

Review

Emilio Maseda^{1,a,b}
José Mensa^{2,b}
Juan-Carlos Valía^{3,a}
Jose-Ignacio Gomez-Herreras^{4,a}
Fernando Ramasco^{5,a}
Enric Samsó^{6,a}
Miguel-Ángel Chiveli^{7,a}
Jorge Pereira^{8,a}
Rafael González^{9,a}
Gerardo Aguilar^{10,a}
Gonzalo Tamayo^{11,a}
Nazario Ojeda^{12,a}
Jesús Rico^{13,a}
María José Gimenez^{14,b}
Lorenzo Aguilar^{14,b}

Bugs, hosts and ICU environment: Countering pan-resistance in nosocomial microbiota and treating bacterial infections in the critical care setting

¹Anesthesiology and Surgical Critical Care Dpt., Hospital Universitario La Paz, Madrid.

²Infectious Diseases Dpt., Hospital Clinic, Barcelona.

³Anesthesiology and Surgical Critical Care Dpt., Hospital General Universitario, Valencia.

⁴Anesthesiology and Surgical Critical Care Dpt., Hospital Clínico Universitario, Valladolid.

⁵Anesthesiology and Surgical Critical Care Dpt., Hospital Universitario La Princesa, Madrid.

⁶Anesthesiology and Surgical Critical Care Dpt., Hospital del Mar, Barcelona.

⁷Anesthesiology and Surgical Critical Care Dpt., Hospital Universitario y Politécnico La Fe, Valencia.

⁸Anesthesiology and Surgical Critical Care Dpt., Complejo Hospitalario de Vigo, Vigo.

⁹Anesthesiology and Surgical Critical Care Dpt., Hospital de León, León.

¹⁰Anesthesiology and Surgical Critical Care Dpt., Hospital Clínico Universitario, Valencia.

¹¹Anesthesiology and Surgical Critical Care Dpt., Hospital de Cruces, Bilbao.

¹²Anesthesiology and Surgical Critical Care Dpt., Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria.

¹³Anesthesiology and Surgical Critical Care Dpt., Hospital Universitario Río Hortega, Valladolid.

¹⁴PRISM-AG, Madrid,

^aGTIPO-SEDAR: Grupo de Trabajo de Infecciones Perioperatorias-Sociedad Española de Anestesiología, Reanimación y Terapéutica del Dolor

^bSEQ: Sociedad Española de Quimioterapia

ABSTRACT

ICUs are areas where resistance problems are the largest, and they constitute a major problem for the intensivist's clinical practice. Main resistance phenotypes among nosocomial microbiota are: i) vancomycin-resistance/heteroresistance and tolerance in grampositives (MRSA, enterococci) and ii) efflux pumps/enzymatic resistance mechanisms (ESBLs, AmpC, metalloβ-lactamases) in gramnegatives. These phenotypes are found at different rates in pathogens causing respiratory (nosocomial pneumonia/ventilator-associated pneumonia), bloodstream (primary bacteremia/catheter-associated bacteremia), urinary, intraabdominal and surgical wound infections and endocarditis in the ICU. New antibiotics are available to overcome non-susceptibility in grampositives; however, accumulation of resistance traits in gramnegatives has led to multidrug resistance, a worrisome problem nowadays. This article reviews by microorganism/infection risk factors for multidrug resistance, suggesting adequate empirical treatments. Drugs, patient and environmental factors all play a role in the decision to prescribe/recommend antibiotic regimens in the specific ICU patient, implying that intensivists should be familiar with available drugs, environmental epidemiology and patient factors.

Key words: MRSA; vancomycin-resistant enterococci; ESBL; *Pseudomonas aeruginosa*; *Acinetobacter baumannii*; critical care

Correspondence:

Emilio Maseda

Anesthesiology and Surgical Critical Care Dpt.

Hospital La Paz, Paseo de la Castellana 261, 28046 Madrid, Spain.

Phone: +34629018689

E-mail: emilio.maseda@gmail.com

Gérmenes, huéspedes y el entorno de la UCI: Contrarrestando la panresistencia en la microbiota nosocomial para tratar las infecciones bacterianas en cuidados críticos

RESUMEN

Las UCI son las áreas con mayor problema de resistencias, y constituye uno de los principales problemas de los intensivistas en su práctica clínica. Los principales fenotipos de resistencia en la microbiota nosocomial son: i) la resistencia/heteroresistencia y la tolerancia a la vancomicina en grampositivos (SARM, enterococo) y ii) las bombas de flujo/mecanismos enzimáticos de resistencia (BLEEs, AmpC, metallobetactamasas) en gramnegativos. Estos fenotipos pueden encontrarse, con distinta frecuencia, en patógenos causantes de infecciones respiratorias (neumonía nosocomial/neumonía asociada a ventilación mecánica), del torrente sanguíneo (bacteriemia primaria/bacteriemia asociada a cateter), urinarias, intraabdominales, de herida quirúrgica y endocarditis en la UCI. Hay nuevos antibióticos disponibles para contrarrestar la no-sensibilidad en grampositivos; sin embargo, la acumulación de factores de resistencia en gramnegativos lleva a la multiresistencia/panresistencia, un problema en nuestros días. Este artículo revisa por microorganismo/infección los factores de riesgo de resistencia/multiresistencia, sugiriendo tratamientos empíricos adecuados. Fármacos, pacientes y factores ambientales tienen todos un papel básico en la decisión de prescribir/recomendar regímenes antibióticos en el paciente específico de la UCI, implicando que los intensivistas deben estar familiarizados con los fármacos disponibles, la epidemiología local y las características del paciente crítico.

Palabras clave: SARM; enterococo resistente a vancomicina; BLEE; *Pseudomonas aeruginosa*; *Acinetobacter baumannii*; cuidados críticos

THE NOSOCOMIAL MICROBIOME AND RESISTOME

Evolution of relationships between human and bacteria are conditioned by environmental changes. Among anthropogenic factors changing the environment and thus, shaping future interactions between human and bacteria^{1,2}, chemical pollution (including antibiotics and antimicrobial strategies) altering microbial biodiversity, new medical technologies (opening the way for opportunistic infections), the increasing number of highly susceptible hosts and control of bacterial access to host are important factors for nosocomial infections, and theoretically, counterbalance colonisation/multidrug resistance in nosocomial microbiota.

The "nosocomial human population", that includes patients and health care personnel, is closely linked to the "nosocomial microbiome" (microbiota from health care personnel and from non-infected and infected patients), with its specific "resistome" (antibiotic resistance genes and genetic elements that participate in resistance gene transfer). The horizontal gene transfer within species and between different species of gram-negative and gram-positive bacteria³, facilitated when bacteria are exposed to antibiotic stress^{4,5}, has driven to multidrug resistance.

Resistance implies the need for new antibiotics that, once introduced, if their mechanism of action is similar to previous compounds may select pre-existing resistances or induce new resistances in the nosocomial resistome that could be further selected, thus implying the need for new antibiotics and closing the circle⁶. Antimicrobial pressure as driving engine for resistance and multidrug resistance is evident in the nosocomial environment, with a well defined relationship between antibiotic use and emergence of multidrug resistant strains⁷⁻⁹.

In the presence of antibiotic stress, antimicrobial resistance can be considered a colonisation factor¹. Accumulation of "genotypic colonisation factors" (phenotypic resistance traits) drives to multidrug resistance, hallmark of nosocomial microbiota since the phenomena of selection of co-resistance and co-selection of resistance are more frequent in hospitals than in the community. If resistance favours "colonisation" of elements of the nosocomial microbiota, strategies aimed to reducing resistance will result not only in a decrease in the resistance prevalence but also in a decrease in colonisation and a subsequent decrease in nosocomial infections.

