Risks for multidrug-resistant pathogens in the ICU

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Purpose of review
The impact of multidrug-resistant organisms (MDROs) is rising and often underestimated. The epidemiology of MDROs is extremely complex and multifactorial. There is increasing antibiotic resistance, mainly related to antibiotic pressure and patients' characteristics.

Recent findings
Emphasis on MDRO epidemiology is needed to better understand current strategies of prevention and management. Among them, antibiotic stewardship has been one of the most successful strategies. It is important to note that there is a controversial issue when considering community and healthcare-related infections. In addition, different strategies have been determined to find the impact and optimal use of recently launched antibiotics for MDRO treatment.

Summary
Infections with MDROs can prolong hospital stay, promote antibiotic use and prolong duration of mechanical ventilation. Some points should be further explored in clinical research such as the heterogeneity of healthcare-associated pneumonia and the need of new drug development. Resistance to non fermentative Gram-negative bacilli, rising minimum inhibitory concentration in methicillin-resistant *Staphylococcus aureus* and spread of MDROs in patients without known risk factors suggest a review of guideline validation, taking into account ecology and severity of patient illness to provide timely and appropriate empiric therapy.

Keywords
Acinetobacter, ICU, methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, sepsis

INTRODUCTION

The impact of multidrug-resistant organisms (MDROs) is rising, but it could be underestimated, as there are a suboptimal detection system, several virulent molecular factors and antibiotic selection pressure [1▪▪]. MDROs are labeled as such because they acquire a variety of mechanisms of resistance to multiple antibiotics [2].

According to the Intensive Care Over Nations prospective 10-day prevalence study in 730 participating ICUs (84 countries worldwide), 3718 patients (36.9%) out of the 10 069 patients had an infection during their ICU stay, 2473 (24.6%) on ICU admission and 1245 (12.3%) with ICU-acquired infection [3▪▪]. Several factors may explain the rapid spread of MDROs in critically ill environments, for example, new mutations, selection of resistant strains and suboptimal stewardship practices. The European Centre for Disease Prevention and Control along with Centers for Disease Control and Prevention (ECDC/CDC) panel created a standardized international terminology to describe acquired resistance profiles: multidrug-resistant (MDR), extensively-drug-resistant (XDR) and pandrug-resistant (PDR) bacteria [4]. One of the main problems for such an increase might be related to the increasing amount of medical resources.

The epidemiology of MDROs is extremely complex and multifactorial. It is in part because of the emerging increase of antibiotic consumption, and therefore resistance makes the importance of MDROs especially relevant with the implementation of antibiotic stewardship (Fig. 1).

ANTIMICROBIAL EMERGING RESISTANCE

There is a causal relationship based on antibiotic use and the emergence of resistance mainly on the basis

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KEY POINTS

- The impact of MDROs is rising and often underestimated.
- There is a causal relationship based on antibiotic use and the emergence of resistance.
- Antibiotic stewardship represents one of the most successful strategies to control the overuse of antibiotics and to decrease MDRO acquisition.
- The reduction of appropriate antibiotic therapy selects MDRO acquisition and increases resistance selection.
- Guidelines should take into account ecology and the severity of illness of the patient to 'think globally but act locally.'

of an evolutionary issue as drugs select resistant bacteria. Gould *et al.* [5] reported almost one decade ago that the annual prevalence of carbapenem resistance in *Pseudomonas aeruginosa* was directly related to the carbapenem use rate. This observation was made in long-term-acute-care hospitals because other variables, such as prior colonization and horizontal transmission of antimicrobial-resistant pathogens, would also be taken into account. The presence of selective pressure that was controlled in the past by the use of narrow coverage drugs is now broken with broad-spectrum antibiotics.

