REVIEW

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

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Abstract ICUs are areas where resistance problems are the largest, and these 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, metallo-beta-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 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.

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The nosocomial microbiome and resistome

Evolution of relationships between human and bacteria is conditioned by environmental changes. Among anthropogenic factors changing the environment and thus, shaping future interactions between human and bacteria, 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, these factors counterbalance colonization-multidrug resistance in nosocomial microbiota.

The "nosocomial human population", which 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 bacteria, facilitated when bacteria are exposed to antibiotic stress, has driven to multidrug resistance.

Resistance implies the need for new antibiotics that, once introduced, if their mechanism of action is similar to that of 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 circle. 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 strains.

In the presence of antibiotic stress, antimicrobial resistance can be considered a colonization factor. Accumulation of "genotypic colonization factors" (phenotypic resistance traits) drives to multidrug resistance, a 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 at reducing resistance will result not only in a decrease in the resistance prevalence.
but also in a decrease in colonization 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.\textsuperscript{10,11} requiring rapid treatment to reduce morbidity and mortality.\textsuperscript{12} Nosocomial infections acquired in the intensive care unit (ICU) represent an area in which much improvement is still achievable.\textsuperscript{13} However it should be taken into account that infection is often the cause of ICU admission.\textsuperscript{14,15} influencing the microbiological environment of the unit.\textsuperscript{16} 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 patient,\textsuperscript{17} implying that personnel involved should be familiar with available drugs and 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 metallobeta lactamases) in nosocomial gram-negative bacteria. Antibiotics/antibiotic regimens for the treatment of nosocomial infections should counter these sometimes emerging, always dispensable 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 spread in hospitals worldwide, with prevalence reaching rates of 25–50% in much of Americas, Australia and Southern Europe.\textsuperscript{17} The global rate of evolution of MRSA among S. aureus in Spanish ICUs from 1994 to 2008 (study ENVIN-UCI including up to 100 ICUs) shows similar ratios (≈25%) in the first and last years with oscillations ranging from 13% in 1997 to 42.3% in 2006.\textsuperscript{18} In addition to intra-ICU transmission dynamics of MRSA (influenced, among others, by colonization of health care workers in the ICU\textsuperscript{19}), MRSA imported cases in the ICU as a predictor of occurrence of nosocomial MRSA infections should be taken into account,\textsuperscript{20} with community-acquired MRSA genotypes as the emerging cause of colonization among patients admitted in adult ICUs in the USA.\textsuperscript{21}

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 in both 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 enterococci.\textsuperscript{22} 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 glycopeptides\textsuperscript{23} but also quinolones\textsuperscript{23,24} and cephalosporins.\textsuperscript{25,26}

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/L.\textsuperscript{26} 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 susceptible population, and only 10% are homogenous vancomycin intermediate (homoresistant; VISA).\textsuperscript{27,28} The prevalence of h-VISA among MRSA is variable worldwide ranging from ≈10 to 50%.\textsuperscript{29–31} MRSA strains resistant to vancomycin have been described but, fortunately, its diffusion is unappreciable nowadays.\textsuperscript{31} Intermediate resistance to vancomycin can also be found in coagulase-negative staphylococci at non negligible rates (≈10%).\textsuperscript{32}

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”,\textsuperscript{33,34} and is expressed as an MBC/MIC quotient of ≥16 or ≥32.\textsuperscript{35} 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 susceptibility.\textsuperscript{36} Tolerance to vancomycin is present in 100% VISA strains, 75% h-VISA and 15% vancomycin-susceptible MRSA,\textsuperscript{36} and this phenomenon is extensive to other glycopeptides as teicoplanin, with teicoplanin tolerance reported in 18.8% of MRSA strains.\textsuperscript{37} In addition, tolerance to glycopeptides has also been described in ≈25% of coagulase-negative staphylococci and ≥40% of group viridans (Streptococcus bovis, Streptococcus sanguis, Streptococcus gordonii, Streptococcus mutans and Streptococcus oralis) isolates,\textsuperscript{34} 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.\textsuperscript{39} A classical study in our country showed a significantly higher mortality in methicillin-susceptible S. aureus bacteraemia in patients treated with vancomycin compared with cloxacillin, in part attributable to the slow vancomycin killing.\textsuperscript{40} This was corroborated in an in vitro study showing that vancomycin was not bactericidal within the dosing interval in contrast to daptomycin, regardless of methicillin susceptibility/resistance of the study strains.\textsuperscript{41}
Some high-inoculum staphylococcal infections such as bacteremia, persistent bacteremia, endocarditis and osteomyelitis have been associated with heteroresistance.\textsuperscript{13,42,43} Vancomycin heteroresistance has been linked to strains susceptible to vancomycin but with high MIC values within the susceptibility category.\textsuperscript{64,45} In turn, the relationship of MICs to clinical failure with vancomycin is striking.\textsuperscript{53} In a published study, high vancomycin MICs, defined as 1.5–2.0mg/ml, was an independent predictor of poor response to vancomycin therapy for MRSA infection, even when vancomycin trough levels >15mg/ml were achieved.\textsuperscript{46} Importantly, vancomycin trough levels >15mg/ml appears to be associated with a 3-fold increased risk of nephrotoxicity.\textsuperscript{57}