Hospital-acquired infections affect a quarter of critically ill patients, and can double the risk of a patient dying^{10,11}, requiring rapid treatment to reduce morbidity and mortality¹². Nosocomial infections acquired in the intensive care unit (ICU) represent an area in which much improvement is still achievable¹³. However it should be taken into account that infection is often the cause of ICU admission^{14,15}, influencing the microbiological environment of the unit¹⁶. The drugs, patient and environmental factors all play a role in the decision to prescribe or recommend (and daily review) antibiotic dosing regimens in a specific patient¹², this implying that personnel involved should be familiar with available drugs, environmental (bacterial epidemiology and resistance traits) and patient factors.

The concrete battlefields in the ICU

An approach to the existing resistome can be done through the choice of indicator microorganisms based on their clinical relevance and their potential for acquisition of genetic determinants of resistance. Nowadays, the main resistance phenotypes among multiresistant nosocomial microbiota are: i) vancomycin-resistance and tolerance in nosocomial gram-positives (MRSA and enterococci) and ii) efflux pumps and enzymatic resistance mechanisms (ESBLs, AmpC and metallo-beta-lactamases) in nosocomial gram-negative bacteria. Antibiotics/antibiotic regimens for the treatment of nosocomial infections should counter these sometimes emerging, always diffusible and clinically worrisome resistance traits.

THE METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA) CASE

Staphylococcal infections became treatable with the introduction of penicillin but, soon after, production of β -lactamase by staphylococci became a reality. Penicillinase-resistant isoxazolyl penicillins were then introduced to counter resistance mediated by β -lactamases, with the subsequent emergence of methicillin resistance. Nowadays, MRSA is worldwide spread in hospitals, with prevalence reaching rates of 25-50% in much of Americas, Australia and Southern Europe¹⁷. The evolution of the global rate of MRSA among *S. aureus* in Spanish ICUs from 1994 to 2008 (study ENVIN-UCI including up to 100 ICUs) shows similar rates (\approx 25%) in the first and last years with oscillations ranging from 13% in 1997 to 42.3% in 2006¹⁸. In addition to intra-ICU transmission dynamics of MRSA (influenced, among others, by colonisation of health care workers in the ICU¹⁹), it should be taken into account MRSA imported cases in the ICU as predictor of occurrence of nosocomial MRSA infections²⁰, with community-acquired MRSA genotypes as emerging cause of colonisation among patients admitted in adult ICUs in the USA²¹.

The dramatic increase in MRSA nosocomial infections led to a substantial increase in the use of vancomycin, and this could be related to the appearance of different vancomycin non-susceptible phenotypes both in enterococci and staphylococci. The risk of emergence of MRSA non-susceptible to vancomycin is much higher in countries with high prevalence of both MRSA and vancomycin-resistant enterococci²². Published studies suggest a link between antibiotic usage at individual and institutional levels and resistance, showing an increase in the risk of acquiring MRSA when using not only glycopeptides²³ but also quinolones^{23,24} and cephalosporins^{24,25}.

The associated problem of vancomycin non-susceptibility and vancomycin tolerance

The first vancomycin non-susceptible strains were designated as vancomycin-intermediate *S. aureus* with vancomycin MICs of 8-16 mg/L²⁶. Among vancomycin-intermediate strains, 90% of strains are heterogeneous vancomycin-intermediate (heteroresistant; h-VISA) characterized by the presence of a

selectable resistant subpopulation in an otherwise fully susceptible population, and only 10% are homogeneously vancomycin-intermediate (homoresistant; VISA)^{27,28}. The prevalence of h-VISA among MRSA is variable worldwide ranging from ≈10 to 50%²⁹⁻³². MRSA strains resistant to vancomycin have been described but, fortunately, its diffusion is unappreciable nowadays³³. Intermediate resistance to vancomycin can also be found in coagulase-negative staphylococci at non-negligible rates (≈10%)³⁴.

In addition, there are MRSA isolates that are susceptible to vancomycin but tolerant to its killing effect. Tolerance is defined as "bacterial capability of survival without growth in the presence of a current lethal concentration"³⁵, and is expressed as an MBC/MIC quotient of ≥ 16 or ≥ 32 ³⁶. Nevertheless, a recent study has shown that even vancomycin-susceptible strains with MBC/MIC ratios of 8, when exposed to simulated vancomycin concentrations in serum, exhibit a pharmacodynamic behaviour similar to that of strains with MBC/MIC ≥ 16 , with no bactericidal activity by vancomycin despite susceptibility³⁷. Tolerance to vancomycin is present in 100% VISA strains, 75% h-VISA and 15% vancomycin-susceptible MRSA³⁶ and this phenomenon is extensive to other glycopeptides as teicoplanin, with teicoplanin tolerance reported in 18.8% of MRSA strains³⁸. In addition, tolerance to glycopeptides has also been described in ≈25% of coagulase negative staphylococci and $\geq 40\%$ of group viridans (*Streptococcus bovis*, *Streptococcus sanguis*, *Streptococcus gordonii*, *Streptococcus mutans* and *Streptococcus oralis*) isolates³⁴, both bacterial groups being important etiological agents in endocarditis.

Clinical impact of non-susceptibility, resistance and/or tolerance

Bactericidal activity is important in infections caused by methicillin-susceptible *S. aureus*³⁹. A classical study in our country showed a significantly higher mortality in methicillin-susceptible *S. aureus* bacteremia in patients treated with vancomycin compared with cloxacillin, in part attributable to the slow vancomycin killing⁴⁰. This was corroborated in an in vitro study showing that vancomycin was not bactericidal within the dosing interval in contrast to daptomycin, regardless methicillin susceptibility/resistance of the study strains⁴¹.

Some high-inoculum staphylococcal infections as bacteremia, persistent bacteremia, endocarditis and osteomyelitis have been associated with heteroresistance^{33,42,43}. Vancomycin heteroresistance has been linked to strains susceptible to vancomycin but with high MIC values within the susceptibility category^{44,45}. In turn, the relationship of MICs to clinical failure with vancomycin is striking³¹. In a published study, high vancomycin MICs, defined as 1.5-2.0 mg/L, was an independent predictor of poor response to vancomycin therapy for MRSA infection, even when vancomycin trough levels >15 mg/L were achieved⁴⁶. Importantly, vancomycin trough levels >15 mg/L appears to be associated with a 3-fold increased risk of nephrotoxicity⁴⁷.

Considering the current situation, it has been suggested

that strains with vancomycin MIC of 1-2 mg/L should be considered h-VISA or VISA⁴⁸ since even the new Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoint for vancomycin (≤ 2 mg/L) may fail to precisely differentiate potential responders to vancomycin therapy^{36,49}, suggesting that, according to clinical data, the breakpoint value should be even lowered to 1 or 0.5 mg/L⁴⁸.

The spectrum of clinical disease caused by MRSA, h-VISA, VISA and tolerant isolates is similar to that caused by non-tolerant methicillin-susceptible *S. aureus*. Since antimicrobial treatment is empirically initiated, there is evidence to show that less than a quarter of patients with MRSA infections receive correct therapy within 48h of hospital admission, and only ≈40% receive appropriate agents after 48h⁵⁰. Clinical implications of heteroresistance and tolerance evidenced as poor clinical outcome, persistence of bacteremia and increased length of stay^{24,51-55}, together with the fact that these phenomena are not routinely tested by microbiologists and reported to treating physicians³⁴, stress the importance of therapeutic strategies to overcome them.