ANTIBIOTIC STEWARDSHIP

Antibiotic stewardship represents the development and implementation of programs and strategies to preserve integrity and proper use of the existing armamentarium. Antibiotic resistance arises because of actions in healthcare (community and hospital actions), the pharmaceutical industry, ecology and the community. In other words, the strategy is mainly related to interventions designed to improve and measure the appropriate use of antimicrobials in a coordinated fashion (Fig. 2). Antimicrobial stewardship programs aim to provide optimal clinical outcomes related to antimicrobial use, to minimize toxicity and other adverse events while reducing the costs of healthcare for infections. Knudsen and Andersen [6▪] conducted a multidisciplinary intervention, on the basis of antibiotic stewardship. Stringent modalities were implemented to reduce the liberal administration of broad-spectrum antibiotics. After a 2-year follow-up, the intervention found a sustained decrease in both antimicrobial consumption and patients infected with extended-spectrum-β-lactamase (ESBL) or AmpC-resistant Enterobacteriaceae infections. Standiford *et al.* [7] performed a descriptive cost analysis before, during and after an antimicrobial stewardship program and found that using an antimicrobial monitoring team was extremely cost effective and decreased the incidence of MDRO infections (ESBL/AmpC-resistant *Klebsiella pneumoniae*). However, the implementation of such programs in the critical care setting (de-escalation, optimizing dosing and reducing colonization or improving 'eradication') is associated with benefits in both clinical outcomes and less MDRO pressure. It is important to consider that these findings are related to observational studies. Interventions and randomized controlled

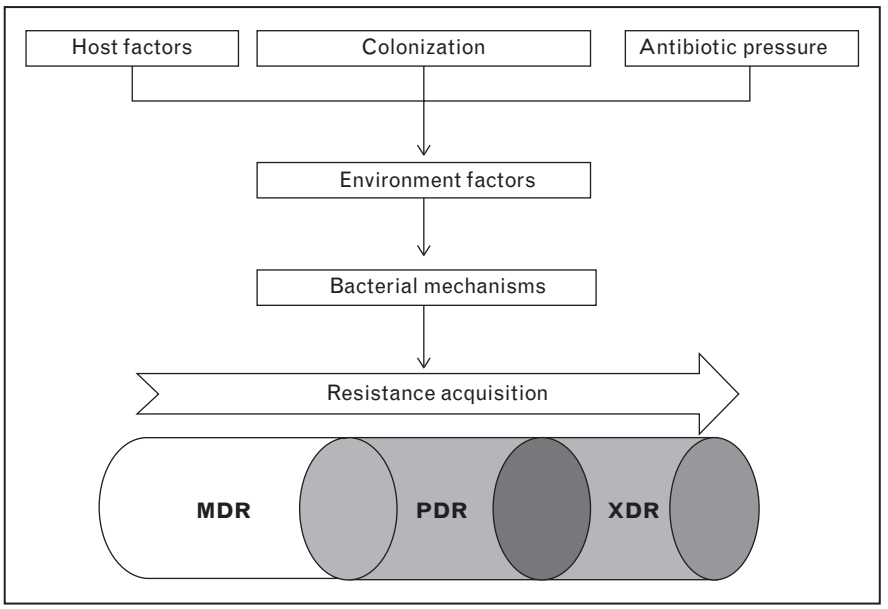

FIGURE 1. Host and microbiological interactions for multidrug-resistant organism acquisition. MDR, multidrug-resistant; XDR, extensively drug-resistant; PDR, pandrug-resistant bacteria.

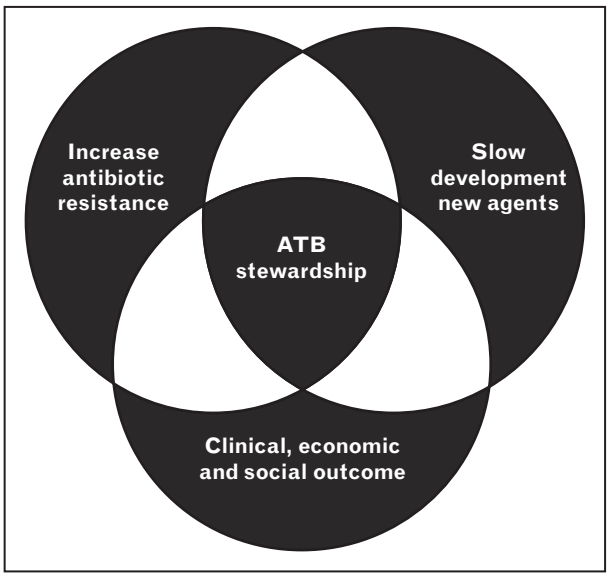

FIGURE 2. Antibiotic stewardship strategies and consequences.

trials (RCTs) are urgently needed to determine the impact of such stewardship programs in ICU settings.