Considering the current situation, it has been suggested that strains with vancomycin MIC of 1–2mg/l should be considered h-VISA or VISA\textsuperscript{46} since even the new Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoint for vancomycin (≤2mg/l) may fail to precisely differentiate potential responders to vancomycin therapy.\textsuperscript{6,49} Suggesting that, according to clinical data, the breakpoint value should be even lowered to 1 or 0.5mg/l.\textsuperscript{46}

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 48h.\textsuperscript{50} Clinical implications of heteroresistance and tolerance evidenced as poor clinical outcome, persistence of bacteremia and increased length of stay,\textsuperscript{24,51–55} together with the fact that these phenomena are not routinely assessed by microbiologists and reported to treating physicians,\textsuperscript{54} 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 infection.\textsuperscript{56} All enterococci show tolerance to vancomycin.\textsuperscript{57} In addition, acquisition of resistance to ampicillin, aminoglycosides (high level) and glycopeptides in E. faecium is a cause of concern,\textsuperscript{58} making E. faecium infections difficult to treat. In USA vancomycin resistance increased in E. faecium isolates from 0% in mid 1980s to 80% in 2007.\textsuperscript{58} In Europe the vancomycin resistance prevalence is variable, ranging from <1% to >40%.\textsuperscript{22,59} In Spain rates of around 14.3% have been reported in E. faecium.\textsuperscript{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 VRE.\textsuperscript{2} 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 pressure.\textsuperscript{61} Factors associated with VRE colonization 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 use.\textsuperscript{62–64} Risk factors for development of VRE infections include prolonged hospitalization, surgical or intensive care units, intravascular or bladder catheter devices, proportion of colonized patients and exposure to antibiotics.\textsuperscript{65,66} Among antibiotics, in addition to vancomycin, certain compounds as ticarcillin/clavulanate and third generation cephalosporins have demonstrated to cause selection.\textsuperscript{57,66} Although initially hospital-associated clones were different from community-associated clones, the latter have become important nosocomial pathogens,\textsuperscript{58} with colonization prior to ICU admission being associated with previous hospitalization and, again, antibiotic exposure.\textsuperscript{59}

In enterococci full resistance to daptomycin, although reported,\textsuperscript{72} is rare, as for linezolid.\textsuperscript{58} The increase in linezolid use has been related to an increase (and to outbreaks) in VRE resistant to linezolid,\textsuperscript{71–73} also in patients not previously exposed to the drug.\textsuperscript{74} Clinical outcomes are worse and mortality higher in patients with VRE infections when compared to that in those infected with susceptible strains.\textsuperscript{65} 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 rule.\textsuperscript{75} 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, such as bacteremia, endocarditis, meningitis and infections in immunocompromised patients.\textsuperscript{59}

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 strain,\textsuperscript{75} and has been successfully used in the treatment of refractory bacteremia by tolerant isolates.\textsuperscript{76} The election of drugs to be included in the combination is important since antagonistic interactions between linezolid and vancomycin or between linezolid and gentamicin have been described.\textsuperscript{77,78} On one hand, and the commented high aminoglycoside resistance in VRE on the other. No antagonistic interactions have been shown between daptomycin and gentamicin, linezolid or vancomycin.\textsuperscript{79}
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*.\(^4\) 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 such 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 pathogens.\(^8\) 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 the proportions are ≈20% (carbapenems), ≈15% (ceftazidime) and ≈25% (aminoglycosides and quinolones).\(^9\) In *K. pneumoniae*, resistance to third-generation cephalosporins and aminoglycosides is ≈10% and ≈18% for quinolones.\(^9\)

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

**ESBL**

After the introduction in the 1980s 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-lactamas that, unlike TEM and SHV ESBLs, did not remain confined to *Klebsiella* and have proliferated in *Escherichia coli*.\(^10\) In Spain the prevalence of ESBL-producing *E. coli* has 8-fold increased from 2000 to 2006;\(^11\) the SMART study reported a frequency of ESBL-producing isolates of ≈8.5% for *E. coli* and for *Klebsiella* spp.\(^12\) Urine, followed by blood, and internal medicine, general surgery and ICUs were the most common sites and wards of isolation, respectively, in another study.\(^13\)

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 of conferring resistance to penicillins, to first-, second- and third-generation cephalosporins and also to aztreonam (but not to cephamycins and carbapenems), but can be inhibited by β-lactamase inhibitors.\(^14\) 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 (≈70% and ≈80%, respectively).\(^15\) In addition, in ESBL-producing strains co-resistance to aminoglycosides and quinolones is present.\(^16\) 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 mortality in 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*.\(^17\)

Selection and diffusion of ESBLs have been associated with antibiotic pressure derived from the use of third-generation cephalosporins (with special importance for ceftazidime), aminoglycosides and quinolones, but not β-lactams/β-lactam inhibitors or carbapenems.\(^18\) In addition to previous antibiotic treatments, other risk factors that have been described for infection by ESBL-producing isolates in ICU patients are previous hospitalization, advanced age, diabetes and use of catheters.\(^19\)

Carbapenems are probably the best options for treating infections caused by ESBL-producing strains,\(^20,17\) but the risk of the emergence of carbapenem resistance should always be considered (see below).

