Review Article

Multidrug resistant bacteria in critically ill patients: a step further antibiotic therapy

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Abstract: Infections by multidrug resistant bacteria (MDR) occur frequently in patients admitted to intensive care unit (ICU) with incidence up to 40% in many world regions and are usually associated to high mortality. In ICU patients, numerous independent risk factors for infections by MDR bacteria have been identified whose careful management associated to an appropriate use of antibiotics are fundamental. Despite the latter may results challenging in many cases, combination of old and novel antibiotics usually permits to provide an *in vitro* effective strategy also in the more resistant strains. Nevertheless, as such antibiotic pressure produces harmful effects on microenvironment and immune response that render ICU patients prone to secondary or breakthrough infections by opportunistic agent. Beyond extensive antibiotic therapy, other factors as older age, chronic pathologies, trauma, surgery and persistent infections may cause ICU acquired immune suppression that involves both innate and adaptive immunity. Therefore, the approach to critically ill patients with sepsis caused by MDR infections should be based not only on the research for the best antibiotic strategy but also on the assessment and treatment of immune-dysfunction. Numerous promising immune-modulating therapy are under evaluation and we hope available in the close future.

Keywords: Antibiotics; critically ill patients; immune dysfunction; multidrug resistant bacteria (MDR)

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Multidrug resistant infections in intensive care unit (ICU): numbers and facts

Since the discovery of penicillin in 1928, antibiotics transformed the management of bacterial infections and saved millions of lives. Many decades later, a rising spread of antibiotic-resistant microorganisms led bacterial infections to become a threat again. The drug-resistance phenomenon already imposes a very heavy burden on healthcare, with 23,000 and 25,000 estimated annual deaths respectively in United States and in Europe. Moreover, some further studies prognosticate worrying trends, with an expected rising impact on global health through years, leading to more than 10 million annual deaths worldwide in 2050 (1-3).

ICUs are often considered the epicentre of development, amplification and dissemination of drug-resistant microorganisms (4,5). Critically ill patients are particularly prone to infections because of exposure to multiple invasive procedures compromising the anatomical barriers' defences, impairment of protective mechanisms such as cough reflex or acid gastric ambient by sedative drugs or stress-ulcer prophylaxis and the frequent impairment of the immune response induced by trauma, surgery and sepsis (6,7). Furthermore, the use of broad-spectrum antibiotics, that is

closely related to development and spread of drug-resistant microorganisms, is really frequent in ICU clinical practice, with studies reporting a 30% to 60% rate of inappropriate or incorrect antibiotic prescriptions (8-10). For these reasons nosocomial infections, often caused by multidrug resistant bacteria (MDR) micro-organisms, are more common in ICUs than in other departments (11).

A large-number of observational studies identified numerous independent risk factors for occurrence of infections by MDR bacteria among ICU patients: central venous access, pulmonary artery catheterization, stress ulcer prophylaxis, urinary catheterization, mechanical ventilation, trauma, ICU length of stay and, mostly, a previous history of infection or colonization by MDR micro-organisms (11,12). The prevalence of infections sustained by MDR bacteria in ICU patients varies in the different regions of the world. In North America, a study on critically ill patients with pneumonia (DEFINE study) reported a 14.1% rate of MDR infections, while a large study on nosocomial bloodstream infections conducted in 24 ICUs distributed worldwide (EUROBACT study) showed on average a 47.8% MDR rate, including 20.5% and 0.5% of isolated microorganisms with extensively drug-resistant (XDR) and pan-drug-resistant (PDR) patterns, respectively, with a consistent variability among different participating countries ranging from 8% (Australia) to more than 75–80% (Turkey, Greece, Croatia, Serbia) (12,13).

Over the past years, as a consequence of the progressive lack of antibiotic active against resistant gram-negative microorganisms, gram positive MDR pathogens have been overtaken by gram negative strain infections (14). Among gram negative bacteria, the most frequent MDR micro-organisms isolated in critically ill patients are extended-spectrum beta-lactamases producers (ESBL) *Enterobacteriaceae* and MDR *Pseudomonas aeruginosa* (PA), *Acinetobacter spp.* and *Stenotrophomonas maltophilia*. Vancomycin-resistant enterococci and methicillin-resistant *Staphylococcus aureus* are the most common gram positive identified, even if their incidence is currently decreasing (14,15).