HEALTHCARE OR COMMUNITY-RELATED INFECTION: SHIFTING MULTIDRUG-RESISTANT ORGANISMS TO VULNERABLE ORGANISMS

In recent years, changes in the healthcare system have shifted a considerable part of patient care from hospitals to the community. As a result, the traditional distinction between community and hospital-acquired infections has become less clear. Infections occurring among outpatients in contact with the healthcare system have been termed 'healthcare–associated infections' [2]. A good example has been manifested with pneumonia. Healthcare-associated pneumonia (HCAP) is pneumonia occurring in outpatients at risk of infections with resistant pathogens through contact with the healthcare system.

Several studies have found that HCAP patients have a high risk for mortality because first, HCAP is caused by pathogens which are more resistant to antibiotics, second, the incidence of inappropriate antibiotic treatment is higher than in community-acquired infections (CAP) and third, patients with healthcare-associated infections often have some type of therapeutic effort limitation and a lower proportion of these patients are admitted to the ICU. It is also important to consider the vicious circle within the HCAP patients as they are often at risk for MDROs, and current guidelines consider the administration of broad-spectrum antibiotics that is 'per se' a risk factor for MDRO acquisition. Therefore, the most important thing is to better identify how the current burden of multiresistance is in this particular situation.

Several studies about HCAP reveal a geographic distribution within the epidemiological variations. The studies performed in the USA and Asia report a high frequency of MDROs [methicillin-resistant *Staphylococcus aureus* (MRSA) and *P. aeruginosa*] [8,9▪▪,10]; by contrast most European (Spain, United Kingdom, etc.) studies report a high frequency of pathogens resembling those causing CAP (*Streptococcus pneumoniae* being the most frequent pathogen) [11,12], suggesting that the empiric antibiotic treatment prescribed for CAP is still adequate for most European HCAP (Fig. 3). However, all HCAP studies have shown that the mortality is higher in patients with HCAP than in those with CAP; still, it is unclear whether mortality was higher because patients with HCAP received inadequate antimicrobial treatment or because they were older and had more comorbidities and treatment restrictions. Recently, Polverino *et al.* [13▪] conducted a prospective multicenter case-control study in patients matched by age, sex and period of admission, and microbial cause did not differ between HCAP and CAP. In addition, Vallés *et al.* [14▪▪] conducted a prospective, observational multicenter study. This study differs from others already published because the population studied is based on critically ill patients admitted to an ICU. HCAP accounted for one-fifth of cases of severe pneumonia admitted to the ICU, but surprisingly did not result in higher mortality than CAP even after immunocompromised patients were excluded. Finally, the authors

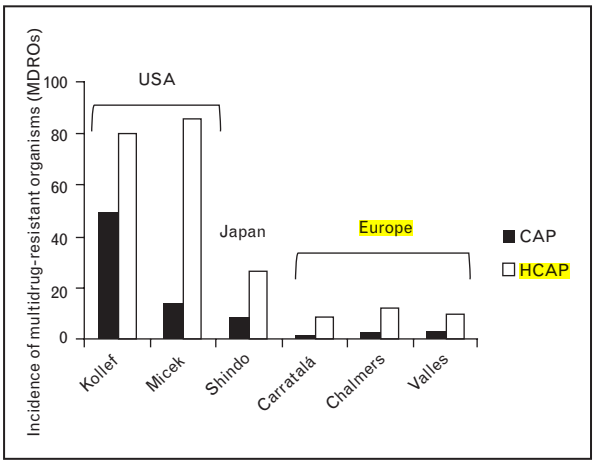

FIGURE 3. Current and classical studies that compared multidrug-resistant organisms in community-acquired infections and healthcare-associated pneumonia according to different regions (USA, Japan and Europe).

found that the empirical antibiotic therapy recommended for CAP was appropriate for 90% of patients with HCAP. Therefore, it seems important looking at the variations in regions to prevent the overuse of antimicrobials; further studies should aim to identify specific subgroups of patients with HCAP that would benefit from broader antibiotic coverage.

IMPACT OF GUIDELINES ON MULTIDRUG-RESISTANT ORGANISM TREATMENT

The reduction of inappropriate initial antibiotic therapy is one of the most known and well explained mechanisms to reduce mortality and morbidity in critically ill patients. However, it is important to acknowledge that a vicious circle is created when MDROs are anticipated, and broad-spectrum antibiotics are used to treat these infections, leading to yet more resistance (Fig. 4). This is particularly important because the number of antimicrobial agents that are currently available in the drug development pipelines of the pharmaceutical industry to combat these has been limited within recent years. Most guidelines have different recommendations depending on the risk of the presence of MDROs.