**AmpC**

Isolates of *Enterobacter cloacae*, *Enterobacter aerogenes*, *Serratia marcescens*, *Citrobacter freundii*, *Providencia rettgeri* and *Morganella morganii* (known as the ESCP group) have the potential to produce AmpC-inducible chromosomal β-lactamas 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.\(^20,21\) 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.\(^22,23\) 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-lactamas.\(^24\)

Derepressed overproduction has been described in 20% infections by *Citrobacter* spp. or *Enterobacter* spp. during third-generation cephalosporin treatment.\(^3\)

AmpC genes have been mobilized to plasmids and spread worldwide, with increasing numbers in the diversity of this type of enzymes.\(^2\) Infections caused by plasmid AmpC-producing isolates significantly increase treatment failure probably due to inadequate initial treatment therapy.\(^25\) 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.\textsuperscript{12,13} In addition, ESBLs have been increasingly described in AmpC producers, which further complicate decisions related to the optimum antimicrobial therapy.\textsuperscript{13}

AmpC- and ESBL-producing isolates exhibit high rates of resistance to penicillins (including piperacillin/tazobactam) and cephalosporins (including cefepime) according to EUCAST breakpoints.\textsuperscript{86} Treatment with carbapenems represents a good option but, again, concerns on the potential emergence of carbapenem resistance arise.

**Carbapenemases**

Most carbapenemase-producers have multiple resistance mechanisms to β-lactams and to aminoglycosides.\textsuperscript{94}

Resistance to carbapenems can arise by the following:

(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 heavy use of carbapenems after dissemination of multidrug resistant *Enterobacteriaceae* (due to ESBL and AmpC β-lactamases) raises the fear of the relationship between the use of these antibiotics and the selection and diffusion of carbapenem-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 no clinically available inhibitors to block MBLs action.\textsuperscript{95} The association of carbapenem production to resistance traits to other antibiotic classes may lead to polymyxins and tigecycline as last active agents, neither of them being 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*.\textsuperscript{96}

**P. aeruginosa**

Pan-resistance in *P. aeruginosa* results from the convergence of multiple resistance mechanisms\textsuperscript{97}: low outer membrane permeability, AmpC β-lactamases, efflux pumps and, less often, production of MBLs.\textsuperscript{75,98} However, in many European countries, mainly in the Mediterranean area, VIM producing *P. aeruginosa* has currently become endemic.\textsuperscript{79} 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 2008.\textsuperscript{100} According to the EARS\textsuperscript{2} study, non-susceptibility rates are ≈8% to piperacillin/tazobactam, ≈15% to ceftazidime, ≈25% to aminoglycosides and quinolones, and ≈20% to carbapenems.\textsuperscript{80} In the ICU, risk factors for multidrug resistance in *P. aeruginosa* are previous exposure to third-generation cephalosporins, to carbapenems or to acylureidopenicillins.\textsuperscript{101}

**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 properties.\textsuperscript{102} Additionally, resistance to carbapenems has been linked to the loss of outer membrane porins and upregulated efflux pumps.\textsuperscript{80} Resistance to carbapenems remained rare until 2000 despite its widespread resistance to other compounds.\textsuperscript{98} However, carbapenem resistance has increased sharply since then, and is mediated by OXA-type, and less often by IMP- and VIM-type, carbapenemases.\textsuperscript{103,104} Several studies have described the OXA-40 gene spread across the Iberian Peninsula.\textsuperscript{103,104} In our country, resistance rates are ≈35% to amikacin, ≈40% to ceftazidime, ≈70% to piperacillin/tazobactam, and ≈45% to carbapenems.\textsuperscript{105} It is considered that resistance to carbapenems is enough to define an isolate as highly resistant.\textsuperscript{106} 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.\textsuperscript{107,108}