The impact of antibiotic resistance on patient's outcome is still a debated topic: even though many studies reported a larger proportion of infections by MDR bacteria in non-survivors compared to survivors, it is still unclear if this is caused by difficulties in initial antibiotic therapy and/or to differences in microorganisms virulence and/or to differences in patients characteristics, particularly in terms of immune response (16). Indeed, MDR susceptibility pattern has been shown to be strongly associated to delay in appropriate antimicrobial treatment, that is one of the major factors influencing survival in patients with sepsis and septic shock (17,18). In fact, broad-spectrum antibiotic therapy within 1 hour after sepsis diagnosis is strongly recommended in the recently proposed Surviving Sepsis Campaign 1 h bundle (19). However, many authors and scientific societies expressed concerns on this recommendation that appears to rough and may encourage an excessive and harmful use of broad-spectrum agents when a more tailored approach might be advisable (20).

Antibiotic therapy: possible effective strategies

As described above, the increased incidence of MDR bacteria in critically ill patients is the consequence of inappropriate antibiotic therapy and large consumption of broad-spectrum antibiotics (21). Institution of an antimicrobial stewardship program (AMS) seems to be an effective strategy and is strongly recommended in ICUs with high prevalence of MDR bacteria with the aim of fighting drug-resistances, improving patient outcomes and reducing health care costs (21). Key issues of AMS programs are halting antibiotics in patients without infection and selection of the appropriate drug for empirical therapy that, as general rules, depends on clinical conditions of the patient, source of infection, local antimicrobial susceptibility patterns, patient microbiological history and previous therapy, avoiding to repeat the same antibiotics (22,23). Moreover, use of adequate dosages, early de-escalation of empirical broad spectrum antibiotics focusing the treatment on the isolated microorganism, switching to mono-therapy whenever possible and short course of therapy are also fundamental elements of AMS in critically ill patients (10).

As well known, nowadays the treatments effective against MDR bacteria are limited or missing for specific PDR strains. Due to their safety profile and broad efficacy against many microorganisms, beta-lactam antibiotics have been considered the first line therapy since many decades. Unfortunately, bacterial production of β lactamase enzymes increased worldwide making beta-lactams unsuitable as first line therapy for nosocomial infections in many regions of the world. As consequence, in the last years the use of carbapenems as first-line empiric therapy in critically ill patients grew enormously leading to a substantial increase in incidence of carbapenem resistant bacteria, by different mechanisms of resistance (24).

In several European regions, *Klebsiella pneumoniae* producing *Carbapenemase* (KPC-KP) is one of the most

common MDR gram-negative pathogens in critically ill patients. Despite of the lack of high-quality studies, many observational experiences showed that combined therapy is more effective than mono-therapy in patients with severe infections whereas no differences were observed in patients with less severe infections (25-28). Various antibiotics with different combination strategies have been proposed for the KPC-KP treatment including colistin, aminoglycosides, tigecycline, fosfomycin, carbapenems at high dosages and, in the last months, ceftazidime/avibactam (29-31). In case of pneumonia, the combination of intravenous and nebulized antibiotics has also been used with success. Several molecules, as for instance meropenem/vaborbactam, imipenem/relebactam, plazomicin and cefiderocol, active against the different mechanisms responsible for carbapenem resistance are under evaluation and will be available in the near future (32).

Acinetobacter baumannii (AB) is also a frequent cause of nosocomial acquired infection in critically ill patients (33). In fact, it is the third microorganisms responsible for ventilator acquired pneumonia in European ICUs, after *S. Aureus* and *P. aeruginosa* (34-36). Although carbapenems are usually considered the first line agents for the management of severe infections by AB (exception for ertapenem, that is no active), their use is becoming limited in many areas because of the increasing resistance (37). In this case, it is reasonable to use alternative strategies including usually sulbactam, tigecycline and colistin, that ought to be preserved for strains resistant to all β-lactams, fluoroquinolones and tigecycline (38-40). The combination of carbapenems, sulbactam and colistin, or colistin and rifampicin, or colistin and anti-gram-positive agents have been also suggested and frequently used even though the clear evidences of effectiveness are lacking.