THE VANCOMYCIN-RESISTANT ENTEROCOCCUS (VRE) CASE

Enterococci, historically regarded as a second-rate pathogen and with low virulence, have become one of the most challenging nosocomial problems. Nowadays, *Enterococcus faecium* is almost as common as *Enterococcus faecalis* as a cause of nosocomial infection⁵⁶. All enterococci show tolerance to vancomycin⁵⁷. In addition, acquisition of resistance to ampicillin, aminoglycosides (high level) and glycopeptides in *E. faecium* is a cause of concern²², making *E. faecium* infections difficult to treat. In USA vancomycin resistance increased in *E. faecium* isolates from 0% in mid 1980s to 80% in 2007⁵⁸. In Europe the vancomycin resistance prevalence is variable, ranging from $<1\%$ to $>40\%$ ^{22,59}. In Spain rates of around 14.3% have been reported in *E. faecium*⁶⁰. At hospital level, the increase in vancomycin use to treat MRSA infections seems to be the origin of VRE. In addition, the intensive use of oral vancomycin for *Clostridium difficile* infections in hospitals is also likely to select and increase faecal carriage of VRE³. In this sense, the description of multidrug resistant, hospital-adapted *E. faecium* clonal complexes without community reservoir can be explained by cross-transmission, selection and diffusion by selective antibiotic pressure⁶¹. Factors associated with VRE colonisation in critically ill patients include prolonged ICU stay (each day in the ICU increases 1.03 times the risk of acquisition), previous antibiotic use and carbapenem use⁶²⁻⁶⁴. Risk factors for development of VRE infections include prolonged hospitalisation, surgical or intensive care units, intravascular or bladder catheter devices, proportion of colonised patients and exposure to antibiotics^{65,66}. Among antibiotics, in addition to vancomycin, certain compounds as ticarcillin/clavulanate and third generation cephalosporins have demonstrated to cause selection^{67,68}. Although initially hospital-associated clones were different than those community-associated, these later

have become important nosocomial pathogens⁵⁸, with colonisation prior to ICU admission being associated with previous hospitalisation and, again, antibiotic exposure⁶⁹.

In enterococci full resistance to daptomycin, although has been reported⁷⁰, is rare, as for linezolid⁵⁸. The increase in linezolid use has been related to an increase (and to outbreaks) of VRE resistant to linezolid⁷¹⁻⁷³, also in patients not previously exposed to the drug⁷⁴.

Clinical outcomes are worse and mortality higher in patients with VRE infections when compared to those infected by susceptible strains⁶⁶. The classical tolerance to the killing capability of penicillins and glycopeptides in enterococci has clinical implications, as evidenced in enterococcal endocarditis where, due to the historical high recurrence rates with penicillin or glycopeptide monotherapy, combined therapy (including an aminoglycoside) is the rule⁷⁵. However, nowadays, due to the high aminoglycoside resistance in VRE, recurrences can occur.

STRATEGIES TO OVERCOME NON-SUSCEPTIBILITY PHENOTYPES IN MRSA AND VRE

Compromise of the bactericidal activity, among other factors, by vancomycin heteroresistance/tolerance (MRSA) or tolerance/resistance (VRE) may have clinical implications. Conceptually, treatments achieving bactericidal activity are preferred than those only presenting bacteriostatic activity, although this has not been clearly demonstrated in clinical trials. There are clinical indications where it is considered that bactericidal activity is absolutely necessary, as bacteremia, endocarditis, meningitis and infections in immunocompromised patients³⁹.

Two strategies can be considered to overcome deterioration of bactericidal activity by non-susceptible phenotypes: i) combined therapy obtaining synergism and ii) bactericidal antibiotics for initial treatment.

The addition of a new antimicrobial is outlined when facing a poor response with vancomycin monotherapy, thus suggesting tolerance of the infecting strain⁵⁵, and has been successfully used in the treatment of refractory bacteremia by tolerant isolates⁷⁶. The election of drugs to be included in the combination is important since there have been described antagonistic interactions between linezolid and vancomycin or between linezolid and gentamicin^{77,78}, on one side, and the commented high aminoglycoside resistance in VRE on the other. No antagonistic interactions have been shown between daptomycin and gentamicin, linezolid or vancomycin⁷⁹.

Regarding initiation of antibiotic therapy with bactericidal drugs, among compounds with potential activity against gram-positives, it should be taken into account that linezolid and tigecycline are bacteriostatic against *S. aureus*, and that quinupristin/dalfopristin, although bactericidal against *S. aureus*, is bacteriostatic against *E. faecium* and non active against *E. faecalis*²⁷. Bactericidal compounds to be used should present activity against gram-positive isolates and lack of tolerance or heteroresistance, in contrast to glycopeptides, as the

lipopeptide daptomycin that represents an adequate option for initial treatment of nosocomial gram-positive infections as staphylococcal bacteremia, endocarditis and skin and soft-tissue infections, but not of pneumonia due to the inhibition of its antibacterial activity by the pulmonary surfactant.

THE EXTENDED SPECTRUM β -LACTAMASE (ESBL), AMPC AND CARBAPENEMASES CASE

Pan-resistance is an increasing problem among nosocomial gram-negatives mainly due to antibiotic inactivating enzymes, sometimes in combination with efflux pumps and/or porine deficits. *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* are specifically addressed as the most problematic and often extensively or pan-drug resistant pathogens⁸⁰. In Spain, the proportion of *A. baumannii* isolates showing resistance to carbapenems, ceftazidime, aminoglycosides and quinolones is around 50% (for the first three) and 87% for ciprofloxacin, and in *P. aeruginosa* isolates proportions are \approx 20% (carbapenems), \approx 15% (ceftazidime) and \approx 25% (aminoglycosides and quinolones)⁸⁰. In *K. pneumoniae*, resistance to third generation cephalosporins and aminoglycosides is \approx 10% and \approx 18% for quinolones⁸⁰.

Different types of β -lactamases are increasingly appearing and diffusing as response to antibiotic pressure at the nosocomial level. In general, β -lactamases diffusing among human microbiota may be classified into three groups: 1) Extended-spectrum β -lactamases (ESBL), 2) AmpC and 3) Carbapenemases.

1) ESBL

After the introduction in the 80's of extended-spectrum third-generation cephalosporins, mutations in both bla_{TEM} and bla_{SHV} genes were reported, mainly in *Klebsiella* spp. In the last decade, there has been a rise in the prevalence of CTX-M β -lactamases that, unlike TEM and SHV ESBLs, did not remain confined to *Klebsiella* and have proliferated in *Escherichia coli*⁸¹. In Spain the prevalence of ESBL-producing *E. coli* has 8-fold increased from 2000 to 2006⁸²; the SMART study reported a frequency of ESBL-producing isolates of \approx 8.5% for *E. coli* and for *Klebsiella* spp.⁸³. Urine, followed by blood, and internal medicine, general surgery and ICUs were the most common sites and wards of isolation, respectively, in another study⁸⁴.

The huge amount of molecular variants widely diffused around the world is creating problems in the treatment of nosocomial infections since these enzymes are capable to confer resistance to penicillins, first-, second- and third- generation cephalosporins and to aztreonam (but not to cephamycins and carbapenems), but can be inhibited by β -lactamase inhibitors⁸⁵. However, non-susceptibility rates (according to EUCAST breakpoints) to piperacillin/tazobactam in CTX-M-producing *E. coli* and *K. pneumoniae* were 27.4% and 38.1%, respectively, with high resistance rates to cefepime (\approx 70% and \approx 80%, respectively)⁸⁶. In addition, in ESBL-producing strains co-resistance to aminoglycosides and quinolones is present⁸⁵. Due to this,

ESBL-producing strains have been clearly associated with poor outcome. In this sense, empirical therapy with cephalosporins or fluoroquinolones was associated with a higher mortality compared with patients treated with a β -lactam/ β -lactamase inhibitor or with carbapenem-based regimens in a Spanish series of patients with bacteremia produced by ESBL-producing *E. coli*⁸⁷.

Selection and diffusion of ESBLs has been associated with antibiotic pressure derived from the use of third-generation cephalosporins (with special importance for ceftazidime), aminoglycosides and quinolones, but not to β -lactams/ β -lactam inhibitors or carbapenems⁸⁵. In addition to previous antibiotic treatments, other risk factors that have been described for infection by ESBL-producing isolates in ICU patients are previous hospitalisation, advanced age, diabetes and use of catheters⁸⁴.