**Enterobacteriaceae**

As previously described, the main multidrug resistance phenotype in enterobacteria is 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 carbapenem 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*.\textsuperscript{109} In Spain, class B carbapenemase-producers (VIM-1 and IMP-22) have been found in specific areas (Madrid, Catalonia, Andalucia, Balearic Islands) with a local prevalence <0.2%.\textsuperscript{110} But the situation may be changing since the description of VIM-producers outbreaks,\textsuperscript{109,111} together with the emergence of the KPC-3\textsuperscript{112} and the New Delhi MBL (NDM-1) β-lactamases in *K. pneumoniae* and *E. coli*.\textsuperscript{116,117} Confirming the dissemination of carbapenemase-producing isolates in our country. Nonetheless, according to last EARS\textsuperscript{2} data in 2011, carbapenem resistance in *K. pneumoniae* in Spain is 0.3%.\textsuperscript{111} 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.\textsuperscript{80,118-123} Carbapenem-resistant *K. pneumoniae* has been independently associated with poor outcome and death.\textsuperscript{108,120,123}
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 sepsis\textsuperscript{124} 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 1 h of prescription.\textsuperscript{12} What is often overlooked is the optimum dose of an antibiotic,\textsuperscript{12} and to avoid empiricism, the PK/PD relation should be exploited.\textsuperscript{80} 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 outcome.\textsuperscript{125} Ideally, the first dose should rapidly reach enough concentrations above the MIC to avoid resistance selection, and these concentrations should be maintained throughout 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 antimicrobials as soon as culture results are ready.\textsuperscript{80} 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).\textsuperscript{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 Cmax/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: Cmax/MIC of 10–12 for aminoglycosides, and AUC\textsubscript{0–24h}/MIC >125 for fluoroquinolones in severe infections and >666 for daptomycin.\textsuperscript{126,127}

2. Antibiotics with time-dependent activity and minimal or moderate post-antibiotic effect. The PK/PD parameter related to efficacy is \( t>MIC \) (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.\textsuperscript{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 ≥15–20 for tigecycline.\textsuperscript{126,127}

Antibiotics belonging to the first group can be used at high doses and the prolonged post-antibiotic effect allows wider dosing intervals. In this sense there is good evidence for extended duration of the dosing interval of aminoglycosides in critically ill patients\textsuperscript{12} that, in addition, reduces renal toxicity.\textsuperscript{127} 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 \textit{P. aeruginosa} strains, but not against resistant strains, and continuous infusion optimized \( t>MIC \) and resulted in bactericidal activity.\textsuperscript{128} Continuous infusion with an initial loading dose (to rapidly obtain bactericidal concentrations) allows adequate concentrations at steady state, minimizing fluctuations of serum concentrations. However, there are scarce clinical studies demonstrating the better efficacy obtained with continuous versus intermittent infusion; with reports using piperacillin/tazobactam\textsuperscript{129} or meropenem.\textsuperscript{130} 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 ICU.\textsuperscript{127}

Finally, for antibiotics in the third group, the increase in concentrations only slightly increases bacterial eradication, but highly increases 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 needed.\textsuperscript{12} Administration of vancomycin by continuous infusion has been advocated to improve clinical outcome, although data from ICU patients are scarce. A published study showed lower mortality in ICU patients with ventilator-associated pneumonia receiving continuous vancomycin infusion.\textsuperscript{131} However, the risk of nephrotoxicity associated with continuous-infusion vancomycin requires further investigation\textsuperscript{132} since acute kidney injury was frequently observed during continuous vancomycin infusion in a study in critically ill patients.\textsuperscript{133} In the case of linezolid, both AUC/MIC and \( t>MIC \) (85%) correlate with eradication and clinical cure in ICU patients.\textsuperscript{134} However, interstitial linezolid concentrations in patients with sepsis suffer high inter-individual variability, supporting more frequent dosing schemes to avoid subinhibitory concentrations in infected tissues.\textsuperscript{135} Continuous infusion has also been suggested for critically ill patients to obtain more stable linezolid levels and adequate AUC/MIC and \( t>MIC \) values.\textsuperscript{136}

Colistin, a polymyxin agent, is in some cases the last option for the treatment of multidrug resistant \textit{A. baumannii} and \textit{P. aeruginosa}. It exhibits a concentration-dependent activity with prolonged post-antibiotic effect at high concentrations.\textsuperscript{131} 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 a 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 overestimated. The lack of PK/PD data results in a difficulty for optimization of its daily dose aimed at maximizing the AUC/MIC ratio, parameter best associated with colistin efficacy.

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 adjustments. 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 optimal. On the contrary, 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 tissue.

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, benzodiazepins, antipsychotics, antiepileptics, antiarrhythmics, loop diuretics and calcium channel blockers. 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 its non-negligible nephrotoxicity, that may increase with the concomitant use of aminoglycosides should be taken into account), daptomycin, linezolid and tigecycline.

**Respiratory tract infections**

Aetiology 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 catarrhalis*, microorganisms associated with community-acquired pneumonia. 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* predominate. 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 MRSA, with enterobacteria and non-fermentative gram-negatives being more frequent in VAP versus non-VAP nosocomial pneumonia.

Of relevance is that 20 to 50% of VAP cases have polymicrobial aetiology 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 episodes.

**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 admissions. Staphylococci seems to predominate both in primary bloodstream infections and in those associated with devices, and although *S. aureus* is a frequent cause, coagulase-negative staphylococci has become the most common cause in the last decades. However, a significant increase in the incidence of bloodstream infections caused by gram-negatives and fungi has been described. 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 anaerobes. The rate of polymicrobial infections was 12%, but in another study in our country the rate was considerably higher (20%). The increase in the empirical use of broad-spectrum antibiotics has increased the rate of non-classical bacterial isolates such as enterobacteria, non-fermenters and fungi in infusion-related and cannula-related infections. Studies in the ICU have shown that *Pseudomonas*, *Acinetobacter* and enterococci in addition to staphylococci (including MRSA) are the common cause of bloodstream infections. In addition, ESBL-producing *E. coli* should not be forgotten as the common cause of nosocomial bloodstream infections.