PA represents one of the most common cause of health-care-associated infection and it is responsible for severe bloodstream, respiratory, urinary tract and soft tissue infections in ICU patients (41,42). In the last years, as for the other gram-negative bacteria, it has been evidenced an important increasing in infections caused by MDR-PA, due to the acquisition of resistance genes from mobile genetic components like transposons and plasmids, or to the variety of expression and function of encoded mechanisms into chromosomes. For many authors the best treatment for MDR-PA infection remains a dilemma between the mono and the combination therapy (43). However, the last option is generally considered more prudent and rational in critically ill patients, in order to extend the spectrum of activity (44). At present, the empirical treatment against a suspected MDR-PA infection, according to the site of infection, is represented by the novel β-lactam and β-lactamase inhibitor combinations (ceftolozane/tazobactam and ceftazidime/avibactam), or by antipseudomonal β-lactam (piperacillin/tazobactam, cefepime, ceftazidime or carbapenem) plus an additional agent such as colistin, fosfomycin, aminoglycoside or quinolones (45). The combination ceftolozane/tazobactam, a new semi-synthetic cephalosporin and a well-established β lactamase inhibitor, is indicated for complicated intra-abdominal or urinary tract infections, while it is still under evaluation for other clinical uses, like pneumoniae.

Immunosuppression in sepsis and relationship with MDR infections

During sepsis, complex immune reactions take place in the host that desperately try to protect the organism from external (pathogens) or internal (self-molecules that start inflammation) insults, and trigger a variety of mechanisms that change with time, and which include the production and utilization of pro- and anti-inflammatory molecules (46). Interestingly, these two classes of molecules, which have opposite effects, are often concomitantly secreted in high amounts (47). As a result, most patients with sepsis rapidly display signs of profound immune activation as well as of immunosuppression (48). This results in a status of immunological paralysis whose resolution is crucial for the life of the patient.

Patients who experience a septic shock caused by MDR microorganisms are however a particular population, which is characterized by a very high mortality risk (49). To understand the reasons of this risk, we have to analyze the following points. On the one side, the previous exposure to an initial inappropriate antibiotic therapy that is not able to control the infection but that can affect the host's defences could be responsible for altering the immune functions of the host (50). Indeed, an empiric antibiotic treatment can have devastating ecologic effects on the microenvironment, as it can promote a superinfection sustained by resistant bacteria or fungi. Noteworthy, important antigens of the pathogen can become cryptic, and/or specific clones that recognize such antigens can undergo inactivation, anergy or even apoptosis after a long chronic stimulation.

On the other side, the continuous activation of an immune system that typically has been fighting with a pathogen for several weeks, if not several months, also plays

a main role. In this perspective, a chronic immune activation affects not only the cells that are supposed to recognize a given antigen, but also creates a microenvironment in which cells of the innate immunity (monocytes, neutrophils, among others), as well as those of the cognitive part (specific T and B cells), receive a variety of stimuli that do not help in performing their activities (51).

Finally, it must be considered that most patients with sepsis have an advanced age. The effects of aging on the immune system are well studied, and it is known that either specific or non-specific responses are involved. Moreover, it has been reported that old individuals display the phenomenon of inflammaging, in which a chronic, subclinical inflammatory status drives all the immune responses, and causes a low quality and often low quantity control of the infection or of autoimmune reactions (52,53).

As a result, clinicians have to cope with a very dangerous and potentially fatal association among a sepsis caused by MDR infections, an aged and chronically stimulated immune system, and the immune-paralysis typical of sepsis (54). Assuming that an MDR pathogen is not sensitive to antibiotics, the only possibility for the survival of the host is to benefit of an efficient immune response, whose modulation is actually the Holy Grail of the treatment of sepsis.