Carbapenems are probably the best options for treating infections caused by ESBL-producing strains^{84,87}, but the risk of the emergence of carbapenem resistance should always be considered (see below).

2) AmpC

Isolates of *Enterobacter cloacae*, *Enterobacter aerogenes*, *Serratia marcescens*, *Citrobacter freundii*, *Providencia rettgeri* and *Morganella morganii* (known as the ESCPM group) have the potential to produce AmpC inducible chromosomal β -lactamases upon exposure to inducing agents: aminopenicillins, first-generation cephalosporins, cephamycins and carbapenems as strong inducers, and second- or third-generation cephalosporins, acylureidopenicillins or monobactams as weakly inducers^{88,89}. When the inducer is removed, AmpC production returns to hardly detectable basal levels; thus, when isolated from patients, bacteria are found to be susceptible to third-generation cephalosporins. However, AmpC production should be suspected in all isolates belonging to these species. When inducer drugs are clinically used, selection of derepressed mutants (constitutively producing β -lactamase) occurs, with contingent clinical failure^{89,90}. An association between the use of third-generation cephalosporins and the emergence of resistance has been established among organisms with inducible chromosomally encoded AmpC β -lactamases⁹⁰. Derepressed overproduction has been described in 20% infections by *Citrobacter* spp. or *Enterobacter* spp. during third-generation cephalosporin treatment³.

AmpC genes have been mobilized to plasmids and spread worldwide, with increasing numbers in the diversity of this type of enzymes³. Infections caused by plasmid AmpC-producing isolates significantly increase treatment failure probably due to inadequate initial treatment therapy⁹¹. The CLSI provides susceptibility breakpoints for third-generation cephalosporins and AmpC producers but advice that resistance can emerge, and many infectious diseases specialists advocate that these compounds should not be used for significant infections caused by AmpC-producing enterobacteria^{92,93}. In addition, ESBLs has been increasingly described in AmpC producers, which further complicate decisions related to the optimum antimicrobial therapy⁹³.

AmpC- and ESBL- producing isolates exhibit high rates of resistance to penicillins (including piperacillin/tazobactam) and cephalosporins (including cefepime) according to EUCAST breakpoints⁹⁶. Treatment with carbapenems represents a good option but, again, concerns on the potential emergence of carbapenem resistance arise.

3) Carbapenemases

Most carbapenemase-producers have multiple resistance mechanisms to β -lactams and to aminoglycosides⁹⁴.

Resistance to carbapenems can arise by:

a) Permeability alterations (efflux pumps and/or porine deficit) plus AmpC (class C β -lactamases) or ESBL (class A) enzymes,

b) Acquisition of non- metallo-carbapenemases mainly of the KPC or OXA (class D β -lactamases) families, and/or

c) Acquisition of metallo- β -lactamases (MBLs; class B β -lactamases), mainly of the IMP- and VIM- families.

The heavily use of carbapenems after dissemination of multidrug resistant *Enterobacteriaceae* (due to ESBL and AmpC β -lactamases) rises the fears of the relationship between the use of these antibiotics and the selection and diffusion of carbapenemase-producing strains. Although nowadays the prevalence of carbapenemases is relatively low, they are sources of considerable concern due to the enzyme spectrum of activity that encompasses almost all known β -lactams, from penicillins to carbapenems, and because they are not susceptible to class A β -lactamase inhibitors and currently there are not clinically available inhibitors to block MBLs action⁹⁵. The association of carbapenemase production to resistance traits to other antibiotic classes may lead to polymyxins and tigecycline as last active agents, neither of them ideal. Resistance mediated by carbapenemases affects primarily *A. baumannii*, *P. aeruginosa* and to lesser extent, *K. pneumoniae*, although its emergence has also been described in *B. fragilis*⁹⁶.

P. aeruginosa

Pan-resistance in *P. aeruginosa* results from the convergence of multiple resistance mechanisms⁹⁷: low outer membrane permeability, AmpC β -lactamases, efflux pumps and less often, production of MBLs^{97,98}. However, in many European countries, mainly in the Mediterranean area, VIM-type producing *P. aeruginosa* has currently become endemic⁹⁹. In Spain the prevalence of carbapenemase-producing *P. aeruginosa* strains among bacteremic isolates resistant to imipenem has increased 10 times in few years, reaching 4% in 2008¹⁰⁰. According to the EARSS study, non-susceptibility rates are \approx 8% to piperacillin/tazobactam, \approx 15% to ceftazidime, \approx 25% to aminoglycosides and quinolones, and \approx 20% to carbapenems⁸⁰. In the ICU, risk factors for multidrug resistance in *P. aeruginosa* are previous exposure to third-generation cephalosporins, to carbapenems or to acylureidopenicillins¹⁰¹.

A. baumannii

A. baumannii is more often resistant. *A. baumannii* produces a naturally occurring AmpC β -lactamase, like *P. aeruginosa*, together with a naturally occurring oxacillinase with carbapenemase properties¹⁰². Additionally, resistance to carbapenems has been linked to the loss of outer membrane porins and upregulated efflux pumps⁸⁰. Resistance to carbapenems remained rare until 2000 despite the widespread of resistance to other compounds⁹⁸. However, carbapenem resistance has increased sharply since then, and is mediated by OXA-type, and less often by IMP- and VIM- types, carbapenemases^{80,98}. Several studies have described the OXA-40 gene spread across the Iberian Peninsula^{103,104}. In our country, resistance rates are $\approx 35\%$ to amikacin, $\approx 40\%$ to ceftazidime, $\approx 70\%$ to piperacillin/tazobactam, and $\approx 45\%$ to carbapenems¹⁰⁵. It is considered that resistance to carbapenems is enough to define an isolate as highly resistant¹⁰⁶. Risk factors for carbapenem resistance in *A. baumannii* are hospital size, ICUs, length of stay in the ICU, recent surgery, invasive procedures and, mainly, previous exposure to antibiotics (carbapenems and third-generation cephalosporins) and mechanical ventilation^{107,108}.

Enterobacteriaceae

As previously described, the main multidrug resistance phenotype in enterobacteria is due to hyperproduction of chromosomal AmpC β -lactamases or ESBLs. Undoubtedly, this phenotype is also represented by carbapenem resistance mainly mediated VIM- and IMP- type MBLs. In the *Enterobacteriaceae* family, *K. pneumoniae* is the species with the highest rates of carbapenem resistance. In the multinational SENTRY study (2007-2009), overall carbapenemase resistance in *K. pneumoniae* was 5.3%, while it was 0.3% in *E. coli*, mainly due to KPC β -lactamases in *K. pneumoniae* and OXA-48 in *E. coli*¹⁰⁹. In Spain, class B carbapenemase-producers (VIM-1 and IMP-22) have been found in specific areas (Madrid, Catalonia, Andalusia, Balearic) with a local prevalence $< 0.2\%$ ¹¹⁰. But the situation may be changing since the description of VIM-producers outbreaks¹¹⁰⁻¹¹⁴, together with the emergence of the KPC-3¹¹⁵ and the New Delhi MBL (NDM-I) β -lactamases in *K. pneumoniae* and *E. coli*^{116,117}, confirming the dissemination of carbapenemase-producing isolates in our country. Nonetheless, according to last EARSS data in 2011, carbapenemase resistance in *K. pneumoniae* in Spain is 0.3%¹¹⁸. Risk factors associated with carbapenem resistance in *K. pneumoniae* are previous exposure to antibiotics (carbapenems, cephalosporins, acylureidopenicillins and quinolones), mechanical ventilation, and stay in the ICU^{80,119-121}. Carbapenem-resistant *K. pneumoniae* has been independently associated with poor outcome and death^{120,122,123}.