**Urinary tract infections (UTIs)**

It has been estimated that UTIs represent 20–50% of all ICU infections, the majority of them associated with the use of urethral catheters. 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)
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)].

<table>
<thead>
<tr>
<th>Infection type</th>
<th>Suspected pathogens</th>
<th>Empirical treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>No risk factors for MDR bacteria</td>
<td>Cefotaxime or ertapenem ± Azithromycin or levofloxacin</td>
<td>IV antibiotic treatment should not exceed &gt;7 days Addition of macrolides/azalides improves the prognosis of pneumococcal pneumonia</td>
</tr>
<tr>
<td></td>
<td>S. pneumoniae</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>H. influenzae</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>S. aureus (methicillin susceptible)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Enterobacteriaceae</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Legionella</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of risk factors for first level of resistance&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Piperacillin/tazobactam or cefepime or meropenem or doripenem PLUS Levofloxacin or amikacin</td>
<td>ESBL-producing isolates are involved in ≈10% pneumonia caused by enterobacteria. When confirmed, monotherapy with carbapenems (meropenem, imipenem, ertapenem) is indicated</td>
<td></td>
</tr>
<tr>
<td>Above microorganisms plus:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESBL-producing enterobacteria</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin-resistant S. pneumoniae</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P. aeruginosa</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MRSA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of risk factors for second level of resistance&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Antipseudomonal betalactam different from those previously used, with preference for carbapenems PLUS Levofloxacin or amikacin PLUS Linezolid</td>
<td>In bacteremic infections by MRSA, consider the association of linezolid + daptomycin Treatment election should consider local epidemiology, previous antibiotic treatments and susceptibility of isolates in surveillance cultures of colonizing flora</td>
<td></td>
</tr>
<tr>
<td>Above microorganisms plus:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fermenter gram negative bacilli</td>
<td></td>
<td></td>
<td>Consider administration of an inhaled antibiotic</td>
</tr>
<tr>
<td>AmpC and/or carbapenemase-producing enterobacteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multidrug-resistant P. aeruginosa</td>
<td></td>
<td></td>
<td>Consider associations with colimycin, fosfomycin and tigecycline</td>
</tr>
<tr>
<td>Infection type</td>
<td>Suspected pathogens</td>
<td>Empirical treatment</td>
<td>Comments</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Bloodstream infections: primary</td>
<td>Coagulase-negative staphylococci</td>
<td>Daptomycin</td>
<td>Gram-negative bacteria should always be suspected in the critically ill patient regardless of site of central venous catheter</td>
</tr>
<tr>
<td>bacteraemia/catheter-associated</td>
<td><em>S. aureus</em> (including MRSA)</td>
<td>PLUS</td>
<td>If methicillin susceptibility in staphylococci is confirmed, change to cloxacillin</td>
</tr>
<tr>
<td>bacteraemia</td>
<td><em>Enterococcus</em> spp.</td>
<td>Cefepime or piperacillin/tazobactam or meropenem or doripenem</td>
<td>In persistent (&gt;5–7 days) or recurrent (without endovascular foci) bacteraemia by <em>S. aureus</em>, a second anti-staphylococcal drug (with or without rifampicin) should be added.</td>
</tr>
<tr>
<td></td>
<td><em>E. coli</em></td>
<td>Amikacin</td>
<td>If the patient is under cloxacillin treatment, add daptomycin, with or without rifampicin.</td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella</em> spp.</td>
<td></td>
<td>If the patient is under daptomycin treatment, add linezolid or fosfomycin or cloxacillin, with or without rifampicin.</td>
</tr>
<tr>
<td></td>
<td>ESCPM group</td>
<td></td>
<td>If the patient is under vancomycin treatment, change to daptomycin + cloxacillin, with or without rifampicin.</td>
</tr>
<tr>
<td></td>
<td><em>P. aeruginosa</em></td>
<td></td>
<td>Due to its high frequency, ESBL-producing enterobacteria should be considered in patients with severe sepsis or septic shock.</td>
</tr>
<tr>
<td></td>
<td><em>Acinetobacter</em> spp.</td>
<td></td>
<td>Treatment election should consider local epidemiology, previous antibiotic treatments and susceptibility of isolates in surveillance cultures of colonizing flora.</td>
</tr>
<tr>
<td></td>
<td><strong>Candida</strong> spp.</td>
<td>Echinocandin or fluconazol</td>
<td>Use of colimycin or tigecyclin may be necessary. Although tigecycline concentrations in urine are not high, it may be useful in case of pyelonephritis.</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>With criteria for severe sepsis or presence of risk factors for first-level of resistance&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Meropenem or doripenem ± Amikacin</td>
<td>Treatment election should consider local epidemiology, previous antibiotic treatments and susceptibility of isolates in surveillance cultures of colonizing flora.</td>
</tr>
<tr>
<td></td>
<td>ESBL-producing enterobacteria</td>
<td></td>
<td>Use of colimycin or tigecyclin may be necessary. Although tigecycline concentrations in urine are not high, it may be useful in case of pyelonephritis.</td>
</tr>
<tr>
<td></td>
<td>Presence of risk factors for second-level of resistance&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Meropenem or Doripenem + Amikacin ± Fluconazol</td>
<td>Use of colimycin or tigecyclin may be necessary. Although tigecycline concentrations in urine are not high, it may be useful in case of pyelonephritis.</td>
</tr>
<tr>
<td></td>
<td>Above microorganisms plus:</td>
<td></td>
<td>Use of colimycin or tigecyclin may be necessary. Although tigecycline concentrations in urine are not high, it may be useful in case of pyelonephritis.</td>
</tr>
<tr>
<td></td>
<td>ESCPM group</td>
<td></td>
<td>Use of colimycin or tigecyclin may be necessary. Although tigecycline concentrations in urine are not high, it may be useful in case of pyelonephritis.</td>
</tr>
<tr>
<td></td>
<td><em>P. aeruginosa</em></td>
<td></td>
<td>Use of colimycin or tigecyclin may be necessary. Although tigecycline concentrations in urine are not high, it may be useful in case of pyelonephritis.</td>
</tr>
<tr>
<td></td>
<td><em>Enterococcus</em> spp.</td>
<td></td>
<td>Use of colimycin or tigecyclin may be necessary. Although tigecycline concentrations in urine are not high, it may be useful in case of pyelonephritis.</td>
</tr>
<tr>
<td></td>
<td><em>Acinetobacter</em> spp.</td>
<td></td>
<td>Use of colimycin or tigecyclin may be necessary. Although tigecycline concentrations in urine are not high, it may be useful in case of pyelonephritis.</td>
</tr>
<tr>
<td></td>
<td><strong>Candida</strong> spp.</td>
<td></td>
<td>Use of colimycin or tigecyclin may be necessary. Although tigecycline concentrations in urine are not high, it may be useful in case of pyelonephritis.</td>
</tr>
</tbody>
</table>

