecycline is presently indicated for the treatment of intraabdominal infections or skin and soft tissue infections. In these situations it is particularly recommended when multiresistant pathogens are or may be implicated, with the participation of MRSA - fundamentally when the MIC for vancomycin is >1.5 mg/l.

Acknowledgements

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