The strategy to block the immune activation and potent inflammation that is typical of early sepsis has given, at present, discouraging results as indicated by the fact that in more than 30 trials of diverse anti-cytokine or anti-inflammatory drugs no benefit was shown, or, in some cases, a reduced survival rate was reported (55). One of the possible reasons is that the negative modulation of inflammation showed detrimental effects because molecules produced during inflammation are crucial for the control of the pathogen. However, only recently a therapeutic approach has been described which is based either on the trigger of the residual immune resources, or on the inhibition of inhibitory molecules, the so-called "check-point inhibitors". The therapeutic benefit of interleukin-7 (IL-7, a cytokine that triggers the production of new lymphocytes from the thymus and can maintain peripheral T cell homeostasis), or of granulocyte macrophage colony-stimulating factor (GM-CSF, a strong stimulator of innate immune response) are nowadays under evaluation by specific clinical trials (56). The last approach, which is successfully used in several types of cancer, including metastatic melanoma, is based upon antibodies against check point inhibitors such as programmed cell death protein-1 (PD1, or CD279) or against is ligand, the programmed cell death ligand 1 (PDL1, or CD274) (57-59).

Adjunctive therapies in MDR infections

Early identification, appropriate antibiotic therapy and prompt fluid resuscitation in patients with hypotension are the cornerstone for treatment of sepsis due to MDR infections. Nevertheless, given the increasing difficulties caused by the antibiotic resistance and the high prevalence of immune-suppression in patients affected by MDR infections, the use of specific adjunctive therapies seems to be reasonable and may have beneficial effects in this patients' population.

Extracorporeal blood purification techniques

In sepsis, the high levels of circulating inflammatory mediators contribute to development of organs dysfunction and to the imbalance of immune response and, thus, different extracorporeal blood purification techniques have been proposed to remove these mediators. The use of high-volume hemofiltration in septic patients did not show any beneficial effects and similar result have been obtained, with cascade hemofiltration (60-62). Hemoperfusion with polymyxin-B cartridge for removal of endotoxins seemed to be effective in improving patients' outcome but the recent negative results of the EUPHRATES trial poses again questions on its efficacy (63-65).

Similarly, plasma exchange appeared to be effective in the removal of inflammatory mediators and the association between plasma filtration and adsorption could be potentially even more effective. Unfortunately, a recent randomized control trial in patients with septic shock did not show significant benefits (66).

Pharmacological approaches

As described above, different molecules have been tested to evaluate the ability to improve host immune response and eventually to exert a synergic effect with antibiotic therapy. Initially, GM-CSF and interferon-γ (INF-γ) have been proposed and studied because of their effects on antigen presenting cells. A randomized trial in septic patients evaluating the effects of GM-CSF administration guided by mHLA-DR expression noticed a prompt restoring of immune-response, a reduced need of mechanical ventilation and a shorter ICU and hospital length of stay in treated patients (67). Furthermore, a meta-analysis of clinical

trials in septic shock showed a more efficiency in infection clearance but no improvement in 28-day mortality in patients treated by GM-CSF (68). The use of INF-γ has been tested in case of trauma and burns with contrasting results. Noteworthy, even in these trials the use of HLA-DR expression on monocytes was used to identify patients that could benefit the most from this adjunctive therapy (69). The PD-1/PD-L pathway, normally acting during the immune response to limit an excessive lymphocytes activation, is highly up-regulated during sepsis and septic shock leading to inhibition of immune cells, anergy and promoting apoptosis (70,71). Murine models of sepsis have been used to demonstrate that block of this pathway is responsible for an improvement in survival moreover an *in vitro* study on lymphocytes from septic patients treated with anti-PD-1 or anti-PD-1L antibodies showed a decrease in apoptosis rate and a higher production of IL-2 and INF-γ (72-74). These observations suggest the use of PD-1 expression on T cells and/or PD-L expression on antigen presenting cells as a sound biomarker for immune dysfunction and, as mentioned above, the potential use of anti-PD-1 and anti-PD-L1 antibody in patients as an adjunctive therapy in patients with sepsis. Other pathways such as TIM-3, LAG-3 and CTLA-4, BTLA have been studied and proposed to monitor and direct immune- therapies in sepsis and septic shock, but so far clinical trials are lacking (75). Potential benefits of recombinant interleukins in sepsis and septic shock have been demonstrated in animals. In different murine models of sepsis, IL-7 administration is able to restore depleted T cells, induce proliferation and INF-γ secretion allowing an improvement in survival. A recent small clinical randomized trial (IRIS-7) reported that recombinant-IL-7 in patients with septic shock and severe lymphopenia is well tolerated and induce a 3- to 4-fold increase in absolute lymphocyte counts and in circulating CD4+ and CD8+ T cells, making it a promising therapy in these patients at high risk for mortality. Finally, the administration of intravenous immunoglobulins (Ig) has been also proposed and used since many years for compensate the reduction of circulating IgG and IgM observed in the first days of septic shock and for modulating the immune response (76,77). Interesting in this filed, two recently published experiences in Italy and Greece reported a beneficial effect with the early use of IgM enriched immunoglobulin preparations in patients with sepsis and septic shock sustained by MDR bacteria (49,78).