<sup>a</sup> Due to its high frequency, ESBL-producing enterobacteria should be considered in patients with severe sepsis or septic shock. If the patient is under vancomycin treatment, change to daptomycin + cloxacillin, with or without rifampicin.

<sup>b</sup> Treatment election should consider local epidemiology, previous antibiotic treatments and susceptibility of isolates in surveillance cultures of colonizing flora.

---

**Table 1 (Continued)**

**Infection type** | **Suspected pathogens** | **Empirical treatment** | **Comments**
--- | --- | --- | ---

**Bloodstream infections:** primary bacteraemia/catheter-associated bacteraemia

- Coagulase-negative staphylococci
- *S. aureus* (including MRSA)
- *Enterococcus* spp.
- *E. coli*
- *Klebsiella* spp.
- ESCPM group
- *P. aeruginosa*
- *Acinetobacter* spp.

**Empirical treatment**

- Daptomycin
- PLUS
- Cefepime or piperacillin/tazobactam or meropenem or doripenem

**Comments**

- Gram-negative bacteria should always be suspected in the critically ill patient regardless of site of central venous catheter.
- If methicillin susceptibility in staphylococci is confirmed, change to cloxacillin.
- In persistent (>5–7 days) or recurrent (without endovascular foci) bacteraemia by *S. aureus*, 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.
- Due to its high frequency, ESBL-producing enterobacteria should be considered in patients with severe sepsis or septic shock.
- Treatment election should consider local epidemiology, previous antibiotic treatments and susceptibility of isolates in surveillance cultures of colonizing flora.

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**Urinary tract infections**

- With criteria for severe sepsis or presence of risk factors for first-level of resistance<sup>a</sup>
- ESBL-producing enterobacteria
- Presence of risk factors for second-level of resistance<sup>b</sup>
- Above microorganisms plus:
- ESCPM group
- Multidrug-resistant *P. aeruginosa*, *Enterococcus* spp.
- *Acinetobacter* spp.
- **Candida** spp.

**Empirical treatment**

- Meropenem or doripenem ± Amikacin

**Comments**

- Use of colimycin or tigecyclin may be necessary. Although tigecycline concentrations in urine are not high, it may be useful in case of pyelonephritis.
### Table 1 (Continued)