PHARMACOKINETICS/PHARMACODYNAMICS (PK/PD) IN THE ICU SETTING

The choice of an antibiotic for empirical treatment of serious bacterial infections in the ICU is based predominantly in

the identity and susceptibility patterns of bacteria commonly isolated in a particular ICU. Serious infections in critically ill patients require rapid treatment to limit morbidity and mortality. Intravenous treatment should begin within the first hour after diagnosis of severe sepsis¹²⁴ as the most important factor affecting outcome. However, this is not always met since as few as 25% of the first doses of antibiotics are administered within 1h of prescription¹². What is often overlooked is the optimum dose of an antibiotic¹² and, to avoid empiricism, the PK/PD relation should be exploited⁸⁰. However, PK/PD parameters predicting efficacy usually rely on steady-state concentrations, avoiding events occurring when the pathogen is exposed to the initial dose, which are relevant for outcome¹²⁵. Ideally, the first dose should rapidly reach enough concentrations above the MIC to avoid resistance selection, and these concentrations should be maintained all over the treatment course. In order to escape resistance, under-dosing should be avoided and the duration of therapy should be limited, starting de-escalation of administered antibiotics as soon as culture results are ready⁸⁰. Considering all these facts and the challenging situation of resistances, the role of clinicians is currently enhanced since they are vital resource in the implementation of strategies against worrisome pathogens.

From the pharmacodynamic perspective, antimicrobials are basically classified according to the type of antibacterial activity (concentration-dependent or time-dependent) and the presence of post-antibiotic effect (time to bacterial regrowth after elimination of the antibiotic from the media)¹²⁶. According to this, three main groups can be defined:

1) Antibiotics with concentration-dependent activity and prolonged post-antibiotic effect. PK/PD parameters related to efficacy are C_{max}/MIC and AUC/MIC . Commonly used antibiotics in the ICU included in this group are: aminoglycosides, fluoroquinolones and daptomycin. Target values of PK/PD parameters are: C_{max}/MIC of 10-12 for aminoglycosides, and $AUC_{0-24h}/MIC > 125$ for fluoroquinolones in severe infections and ≥ 666 for daptomycin^{126,127}.

2) Antibiotics with time-dependent activity and minimal or moderate post-antibiotic effect. The PK/PD parameter related to efficacy is $fT > MIC$ (time that free concentrations exceed the MIC, expressed as % of the dosing interval). Commonly used antibiotics in the ICU included in this group are: penicillins, cephalosporins, monobactams, carbapenems and macrolides, with target values of $> 50\%$ for penicillins, $> 60-70\%$ for cephalosporins and monobactams, $> 30-40\%$ for carbapenems and $> 40\%$ for macrolides^{126,127}.

3) Antibiotics with concentration-independent action and prolonged antibiotic effect. The PK/PD parameter related to efficacy is the AUC/MIC . Commonly used antibiotics in the ICU included in this group are: vancomycin, linezolid, azalides and tigecycline, with target values of ≥ 400 for vancomycin, ≥ 100 for linezolid, ≥ 25 for azalides and $\geq 15-20$ for tigecycline^{126,127}.

Antibiotics belonging to the first group can be used at high doses and the prolonged post-antibiotic effect allows wider dos-

ing intervals. In this sense there is good evidence for extended duration of the dosing interval of aminoglycosides in critically ill patients¹² that, in addition, reduces renal toxicity¹²⁷. For antibiotics in the second group, the objective is the consecution of a long bacterial exposure to the antibiotic; for this reason, continuous infusion (when possible) is the best regimen since antibiotic serum concentrations are constantly above the MIC for the duration of treatment. In an in vitro model the intermittent infusion of ceftazidime provided bactericidal activity against susceptible *P. aeruginosa* strains, but not against resistant strains, and continuous infusion optimised $t > MIC$ and resulted in bactericidal activity¹²⁸. Continuous infusion with an initial loading dose (to rapidly obtain bactericidal concentrations) allows adequate concentrations at steady-state, minimising fluctuations of serum concentrations. However, there are scarce clinical studies demonstrating the better efficacy obtained with continuous versus intermittent infusion; with reports using piperacillin/tazobactam¹²⁹ or meropenem¹³⁰. In contrast, no significant differences in outcomes and toxicity between bolus and continuous infusion of β -lactams are usually described, with a lack of studies in the ICU¹²⁷.

Finally, for antibiotics in the third group the increase in concentrations only slightly increase bacterial eradication, but highly increase a prolonged inhibition of bacterial growth. One of the principal difficulties for vancomycin dosing is predicting future doses from trough level data in the ICU, and therapeutic drug monitoring is needed¹². Administration of vancomycin by continuous infusion has been advocated to improve clinical outcome, although data from ICU patient are scarce. A published study showed lower mortality in ICU patients with ventilator-associated pneumonia receiving continuous vancomycin infusion¹³¹. However, the risk of nephrotoxicity associated with continuous-infusion vancomycin requires further investigation¹³² since acute kidney injury was frequently observed during continuous vancomycin infusion in a study in critically ill patients¹³³. In the case of linezolid, both AUC/MIC and $t > MIC$ (85%) correlate with eradication and clinical cure in ICU patients¹³⁴. However, interstitial linezolid concentrations in patients with sepsis suffer high inter-individual variability, supporting more frequent dosing schemes to avoid subinhibitory concentrations in infected tissues¹³⁵. Continuous infusion has also been suggested for critically ill patients to obtain more stable linezolid levels and adequate AUC/MIC and $t > MIC$ values¹³⁶.

Colistin, a polymyxin agent, is in some cases the last option for the treatment of multidrug resistant *A. baumannii* and *P. aeruginosa*. It exhibits a concentration-dependent activity with prolonged post-antibiotic effect at high concentrations¹³⁷. Due to its poor gastrointestinal absorption and the classically reported nephrotoxicity and neurotoxicity of the intravenous formulation, in the ICU setting colistin is usually used as nebulized drug. However, colistin can be the sole agent active against multi-drug resistant gram-negatives in critical care, and it has been suggested that its toxicity may have been overestimated¹³⁷. The lack of PK/PD data results in a difficulty for optimisation of its daily dose aimed to maximise the AUC/

MIC ratio, parameter best associated with colistin efficacy¹³⁸.

In critically ill patients, in addition to alterations in hepatic or renal functions, variations in the extravascular fluid affect drug disposition. Hydrophilic drugs (β -lactams, aminoglycosides and glycopeptides) and renally excreted moderately lipophilic agents (quinolones) have a considerable risk of presenting daily fluctuations in plasma concentrations that may require dose adjustments¹³⁹. Hydrophilic compounds tend to have much larger volume of distribution and tend to expand when the volume of extracellular water expands greatly, as occurs during the acute inflammatory phase, thus high starting doses may be optimal¹². On the other hand, for lipophilic agents (as linezolid and macrolides), the dilution in interstitial fluids is less relevant, but they penetrate deeper into fatty tissues and thus, published evidence supports larger doses in patients with a greater amount of adipose tissue¹⁴⁰.

Critically ill patients are predisposed to drug interactions due to the complexity of drug regimens. In critically ill patients, interactions of antimicrobials with other pharmacological classes have been described, including immunosuppressants, statins, benzodiazepines, antipsychotics, antiepileptics, antiarrhythmics, loop diuretics and calcium channel blockers¹⁴¹. The drug interaction profile of β -lactams is typically associated with the inhibition of their renal secretion while interactions of macrolides and azalides depend on the inhibition of the CYP450 system and P-glycoprotein. Main interactions of aminoglycosides derive from additive or synergistic effects with other drugs for nephrotoxicity, ototoxicity and neuromuscular blockade. For quinolones, in addition to chelation-related interactions, the risk of QTc prolongation implies monitoring in patients with history of QT prolongation or uncorrected electrolyte abnormalities and those receiving antiarrhythmics. Few drug interactions have been described for vancomycin (but it should be taken into account its non-negligible nephrotoxicity, that may increase with the concomitant use of aminoglycosides), for daptomycin, linezolid and tigecycline¹⁴¹.