Ibrahim *et al.* [15] reported that the implementation of clinical guidelines for the treatment of ventilator-associated pneumonia (VAP) is associated with a higher appropriate antibiotic rate. More recently, Wilke *et al.* [16] analyzed the economic relevance of guideline-adherent antibiotic therapy. Apart from significantly better clinical outcomes, patients with guideline-adherent initial intravenous antibiotic treatment incurred lower total costs (EUR 28 033 vs. EUR 36 139, $P = 0.006$) and lower ICU-related costs (EUR 13 308 vs. EUR 18 666, $P = 0.003$). Although strategies like these seem to promote good clinical and economic outcomes, other authors such as Kett *et al.* [17] published a very controversial study that found a higher mortality in the 'compliant' group at 28 days (34% vs. 20%, $P = 0.004$). This work is a good example of why guidelines should be revisited as this study had several problems that should be taken into account for interpretation. The choice of therapy was not randomized, compliant patients were sicker: more severe sepsis (91% vs. 76%), more prior antibiotics, significantly higher Acute Physiology And Chronic Health Evaluation II, more Pseudomonal pneumonia (26% vs. 10%) and eventually some important points of 'compliance' were not measured: de-escalation (25% without *P. aeruginosa* or *Acinetobacter baumannii*, 50% without MRSA continued for these MDROs), dosing and timing of therapy.

Depuydt *et al.* [18] found that MDROs had an increased mortality. MDRO acquisition was related to the number and class of antibiotics received. On the other hand, coma on ICU admission was also associated with MDROs. The presence of coma has been classically related to early VAP. The decision for prescription of broad-spectrum antibiotic

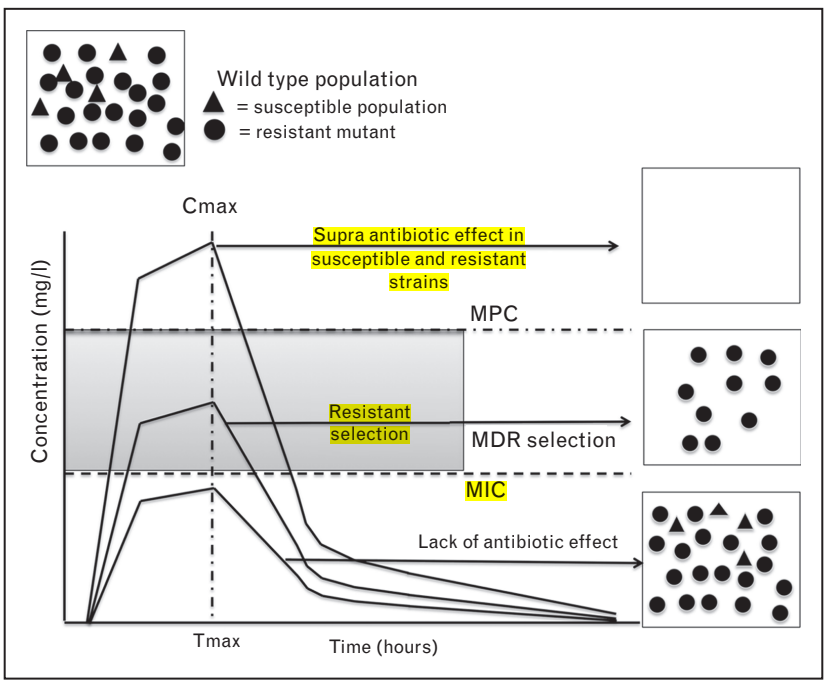

FIGURE 4. Selection of resistance based on microbiological eradication. The reduction of appropriate antibiotic therapy selects multidrug-resistant organism acquisition and increases resistance selection.

therapy remains the key question for future guidelines. In 2005, the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) (ATS/IDSA) updated the 1996 nosocomial pneumonia guidelines to simplify this decision based on the presence of late onset and/or risk factors for MDROs that included prior antimicrobial therapy (90 days), hospitalization for more than 5 days, high frequency of antibiotic resistance in the community or the hospital unit and immunosuppressive disease or therapy. The 2005 (and current to date) guidelines attempted to simplify the categories proposed in 1996; however, the adherence of the current ones needed to be validated. Ferrer *et al.* [19] found that the microbial prediction was lower in patients with early onset without risk factors for MDROs than in patients with late onset or risk factors for MDROs. Reclassifying patients according to the risk factors for MDROs of the former 1996 ATS/IDSA guidelines increased microbial prediction. In the same line, Giantsou *et al.* [20] described that both early-onset and late-onset VAP could be caused mainly by MDROs, and the antibiotic modification was significantly frequent in patients with early onset based on inadequate coverage.