<table>
<thead>
<tr>
<th>Infection type</th>
<th>Suspected pathogens</th>
<th>Empirical treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraabdominal infections</td>
<td>No risk factors for MDR bacteria &lt;br&gt; <em>E. coli</em> &lt;br&gt; <em>K. pneumoniae</em> &lt;br&gt; <em>B. fragilis</em> &lt;br&gt; Presence of risk factors for first-level of resistance&lt;sup&gt;a&lt;/sup&gt; &lt;br&gt; Above microorganisms plus: &lt;br&gt; ESBL-producing enterobacteria &lt;br&gt; <em>P. aeruginosa</em> &lt;br&gt; <em>Enterococcus spp.</em> &lt;br&gt; MRSA &lt;br&gt; Presence of risk factors for second-level of resistance&lt;sup&gt;b&lt;/sup&gt; &lt;br&gt; All the above microorganisms plus: &lt;br&gt; Non-fermenter gram negative bacilli &lt;br&gt; AmpC and/or carbapenemase-producing enterobacteria &lt;br&gt; Multidrug-resistant <em>P. aeruginosa</em> &lt;br&gt; <em>Candida spp.</em></td>
<td>Ertapenem or cefotaxime + metronidazole &lt;br&gt; Meropenem or imipenem or ertapenem &lt;br&gt; ± Daptomycin or linezolid or vancomycin or amikacin &lt;br&gt; OR Tigecycline &lt;br&gt; ± Piperacillin/tazobactam or cefepime or amikacin &lt;br&gt; Meropenem or doripenem + daptomycin or linezolid or vancomycin or amikacin &lt;br&gt; OR Tigecycline + piperacillin/tazobactam or cefepime &lt;br&gt; ± Amikacin</td>
<td>In case of lack of control of the infectious foci, follow treatment recommendations in the presence of risk factors for first-level resistance &lt;br&gt; In case of lack of control of the infectious foci, follow treatment recommendations in the presence of risk factors for second-level resistance &lt;br&gt; Treatment election should consider local epidemiology, previous antibiotic treatments and susceptibility of isolates in surveillance cultures of colonizing flora</td>
</tr>
<tr>
<td>Endocarditis</td>
<td><em>S. aureus</em> &lt;br&gt; Coagulase-negative staphylococci &lt;br&gt; Viridans group streptococci &lt;br&gt; <em>Enterococcus spp.</em> &lt;br&gt; <em>Streptococcus bovis</em> &lt;br&gt; HACEK group</td>
<td>Amoxicillin + cloxacillin &lt;br&gt; Gentamicin (3–5 days)</td>
<td>In critically ill patients, echinocandins are the elective treatment for Candida antifungal therapy. If glomerular filtrate is &lt;40 ml/min or concomitant treatment with potentially neurotoxic drugs, change gentamicin by daptomycin</td>
</tr>
<tr>
<td>Infection type</td>
<td>Suspected pathogens</td>
<td>Empirical treatment</td>
<td>Comments</td>
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</tr>
<tr>
<td>Risk for MRSA (including intravenous drug users and healthcare facilities)</td>
<td>Ampicillin + daptomycin + fosfomycin ± Gentamicin (3–5 days)</td>
<td>If vancomycin MIC ≥ 1 mg/l, severe sepsis or bacteremia for &gt;5 days, consider heteroresistance or tolerance and change to daptomycin</td>
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</tr>
<tr>
<td>OR</td>
<td>Ampicillin + vancomycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prosthetic valve &lt;12 months post-surgery</td>
<td>Daptomycin + rifampicin (3–5 days) ± fosfomycin ± gentamicin or amikacin PLUS Meropenem</td>
<td>Addition of gentamicin should be avoided if glomerular filtrate is &lt;40 ml/min. Consider change to cotrimoxazole.</td>
<td></td>
</tr>
<tr>
<td>MRSA</td>
<td>Vancomycin</td>
<td>Addition of fosfomycin should be avoided if MIC ≥ 32 mg/l. Consider change to vancomycin</td>
<td></td>
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<tr>
<td>Coagulase-negative staphylococci</td>
<td></td>
<td>Vancomycin could be considered when MIC ≤ 1 mg/l for the MRSA and normal renal function</td>
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<tr>
<td>Viridans group streptococci</td>
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<tr>
<td>Enterococcus spp.</td>
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<tr>
<td>Streptococcus bovis</td>
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<tr>
<td>HACEK group</td>
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<tr>
<td>E. coli</td>
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<tr>
<td>K. pneumoniae</td>
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<td></td>
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<tr>
<td>Salmonella enteritidis</td>
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<td></td>
<td></td>
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<tr>
<td>P. aeruginosa</td>
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<tr>
<td>Skin and soft tissue infections</td>
<td>Piperacillin/tazobactam or meropenem PLUS</td>
<td>Consider gentamicin if Enterococcus spp. is isolated</td>
<td></td>
</tr>
<tr>
<td>Necrotizing fasciitis (Fournier’s gangrene, early surgical wound infection 24–48 h post-surgery)</td>
<td></td>
<td>In infections by S. aureus producing Panton Valentine leukokidin or superantigens, the antibiotic regimen should include linezolid or clindamicin</td>
<td></td>
</tr>
<tr>
<td>Mixed polymicrobial infection: Enterococcus spp. Bacillus cereus E. coli P. aeruginosa Klebsiella spp. Proteus spp. Peptostreptococcus spp. Bacteroides spp.</td>
<td>Daptomycin or linezolid or clindamycin OR Tigecycline</td>
<td>Consider high doses of tigecycline in moderately severe polymicrobial infections involving MRSA and in patients with allergy to β-lactams</td>
<td></td>
</tr>
</tbody>
</table>