INFECTIONS IN THE ICU ENVIRONMENT

Hospital-acquired infections affect a quarter of critically ill patients and can double the risk of patient dying¹⁰, with more than one-quarter of all nosocomial infections diagnosed in the ICU¹⁴². Principal infections diagnosed and/or treated in ICU patients are: respiratory tract infections (nosocomial pneumonia/ventilator-associated pneumonia (VAP)), bloodstream infections (primary bacteremia/catheter-associated bacteremia), urinary tract infections, intraabdominal infections, endocarditis, and surgical wound infections. Table 1 shows by type of infection, microorganisms to be suspected in relation to the presence or not of risk factors for multidrug resistance, and suggested empirical treatments. Table 2 shows recommended antibiotic regimens for critically ill patients.

Respiratory tract infections

Etiology of early-onset infections may be distinguished

from that of late-onset infections. When the disease develops within 4 days of admission or intubation, core organisms are *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catharralis*, microorganisms associated with community-acquired pneumonia¹⁴³. When the disease develops after 5 days, in addition to these core organisms, enterobacteria (*K. pneumoniae*, *E. coli* and the AmpC-producing microorganisms included in the ESCPM group) and *S. aureus* predominate¹⁴³. These last organisms also predominate in patients with severe comorbidities and recent antimicrobial therapy, thus the distinction between early and late onset is far from absolute. In addition, longer duration of mechanical ventilation and treatments with broad-spectrum antimicrobial therapy increase the risk for *P. aeruginosa*, *Acinetobacter* spp. and MRSA¹⁴³, being enterobacteria and non-fermentative gram-negatives more frequent in VAP vs. non-VAP nosocomial pneumonia¹⁴⁴. Of relevance is that 20 to 50% of VAP cases have polymicrobial etiology¹⁴³, and that ESKAPE organisms (*E. faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa* and *Enterobacter* spp.), with their associated resistance profile, constitute 80% of VAP episodes¹⁴⁵.

Bloodstream infections

Critically ill patients carry much higher rates of bloodstream infections than patients in general wards, with an incidence in the ICU ranging from 3 to 10 episodes/100 ICU admissions¹⁴⁶. Staphylococci seems to predominate both in primary bloodstream infections and in those associated with devices¹⁴⁷⁻¹⁴⁹, and although *S. aureus* is a frequent cause, coagulase-negative staphylococci has become the most common cause in last decades¹⁵⁰. However, a significant increase in the incidence of bloodstream infections caused by gram-negatives and fungi has been described¹⁵¹. In a recent multinational study including 162 ICUs, ≈58% bloodstream infections were caused by gram-negatives, 32.8% by gram-positives, 7.8% by fungi and 1.2% by strict anaerobes¹⁵². The rate of polymicrobial infections was 12%¹⁵², but in another study in our country the rate was considerably higher (20%)¹⁵³. The increase in the empirical use of broad-spectrum antibiotics has increased the rate of non-classical bacterial isolates as enterobacteria, non-fermenters and fungi in infusion-related and cannula-related infections¹⁵⁰. Studies in the ICU have shown that *Pseudomonas*, *Acinetobacter* and enterococci in addition to staphylococci (including MRSA) are common cause of bloodstream infections^{147,148}. In addition, ESBL-producing *E. coli* should not be forgotten as common cause of nosocomial bloodstream infections¹⁵⁴.

Urinary tract infections (UTIs)

It has been estimated that UTIs represent 20-50% of all ICU infections¹⁵⁵, the majority of them associated with the use of urethral catheters¹⁵⁶. Duration of catheterization is the main risk factor, with short-term (<30 days) duration associated with a prevalence of 30% and long-term (≥30 days) duration with a 90% prevalence of UTI¹⁵⁷. *E. coli*, *Klebsiella*, *Pseudomonas* and enterococci are target bacteria associated with

short-term duration of catheterization whereas long-term duration is associated, in addition to the previously cited microorganisms, with members of the ESCPM group (with their AmpC production), and with the possibility of polymicrobial infection¹⁵⁷. It should be considered that the most frequent source of bacteremia caused by ESBL-producing bacteria was UTI infection in a Dutch multicenter study¹⁵⁸, and that multi-drug resistant UTIs may be very frequent among patients with sepsis admitted in the ICU¹⁵⁹.

Intraabdominal infections

Core microorganisms are enterobacteria, as *E. coli* or *K. pneumoniae*, and *Bacteroides* spp. (mainly, *Bacteroides fragilis*) in infections in patients with less than 5 days of hospitalization. There are discussions about the role of *Enterococcus* spp., which in some studies plays a minor role in secondary peritonitis¹⁶⁰ but in others increases the rate of morbidity¹⁶¹. In a published study on secondary bacterial peritonitis, higher rates of isolation were found when there was a nosocomial onset of the disease, higher values of Charlson and APACHE II scores, rapidly fatal disease and ICU admission¹⁶². When the onset of the infection occurs in patients with >5 days of hospitalization, and thus there are risks for infection by multidrug resistant bacteria, in addition to core microorganisms, non-fermentative gram-negatives (*P. aeruginosa*, *Acinetobacter* spp.) and ESBL-producing *E. coli* and *K. pneumoniae* should also be suspected. *P. aeruginosa* is more frequently isolated in intraabdominal infections of nosocomial origin and the frequency of ESBL-producers in intraabdominal infections in a multicenter study in our country was ≈8.5% for *K. pneumoniae* and *E. coli*¹⁶³. Importantly, the second most frequent source of bacteremia caused by ESBL-producing bacteria in the Dutch multicenter study previously commented was intraabdominal infection (after UTI)¹⁵⁸.

Endocarditis

Infective endocarditis still carries high morbidity and mortality for the subset of patients requiring ICU admission. Staphylococci and streptococci account for the majority of cases, with trends towards a rising prevalence of cases by staphylococcal skin flora from nosocomial iatrogenic origin¹⁶³. Common blood cultures in infective endocarditis include *S. aureus* (with special importance in intravenous drug users), viridans streptococci (among them *Streptococcus bovis* in the elderly is often associated with underlying gastrointestinal neoplasm), enterococci and coagulase-negative staphylococci¹⁶³⁻¹⁶⁵. Culture-negative infective endocarditis may be up to one-third cases¹⁶⁶, and the HACEK group (*Haemophilus* spp., *Aggregatibacter* -formerly *Actinobacillus*- *actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella* spp.) accounts for 5-10% of all cases of infective endocarditis¹⁶⁷. Percentages for each etiological agent may differ if endocarditis affects native valves or intracardiac devices. While viridans streptococci is more frequent in native valve endocarditis in non-drug users, coagulase-negative staphy-