The variability of microbiology and patterns of resistance must be taken into account among different hospitals and ICUs within the same hospital. Koulenti *et al.* [21] found important variations in cause when comparing the microbial etiology reporting in 827 patients with hospital-acquired pneumonia (HAP) or VAP in 27 ICUs from nine European countries. Moreover, this difference in 'ICU ecology' was also shown in different ICUs within the same hospital. Martin-Loeches *et al.* [22▪▪] confirmed all this evidence as patients without acknowledged risk factors by the 2005 guidelines had a high prevalence of MDROs (50.7%). Patients who were admitted to ICUs with greater than a 25% prevalence of MDROs showed a higher prevalence of potentially resistant microorganisms in patients with HAP without risk factors for resistant organisms. We proposed that ecology has to be taken into account as it has been reported but not well acknowledged by the guidelines. Guidelines should 'think globally but act locally.'

CURRENT TREATMENT OF MULTIDRUG-RESISTANT ORGANISMS: THE DISCOVERY GAP

Over the last few years, a significant number of RCTs have been or are being conducted to determine the efficacy of new drugs for MDROs, namely *P. aeruginosa*, *A. baumannii*, MRSA, *K. pneumoniae* and Carbapenemase (KPC)-producing bacteria. To achieve this goal, IDSA has launched a new collaboration titled the '10 × '20' initiative to develop 10 new antibacterial drugs by 2020 [23]. Many antibiotics are currently under identification and development, especially those with new modes of action. A total of 22 new antibiotics have been launched since 2000 with drug pharmacophore (natural product, natural product derived, synthetic or protein/mammalian peptide) in the pipeline [24].

NONFERMENTATIVE GRAM-NEGATIVE BACILLI

A. baumannii pneumonia is a very effective human colonizer in hospitalized patients that causes numerous global outbreaks. There is a considerable controversy to distinguish between infection and colonization. It is important to also distinguish *A. baumannii* pneumonia from multidrug-resistant *A. baumannii* (MDRAB) pneumonia. The latter entity is commonly associated with a high disease severity, bilateral pneumonia, and predicts failure of clinical resolution, and increased F pneumonia-predicted mortality. It is also often difficult to define whether infections caused by this pathogen lead to unfavorable outcomes or represent an indicator of severe illness, with an associated mortality of approximately 30%. For patients with MDRAB pneumonia, treatment is guided foremost by in-vitro antimicrobial susceptibility assays. Few antibiotics are active against this infection. Although patients treated with colistin or ampicillin-sulbactam have similar clinical cure rates, colistin has been associated with higher rates of microbiologic failure, a reduction in renal function and an increased 30-day mortality. Moreover, tigecycline has been studied, but a comparative study of colistin vs. tigecycline for MDRAB pneumonia was lacking. Ramirez *et al.* [25] also found that the use of two higher doses of tigecycline compared with imipenem/cilastatin was associated with a higher clinical response in patients with HAP. Chuang *et al.* [26▪] conducted a propensity score analysis in patients with MDRAB pneumonia and found a worse progression with the use of tigecycline-based treatment when tigecycline and colistin susceptibilities are unknown because choosing tigecycline-based treatment might result in higher mortality. Importantly, the excess mortality of tigecycline was significant only among those with higher minimum inhibitory concentration (MIC) (>2 μg/ml). Another strategy to fight against this difficult-to-treat infection might be based on the potent synergy of a glycopeptide–colistin combination. However, Garnacho-Montero *et al.* [27▪] could not find a better clinical outcome in patients

treated with colistin plus vancomycin, but it did increase the risk of renal failure.