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

Risk 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.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (iv)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>20–30 mg/kg/24 h</td>
<td>1–2 g as initial dose followed by 8 g in 24 h continuous infusion</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>2 g/6 h</td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>500 mg/24 h</td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>2 g/8 h</td>
<td>1–2 g as initial dose followed by 6 g in 24 h continuous infusion</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>2 g/8 h</td>
<td>1–2 g as initial dose followed by 6 g in 24 h continuous infusion</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>2 g/6–8 h</td>
<td>1–2 g as initial dose followed by 6 g in 24 h continuous infusion</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>400 mg/8 h</td>
<td>1–2 g as initial dose followed by 12 g in 24 h continuous infusion</td>
</tr>
<tr>
<td>Cloxacillin</td>
<td>2 g/4 h</td>
<td></td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>5 mg/kg of trimetropin/8 h</td>
<td></td>
</tr>
<tr>
<td>Colimycin</td>
<td>9 × 10⁶ U followed by 4.5 × 10⁶ U/12 h</td>
<td>May be administered as bolus</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>10 mg/kg/day</td>
<td>Administered as intermittent slow infusion (4 h)</td>
</tr>
<tr>
<td>Doripenem</td>
<td>1 g/8 h</td>
<td></td>
</tr>
<tr>
<td>Ertapenem</td>
<td>1 g/12 h</td>
<td>Administered as intermittent slow infusion (4 h) or continuous infusion</td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>4–8 g/8 h</td>
<td>referred to adjusted body weight; body weight = ideal body weight × 0.4 × (total weight – ideal weight)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>7–9 mg/kg/d (1 dose)</td>
<td>Intermittent slow infusion (2 h)</td>
</tr>
<tr>
<td>Imipenem</td>
<td>1 g/8 h</td>
<td></td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>500 mg/12 h</td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td>600 mg/8–12 h</td>
<td>1200 mg in 24 h continuous infusion</td>
</tr>
<tr>
<td>Meropenem</td>
<td>2 g/8 h</td>
<td>Intermittent slow infusion (3 h)</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>500 mg/8 h</td>
<td></td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>4–0.5 g/6 h</td>
<td>2 g as initial dose followed by 16 g in 24 h continuous infusion</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>600 mg/12–24 h</td>
<td></td>
</tr>
<tr>
<td>Tigecycline</td>
<td>100–200 mg followed by 50–100 mg/12 h</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>15–20 mg/kg/8 h (in 1–2 h) 35 mg/kg followed by 35 mg/kg/day in continuous infusion</td>
<td>kg referred to total body weight</td>
</tr>
</tbody>
</table>

duration with a 90% prevalence of UTI. 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 infection. It should be considered that the most frequent source of bacteremia caused by ESBL-producing bacteria was UTI in a Dutch multicenter study, and that multidrug resistant UTIs may be very frequent among patients with sepsis admitted in the ICU.

Intraabdominal infections

Core microorganisms are enterobacteria, such 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 peritonitis but in others increases the rate of morbidity. 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 admission. 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. 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).
Endocarditis

Infecactive 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 of nosocomial iatrogenic origin.\(^{163}\) Common blood cultures in infective endocarditis include \textit{S. aureus} (with special importance in intravenous drug users), viridans streptococci (among them \textit{Streptococcus bovis} in the elderly is often associated with underlying gastrointestinal neoplasm), enterococci and coagulase-negative staphylococci.\(^{163-165}\) Culture-negative infective endocarditis may account for one-third cases,\(^{166}\) and the HACEK group (\textit{Haemophilus} spp., \textit{Aggregatibacter} – formerly \textit{Actinobacillus} – \textit{actinomyctecomitans}, \textit{Cardiobacterium hominis}, \textit{Eikenella corrodens}, \textit{Kingella} spp.) for 5–10% of all cases of infective endocarditis.\(^{167}\) Percentages for each etiological agent may differ if endocarditis affects native valves or intracardiac devices. While viridans streptococci are more frequent in native valve endocarditis in non-drug users, coagulase-negative staphylococci is more frequent in infective endocarditis in patients with intracardiac devices\(^{168}\) but, in all cases, \textit{S. aureus} is the most frequent pathogen.\(^{168}\)

Surgical wound infections

Bacterial contamination of surgical wounds is inevitable, but common wound pathogens depend on clean/contaminated surgical procedures.\(^{169}\) 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. \textit{S. aureus} colonization appears to be the major risk factor for developing \textit{S. aureus} wound infection. This has particular importance in selected populations where colonization rates exceed 50%, such as diabetic individuals and hemodialyzed patients.\(^{169}\) Considering the high rates of methicillin resistance among \textit{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 (\textit{E. coli} and \textit{Klebsiella}) and \textit{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 context.\(^{170}\)

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 led 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 interest

All authors complied with ethical responsibilities and authors’ requirements, and declare no conflict of interest.

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References