Table 1			
By type of infection, microorganisms to be suspected in relation to the presence or not of risk factors for multidrug resistance and suggested empirical treatments [VAP: ventilator-associated pneumonia; MDR: multidrug resistance; ESBL: extended-spectrum β -lactamase; ESCPM group (<i>Enterobacter cloacae</i> , <i>Enterobacter aerogenes</i> , <i>Serratia marcescens</i> , <i>Citrobacter freundii</i> , <i>Providencia rettgeri</i> and <i>Morganella morganii</i>); MRSA: methicillin-resistant <i>S. aureus</i> ; HACEK (<i>Haemophilus</i> spp., <i>Aggregatibacter</i> -formerly <i>Actinobacillus-actinomycetemcomitans</i> , <i>Cardiobacterium hominis</i> , <i>Eikenella corrodens</i> , <i>Kingella</i> spp)]			
INFECTION TYPE	SUSPECTED PATHOGENS	EMPIRICAL TREATMENT	COMMENTS
Pneumonia	No risk factors for MDR bacteria	Cefotaxime or ertapenem	IV antibiotic treatment should not exceed >7 days
	<i>S. pneumoniae</i>	±	Addition of macrolides/azalides improves the prognosis of pneumococcal pneumonia
	<i>H. influenzae</i>	Azithromycin or levofloxacin	
	<i>S. aureus</i> (methicillin-susceptible)		
<i>Enterobacteriaceae</i>			
	<i>Legionella</i>		
	Presence of risk factors for first-level of resistance ¹	Piperacillin/tazobactam or cefepime or meropenem or doripenem	ESBL-producing isolates are involved in ~10% pneumonia caused by enterobacteria. When confirmed, monotherapy with carbapenems (meropenem, imipenem, ertapenem) is indicated
	Above microorganisms plus:	PLUS	
	ESBL-producing enterobacteria		
	Penicillin-resistant <i>S. pneumoniae</i>	Levofloxacin or amikacin	Suspicion of infection by <i>P. aeruginosa</i> : It is recommended the association of two antipseudomonal compounds
	<i>P. aeruginosa</i>	±	
	MRSA	Linezolid	In bacteremic infections by MRSA, consider the association of linezolid + daptomycin
	Presence of risk factors for second-level of resistance ²	Antipseudomonal betalactam different from those previously used, with preference for carbapenems	Treatment election should consider local epidemiology, previous antibiotic treatments and susceptibility of isolates in surveillance cultures of colonizing flora
	Above microorganisms plus:	PLUS	Consider administration of an inhaled antibiotic
	Non-fermenter gramnegative bacilli		
	AmpC and/or carbapenemase-producing enterobacteria	Levofloxacin or amikacin	Consider associations with colimycin, fosfomycin and tigecycline
	Multidrug-resistant <i>P. aeruginosa</i>	PLUS	
		Linezolid	

Table 1 By type of infection, microorganisms to be suspected in relation to the presence or not of risk factors for multidrug resistance and suggested empirical treatments [VAP: ventilator-associated pneumonia; MDR: multidrug resistance; ESBL: extended-spectrum β -lactamase; ESCPM group (*Enterobacter cloacae*, *Enterobacter aerogenes*, *Serratia marcescens*, *Citrobacter freundii*, *Providencia rettgeri* and *Morganella morganii*); MRSA: methicillin-resistant *S. aureus*; HACEK (*Haemophilus* spp., *Aggregatibacter* –formerly *Actinobacillus-actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella* spp)] (CONT.)

INFECTION TYPE	SUSPECTED PATHOGENS	EMPIRICAL TREATMENT	COMMENTS
Bloodstream infections: primary bacteremia/ catheter-associated bacteremia	Coagulase-negative staphylococci <i>S. aureus</i> (including MRSA)	Daptomycin PLUS	Gram-negative bacteria should always be suspected in the critically ill patient regardless site of central venous catheter
	<i>Enterococcus</i> spp. <i>E. coli</i> <i>Klebsiella</i> spp. ESCPM group <i>P. aeruginosa</i> <i>Acinetobacter</i> spp.	Cefepime or piperacillin/tazobactam or meropenem or doripenem \pm Amikacin	If methicillin-susceptibility in staphylococci is confirmed, change to cloxacillin In persistent (>5-7 days) or recurrent (without endovascular foci) bacteremia by <i>S. aureus</i> , a second anti-staphylococcal drug (with or without rifampicin) should be added. If the patient is under cloxacillin treatment, add daptomycin with or without rifampicin. If the patient is under daptomycin treatment, add linezolid or fosfomycin or cloxacillin, with or without rifampicin. If the patient is under vancomycin treatment, change to daptomycin + cloxacillin, with or without rifampicin
	<i>Candida</i> spp.	Echinocandin or fluconazol	An antifungal drug with activity against <i>Candida</i> spp. should be considered in critically ill patients with central venous catheter in the femoral vein and/or parenteral nutrition, severe sepsis or recent abdominal surgery
Urinary tract infections	With criteria for severe sepsis or presence of risk factors for first-level of resistance ¹ ESBL-producing enterobacteria	Meropenem or doripenem \pm Amikacin	Due to its high frequency, ESBL-producing enterobacteria should be covered in patients with severe sepsis or septic shock
	Presence of risk factors for second-level of resistance ² Above microorganisms plus: ESCPM group Multidrug-resistant <i>P. aeruginosa</i> , <i>Enterococcus</i> spp. <i>Acinetobacter</i> spp. <i>Candida</i> spp.	Meropenem or doripenem + amikacin \pm Fluconazol	Treatment election should consider local epidemiology, previous antibiotic treatments and susceptibility of isolates in surveillance cultures of colonizing flora Use of colimycin or tigecycline may be necessary. Although tigecycline concentrations in urine are not high, it may be useful in case of pyelonephritis

Table 1	By type of infection, microorganisms to be suspected in relation to the presence or not of risk factors for multidrug resistance and suggested empirical treatments [VAP: ventilator-associated pneumonia; MDR: multidrug resistance; ESBL: extended-spectrum β -lactamase; ESCPM group (<i>Enterobacter cloacae</i> , <i>Enterobacter aerogenes</i> , <i>Serratia marcescens</i> , <i>Citrobacter freundii</i> , <i>Providencia rettgeri</i> and <i>Morganella morganii</i>); MRSA: methicillin-resistant <i>S. aureus</i> ; HACEK (<i>Haemophilus</i> spp., <i>Aggregatibacter</i> -formerly <i>Actinobacillus-actinomycetemcomitans</i> , <i>Cardiobacterium hominis</i> , <i>Eikenella corrodens</i> , <i>Kingella</i> spp)] (CONT.)		
INFECTION TYPE	SUSPECTED PATHOGENS	EMPIRICAL TREATMENT	COMMENTS
Intraabdominal infections	No risk factors for MDR bacteria <i>E. coli</i> <i>K. pneumoniae</i> <i>B. fragilis</i>	Ertapenem or cefotaxime + metronidazole	In case of lack of control of the infectious foci, follow treatment recommendations in the presence of risk factors for first-level resistance
	Presence of risk factors for first-level of resistance ¹ Above microorganisms plus:	Meropenem or imipenem or ertapenem \pm Daptomycin or linezolid or vancomycin	In case of lack of control of the infectious foci, follow treatment recommendations in the presence of risk factors for second-level resistance
	ESBL-producing enterobacteria <i>P. aeruginosa</i> <i>Enterococcus</i> spp. MRSA	OR Tigecycline \pm Piperacillin/tazobactam or ceftipime or amikacin	
	Presence of risk factors for second-level of resistance ² All the above microorganisms plus:	Meropenem or doripenem + daptomycin or linezolid or vancomycin OR	Treatment election should consider local epidemiology, previous antibiotic treatments and susceptibility of isolates in surveillance cultures of colonizing flora
	Non-fermenter gramnegative bacilli AmpC and/or carbapenemase-producing enterobacteria Multidrug-resistant <i>P. aeruginosa</i>	Tigecycline + piperacillin/tazobactam or ceftipime \pm Amikacin \pm	
	<i>Candida</i> spp.	Echinocandin	In critically ill patients, echinocandins are the elective treatment for <i>Candida</i> antifungal therapy