Immunization against MDR pathogens

Recently murine models have been also used to test the efficacy of immunization against infections caused by MDR pathogens. The progressive emergence of MDR-AB as important opportunistic pathogen characterized by limited treatment options induced different groups to focus their attention on the development of a vaccine to prevent infection. Ainsworth *et al.* showed that the use of an attenuated strain of MDR AB, obtained deleting the thioredoxin gene from a clinical isolate, to vaccinate mice is able to protect from a lethal form of infection inducing Ig production and resulting in a reduced pathology and organ burden compared to non-vaccinated mice (79). Also the use of specific outer membrane protein A obtained by AB has been used to vaccinate mice and showed an improvement in survival after MDR-AB infection compared to non-immunized mice (80). Other MDR pathogens, such as *Mycobacterium tuberculosis* and PA, are under study and antigen candidates have been identified as potential protective vaccines (81,82).

Conclusions

Sepsis continues to be the most important cause of mortality in ICU patients, particularly when infection is caused by difficult to manage infections as those sustained by MDR-PDR-XDR micro-organisms. Appropriate and timely antibiotic therapy using combination strategies or novel molecules is the cornerstone for treatment of complex infections. However, even in case of appropriate antibiotic strategies, the mortality rate of patients with infections by MDR agents remains higher than that observed in patients with sepsis by no-MDR bacteria, especially in patients infected by opportunistic PDR-XDR bacteria or fungi. In the last years, it has become clear that persistent immune dysfunction, a frequent occurrence in critically ill patients, plays a pivotal role in acquisition of secondary/breakthrough infections and, thus, special attention ought to be dedicated, together with the best antibiotic strategy and standard of care, to identification and management of this dysfunction in ICU patients with difficult infections (*Table 1*). To this aim, different promising strategies have been considered and are under evaluation by appropriate trials with the hope to finally win the fight against infections by MDR bacteria in the near future.

Table 1 Standard 1-hour bundle proposed by the evidence-based guidelines of the Surviving Sepsis Campaign in 2018 and the possible adaptation in patients with sepsis or septic shock sustained by multidrug resistant infections

SSC 1-hour bundle	MDR bundle
Measure lactate level	Measure lactate level
	Assess possible immune-dysfunction (e.g., lymphocytes count, HLA-DR expression on monocytes, viral reactivation)
Obtain blood cultures before administering antibiotics	Obtain blood cultures before administering antibiotics
	Obtain surveillance cultures as soon as possible and use of rapid methods for microbial identification including resistances patterns (e.g., multiplex PCR, rapid phenotyping)
Administer broad-spectrum antibiotics	Administer combination of broad-spectrum antibiotics
Begin to rapidly administer 30 mL/h crystalloid for hypotension or lactate ≥4 mmol/L	Begin to rapidly administer 30 mL/h crystalloid for hypotension or lactate ≥4 mmol/L
Administer vasopressors if hypotension despite fluid challenge	Administer vasopressors if hypotension despite fluid challenge
	Consider early use (within 12–24 hours) of adjunctive immune-modulatory treatments (e.g., blood purifications, immunoglobulins, GM-CSF, IL-7, anti-PD-1)

SSC, surviving sepsis campaign; MDR, multidrug resistant; HLA-DR, human leukocyte antigen - DR isotype; GM-CSF, granulocyte-monocyte colony stimulating factor; IL-7, interleukin 7; anti-PD-1, programmed cell death protein-1.

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Footnote

Conflicts of Interest: Massimo Girardis participated to advisory board and served as speaker for Accelix, Biomerieux, Biotest, MSD and Pfzier. The other authors have no conflicts of interest to declare.

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