P. aeruginosa exhibits a remarkable capacity to become resistant to the vast majority of antibiotics. Planquette *et al.* [28▪], on the basis of 393 *P. aeruginosa*–VAP episodes, found that factors associated with treatment failure were age, the presence of comorbid conditions and a high Sepsis-related Organ Failure Assessment score. Neither resistance profile nor dual antibiotic therapy decreased the risk of *P. aeruginosa*–VAP treatment failure. However, the profile of *P. aeruginosa* resistance prolonged the length of stay. Tumbarello *et al.* [29] found that half of the episodes of culture-confirmed *P. aeruginosa* pneumonia received inadequate initial antibiotic therapy (IIAT). Interestingly, in patients who survived, those who received IIAT or had MDR *P. aeruginosa* pneumonia had significantly longer periods of mechanical ventilation after pneumonia onset, compared with those whose initial therapy was adequate and those whose infections were caused by non-MDR *P. aeruginosa*. One potential way to reduce the number of *P. aeruginosa* infections is prevention. Van Delden *et al.* [30] conducted a randomized, blind, multicenter trial, in patients colonized by *P. aeruginosa*, to receive either placebo or 300 mg/day intravenous azithromycin and found a trend toward reduced incidence of VAP in colonized azithromycin-treated patients (4.7% vs. 14.3% VAP, $P = 0.156$). Azithromycin significantly prevented VAP in those patients at high risk of quorum sensing-regulated virulence factor rhamnolipids dependent VAP. These results show that virulence inhibition is a promising antimicrobial strategy. Another prevention strategy will be the administration of IC43 (recombinant outer membrane protein-based vaccine against *P. aeruginosa*). Recently published, a randomized, placebo-controlled phase I study found that this therapy could induce a plateau of immunoglobulin antibody responses in healthy volunteers [31▪▪]. Currently, a phase II and III study is being conducted in mechanically ventilated patients (ClinicalTrials.gov Identifier: NCT01563263).

Because of emergent increase of nonfermentative Gram-negative bacilli worldwide, there are limited, but promising, data with the use of inhaled antibiotics in mechanically ventilated patients administered alone or in combination [32▪▪]. For mechanically ventilated patients, aminoglycosides and polymyxins are the most commonly used antibiotics. Niederman *et al.* [33] conducted an RCT with BAY41–6551 (combination of amikacin, formulated for inhalation) and found that the molecule achieved microbiologically relevant amikacin concentrations in the pulmonary secretions of patients with Gram-negative VAP and a reduction in systemic antimicrobial use and a lower rate of failure. Inhaled Amikacin solution (BAY 41-6551) as adjunctive therapy in the treatment of Gram-Negative Pneumonia-2 (ClinicalTrials.gov Identifier: NCT00805168) will be a large multicenter global study that will try to demonstrate if adjunctive-inhaled amikacin may offer efficacy benefits over systemic antibiotics alone. It is important to highlight that, although promising, this route has not been approved until now by either the Food and Drug Administration or the European Medicines Agency in patients under mechanical ventilation.

ENTEROBACTERIACEAE

Extended-spectrum beta-lactamases (ESBLs) are a rapidly evolving group of β-lactamases, which share the ability to hydrolyze third-generation cephalosporins, and aztreonam yet are inhibited by clavulanic acid. The true prevalence of ESBLs is not well known and might be underestimated because of detection difficulties. ESBL-producing organisms are responsible for outbreaks worldwide, and their prevalence is increasing. Critically ill patients infected with ESBL-producing organisms are at risk for high mortality due to the high-level resistance. β-Lactamase inhibitors, such as clavulanic acid, sulbactam or tazobactam, usually inhibit ESBLs. Although the number of antibiotics to face ESBL infections is limited, some promising drugs are in the pipeline, namely CXA-201 [ceftolozane (CXA-101, FR264205)]/tazobactam and CAZ104 (ceftazidime/avibactam). Avibactam is also being evaluated in phase-II and phase-I trials in combination with ceftaroline and aztreonam, respectively [24].

Carbapenem-resistant Enterobacteriaceae are a group of emerging highly drug-resistant Gram-negative bacilli causing infections associated with significant morbidity and mortality due to delays in effective treatment and a high rate of clinical failures. The most challenging problem associated with these pathogens is related to their highly multi or pandrug-resistance that is not consistently identified by routine screening methods. Polymyxins, tigecycline and occasionally aminoglycosides are the only currently effective, although limited, therapy. Combinations of colistin and rifampicin, and less frequently tigecycline, exhibit synergistic activity [34]. Several studies are being conducted to test effectiveness with such pathogens, but results are still awaited.

GRAM-POSITIVE BACTERIA

MRSA is the most common Gram-positive MDRO that causes infections in critically ill patients.