Table 1	By type of infection, microorganisms to be suspected in relation to the presence or not of risk factors for multidrug resistance and suggested empirical treatments [VAP: ventilator-associated pneumonia; MDR: multidrug resistance; ESBL: extended-spectrum β -lactamase; ESCPM group (<i>Enterobacter cloacae</i> , <i>Enterobacter aerogenes</i> , <i>Serratia marcescens</i> , <i>Citrobacter freundii</i> , <i>Providencia rettgeri</i> and <i>Morganella morganii</i>); MRSA: methicillin-resistant <i>S. aureus</i> ; HACEK (<i>Haemophilus</i> spp., <i>Aggregatibacter</i> -formerly <i>Actinobacillus-actinomycetemcomitans</i> , <i>Cardiobacterium hominis</i> , <i>Eikenella corrodens</i> , <i>Kingella</i> spp)] (CONT.)		
INFECTION TYPE	SUSPECTED PATHOGENS	EMPIRICAL TREATMENT	COMMENTS
Endocarditis	<i>S. aureus</i>	Ampicillin + cloxacillin	If glomerular filtrate is <40 ml/min or concomitant treatment with potentially neurotoxic drugs, change gentamicin by daptomycin
Native valve	Coagulase-negative staphylococci	±	
Prosthetic valve >12 months post-surgery	Viridans group streptococci	Gentamicin (3-5 days)	
	<i>Enterococcus</i> spp.		
	<i>Streptococcus bovis</i>		
	HACEK group		
	Risk for MRSA (including intravenous drug users and healthcare facilities)	Ampicillin + daptomycin + fosfomicin ± Gentamicin (3-5 days)	If vancomycin MIC \geq 1 mg/L, severe sepsis or bacteremia for >5 days, consider heteroresistance or tolerance and change to daptomycin
		OR	Addition of gentamicin should be avoided if glomerular filtrate is <40 ml/min. Consider change to cotrimoxazole.
		Ampicillin + vancomycin	Addition of fosfomicin should be avoided if MIC \geq 32 mg/L. Consider change to cotrimoxazole
Prosthetic valve <12 months post-surgery	MRSA	Daptomycin + rifampicin (3-5 days) ± fosfomicin ± gentamicin or amikacin	Vancomycin could be considered when MIC \leq 1 mg/L for the MRSA and normal renal function
	Coagulase-negative staphylococci	PLUS	Addition of gentamicin should be avoided if glomerular filtrate is <40 ml/min. Consider change to cotrimoxazole.
	Viridans group streptococci	Meropenem	Addition of fosfomicin should be avoided if MIC \geq 32 mg/L. Consider change to cotrimoxazole
	<i>Enterococcus</i> spp.		Consider gentamicin if <i>Enterococcus</i> spp. is isolated
	<i>Streptococcus bovis</i>		
	HACEK group		
	<i>E. coli</i>		
	<i>K. pneumoniae</i>		
	<i>Salmonella enteritidis</i>		
	<i>P. aeruginosa</i>		

INFECTION TYPE	SUSPECTED PATHOGENS	EMPIRICAL TREATMENT	COMMENTS
Skin and Soft tissue infections Necrotizing fasciitis (Fournier's gangrene, early surgical wound infection 24-48 h post-surgery)	Group A streptococci	Piperacillin/tazobactam or meropenem	In infections by <i>S. aureus</i> producing panton valentine leukocidin or superantigens, the antibiotic regimen should include linezolid or clindamicin
	<i>Clostridium perfringens</i>	PLUS	
	<i>Clostridium septicum</i>	Daptomycin or linezolid or clindamycin	Consider high doses of tigecycline in moderately severe polymicrobial infections involving MRSA and in patients with allergy to β -lactams
	<i>Staphylococcus aureus</i>	OR	
	Mixed polymicrobial infection:	Tigecycline	
	<i>Enterococcus</i> spp.		
	<i>Bacillus cereus</i>		
	<i>E. coli</i>		
	<i>P. aeruginosa</i>		
	<i>Klebsiella</i> spp.		
<i>Proteus</i> spp.			
<i>Peptostreptococcus</i> spp.			
<i>Bacteroides</i> spp.			

¹Risk factors for first-level of resistance: Significant comorbidities and/or antibiotic treatment for >3-5 days

²Risk factors for second-level of resistance: Hospital admission and/or prolonged antibiotic treatment (>7 days)

Table 2 Doses of common antibiotics for the treatment of infections in the critically ill patient

Drug	Dose (iv)	Comments
Amikacin	20-30 mg/kg / 24 h	
Ampicillin	2 g / 6 h	1-2 g as initial dose followed by 8g in 24h continuous infusion
Azithromycin	500 mg / 24 h	
Cefepime	2 g / 8 h	1-2 g as initial dose followed by 6g in 24h continuous infusion
Ceftazidime	2 g / 8 h	1-2 g as initial dose followed by 6g in 24h continuous infusion
Cefotaxime	2 g / 6-8 h	1-2 g as initial dose followed by 6g in 24h continuous infusion
Ciprofloxacin	400 mg / 8 h	
Cloxacillin	2 g / 4 h	1-2 g as initial dose followed by 12g in 24h continuous infusion
Cotrimoxazole	5 mg/kg of trimetropin / 8 h	
Colimycin	9x10 ⁶ U followed by 4.5x10 ⁶ U / 12 h	
Daptomycin	10 mg/kg/day	May be administered as bolus
Doripenem	1 g / 8 h	Administered as intermittent slow infusion (4 h)
Ertapenem	1 g / 12 h	
Fosfomicin	4-8 g / 8 h	Administered as intermittent slow infusion (4 h) or continuous infusion
Gentamicin	7-9 mg/kg/day (1 dosis)	Referred to adjusted body weight; body weight = ideal body weight + 0.4 x (total weight - ideal weight)
Imipenem	1 g / 8 h	Intermittent slow infusion (2 h)
Levofloxacin	500 mg / 12 h	
Linezolid	600 mg / 8-12 h	1200 mg in 24 h continuous infusion
Meropenem	2 g / 8 h	Intermittent slow infusion (3 h)
Metronidazole	500 mg / 8 h	
Piperacillin-tazobactam	4-0.5 g / 6 h	2 g as initial dose followed by 16g in 24h continuous infusion
Rifampicin	600 mg / 12-24 h	
Tigecycline	100- 200 mg followed by 50- 100 mg / 12 h	
Vancomycin	15-20 mg/kg / 8 h (in 1-2 h) 35 mg/kg as loading dose followed by 35 mg/kg / day in continuous infusion	Kg referred to total body weight

lococci is more frequent in infective endocarditis in patients with intracardiac devices¹⁶⁸ but, in all cases, *S. aureus* is the most frequent pathogen¹⁶⁸.

Surgical wound infections

Bacterial contamination of surgical wounds is inevitable, but common wound pathogens depend on clean / contaminated surgical procedures¹⁶⁹. For clean surgical procedures, staphylococci are the most common cause of wound infections, and the patient's microbiota has been implicated as the most likely source. *S. aureus* rare colonization appears to be the major risk factor for developing *S. aureus* wound infection. This has particular importance in selected populations where colonization rates exceed 50%, as diabetic individuals and hemodialyzed patients¹⁶⁹. Considering the high rates

of methicillin resistance among *S. aureus*, the possibility of infection by MRSA isolates should always be suspected.

For contaminated procedures, wound pathogens frequently are among those species that comprise normal flora of the viscus entered during the surgical procedure. In this sense, polymicrobial infections are common in digestive surgery involving colorectal procedures, with enterobacteria (*E. coli* and *Klebsiella*) and *B. fragilis* as target bacteria. The possibility of a high prevalence of intestinal colonization with ESBL-producing enterobacteria on ICU admission should always be considered in this context¹⁷⁰.

CONCLUSIONS

Antibiotic treatment and use of medical devices are highly frequent in severely ill patients requiring specialized care.

This fact and the concentration of high-risk patients in ICUs constitute accumulative factors for multidrug antibiotic resistance. In hospitals, ICUs are considered areas where antibiotic resistance problems are the largest, and ICU physicians feel that this problem is major and significant in their clinical practice. Recently new antibiotics have been available to overcome non-susceptibility phenotypes in gram-positive microorganisms. However, the plethora of mechanisms of resistance in gram-negative bacteria, new emerging mechanisms and accumulation of resistance traits have lead to multidrug resistance, a worrisome problem in the treatment of gram-negative infections. Intensive care physicians should be aware of the local epidemiology of resistance to select the most appropriate drugs in the antibiotic regimen.

CONFLICT OF INTERESTS

All authors comply with ethical responsibilities and author's requirements, and declare no conflict of interest.

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