Pasquale *et al.* [35▪▪] found that the incidence of MRSA late-onset was higher than the early-onset nosocomial pneumonia; however, patients with early-onset and late-onset had similar frequencies of isolates exhibiting panton-valentine leukocidin and staphylococcal cassette chromosome mec type IV. This finding shows the continued migration of community-associated MRSA into the healthcare setting in America. Vancomycin has been the drug of choice in the treatment of MRSA infections and was recommended as such by clinical guidelines. High-dose vancomycin is often prescribed for critically ill patients. A supratherapeutic trough level of greater than 20 mg/l has been recently reported to be an independent predictor of acute kidney injury and mortality in trauma patients [36]. Several alternatives to vancomycin are currently in the pipeline. Although daptomycin seems to be a good option, it is inactivated by surfactant and will not be an option for pneumonia [37]; tigecycline has been reported inferior to imipenem (± vancomycin) in a prospective study in patients with nosocomial pneumonia, but not designed for MRSA pneumonia [38] and quinupristin-dalfopristin is not approved for the treatment of MRSA pneumonia in the USA because of lower clinical cure rates than vancomycin in clinical trials [39]. Linezolid has demonstrated efficacy because of high penetration into the epithelial lining fluid of patients with VAP and showed statistically superior clinical efficacy vs.vancomycin in the treatment of MRSA in a phase IV, randomized, controlled study of nosocomial pneumonia with suspected or proven MRSA (ZEPHYR trial). Despite the limitations of the ZEPHYR trial because of the inclusion of unbalanced treatment groups at baseline and the number of patients excluded, linezolid has been shown to be a cost-effective drug [40]. It should possibly be used with daptomycin in bacteremia and could be the ideal therapy when vancomycin MICs are greater than 1 μg/ml. Other options on the basis of new lipoglycopeptides (dalbavancin, oritavancin and telavancin) also seem promising [41]. Specifically, telavancin has been shown to be superior to vancomycin for clinical response in the treatment of HAP because of Gram-positive pathogens [42].

Vancomycin-resistant enterococci (VRE) spread rapidly and represent a major healthcare problem in many ICUs. Enterococci are naturally resistant to a wide range of antimicrobial agents. In addition, some enterococci, known as VRE, have become resistant to glycopeptide antibiotics. The therapeutic options for VRE infections are therefore very limited. VRE own the ability to acquire resistance to most of the currently available antibiotics, either by mutation or by receipt of foreign genetic material. Recently, BC-3781, a semisynthetic pleuromutilin, protein synthesis inhibitor that displays antibacterial activity against *Enterococcus faecium*, completed a phase-II trial. It is important to highlight that there is a relatively high rate of vancomycin-resistant *E. faecium* not susceptible to linezolid observed in ICU patients. Linezolid-resistant isolates carried the G2576T mutation in the 23S rRNA gene. Other alternatives are daptomycin and tigecycline that have shown excellent potential for treating VRE infection.

CLOSTRIDIUM DIFFICILE

C. difficile infection (CDI) is one of the most difficult microorganisms to eradicate in the environment. This pathogen can secrete extracellular toxins that contribute greatly to virulence and have been targeted by screening campaigns to identify inhibitors that attenuate virulence. Recently, it has been shown that 027 was the most frequent ribotype isolated between 2011 and 2013, from 32 United States hospitals, although rates varied by geographic region. Interestingly, ribotype 014 or 020 isolates appear to be emerging [43▪▪]. Several strategies such as the administration of intravenous metronidazole and oral vancomycin have been used, but unfortunately both clindamycin and moxifloxacin resistance with a reduced susceptibility to vancomycin has been observed over the last years [44]. Several nonantibiotic therapy strategies have also been proposed: probiotic therapy, transplantation of intestinal microbiomes (fecal transplants) and monoclonal antibodies for the treatment of severe gastrointestinal disease caused by CDI [45▪▪]. Regarding new treatments, rifaximin and fidaxomicin have been shown to decrease the rate of recurrence of CDI [46▪▪].

CONCLUSION

Infections with MDROs are currently a common problem in hospital settings. Infections with MDROs can prolong hospital stay, promote antibiotic use and prolong the duration of mechanical ventilation. Some points should be further explored in clinical research such as the heterogeneity of HCAP and the need for new drug development. Rising MICs in MRSA and spread of MDROs in patients without known risk factors suggest a review of guidelines, taking into account ecology and severity of the patient to provide timely and appropriate empiric therapy.

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Conflicts of interest

There are no conflicts of interest.

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- ■■ of outstanding interest

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