Review

Treatment of Severe Infections Due to Metallo-Betalactamases Enterobacterales in Critically Ill Patients

Jean-François Timsit 1,2,*, Paul-Henri Wicky 1 and Etienne de Montmollin 1,2

1 APHP, Service de Médecine Intensive et Réanimation Infectieuse, Hôpital Bichat Claude-Bernard, 46 Rue Henri Huchard, 75018 Paris, France; jean-francois.timsit@u-paris-sante.fr (P.-H.W.);
etienne.demontmollin@aphp.fr (E.d.M.)
2 IAME, INSERM, University of Paris, 75018 Paris, France
* Correspondence: jean-francois.timsit@aphp.fr

Abstract: Metallo-beta-lactamases-producing (MBL) Enterobacterales is a growing problem worldwide. The optimization of antibiotic therapy is challenging. The pivotal available therapeutic options are either the combination of ceftazidime/avibactam and aztreonam or cefiderocol. Colistin, fosfomycin, tetracyclines and aminoglycosides are also frequently effective in vitro, but are associated with less bactericidal activity or more toxicity. Prior to the availability of antibiotic susceptibility testing, severe infections should be treated with a combination therapy. A careful optimization of the pharmacokinetic/pharmacodynamic properties of antimicrobials is instrumental in severe infections. The rules of antibiotic therapy are also reported and discussed. To conclude, treatment of severe MBL infections in critically ill patients is difficult. It should be individualized with a close collaboration of intensivists with microbiologists, pharmacists and infection control practitioners.

Keywords: metallo-beta-lactamases; sepsis; critically ill; aztreonam; cefiderocol; avibactam; NDM; VIM; pneumonia; bloodstream infections

1. Introduction

Carbapenem-resistant Enterobacterales (CRE) is a growing problem worldwide [1–6]. Carbapenem resistance in Enterobacterales is mostly due to carbapenemases. Carbapenemases are characterized as either metallo-beta lactamases (MBL) in Ambler class B or serine beta-lactamases in Ambler class A or D. MBL can inactivate all bi-cyclic beta-lactams and serine beta-lactamase inhibitors that are used in human medicine, such as sulbactam, tazobactam, clavulanic acid, avibactam and vaborbactam. Class B1 enzymes includes Verona integron-encoded MBLs (VIM), imipenemases (IMP) and New Delhi MBL (NDM). MBL per se cannot hydrolyze monobactams.

The rapid spread of MBLs worldwide is responsible for life-threatening infections which are particularly difficult to treat given the paucity of active available antimicrobials. In this review, we will focus on the optimization of treatment of MBL infections in critically ill patients.

2. Trends in Epidemiology

MBLs have spread globally within Enterobacterales in the past decade. CRE rates increased by more than 2.5-fold from 2013 to 2020. Globally, it represents one fifth of the carbapenem-resistant Enterobacterales isolated from clinical samples [2,7]. NDM represents more than half of the MBL. The rapid spread of the blaNDM gene may partly be due to a limited fitness cost of this enzyme to Enterobacterales [8]. There is important variability of the rate of MBL producing Enterobacterales among CRE between regions. MBLs represent less than 6% of the carbapenem-resistant Enterobacterales in North and Latin America, but more than 40% in the Middle East, Africa and Asia/South Pacific [2]. In Europe, VIM
represents about 8% of the CRE, mainly in Southern Europe. NDM has spread to all European countries and represents more than 7% of CRE.

3. Risk Factors

Risk factors of MBL infections are similar to the risk factors of infections with other CREs. These risk factors include prior colonization, prior antimicrobial use, healthcare exposure, comorbidities, ICU admission, mechanical ventilation, dialysis and the presence of indwelling catheters [9]. Snyder et al. performed a retrospective case-control study in India to identify risk factors of bloodstream infections (BSIs) caused by NDM-1-producing strains. As compared to BSI due to other multidrug-resistant strains, prior carbapenem use (OR 8.4) and central venous catheter (OR 4.8) predicted the acquisition of an NDM-1 strain [10].

The risk of mortality associated with MBL Enterobacterales infections is considerable. In a study performed in Athens, one third of the patients died within 14 days following infections with VIM-positive Klebsiella pneumoniae [11]. Similar mortality was observed in India and South Africa in patients with bloodstream infections (BSI) due to NDM-producing Enterobacterales [10,12]. Two recent studies suggested that prognosis recently improved with the growing use of active beta-lactams antibiotics. In a multicenter study including 102 BSI episodes in Italy and Greece, 30-day mortality was 31.4% [13]. Of 57 nosocomial infections due to NDM-producing bacteria in India (72% in ICU), 30-day mortality was 21% [14].

4. From Empirical to Early Documented Therapy

In critically ill patients, antibiotic therapy must be immediately effective on the pathogens [15]. In routine practice, the decision to start treatment active against MBL is based on the answers to important questions [16].

The risk of MBL infection will depend on local epidemiology and the history of recent MBL outbreaks [17]. Previous colonization markedly amplifies the risk of subsequent infection with MBL and is a key component of an empirical therapy [18,19]. However, the positive predictive value of this risk factor is low [17]. In one study, the rates of infection among carbapenemase-producing Enterobacterales carriers were higher for KPC-producing (60%) than for NDM-producing Enterobacterales (12%) [20].

The risk of MBL infections is higher in patients with advanced co-morbid illnesses, prolonged hospital stays, and who had undergone invasive procedures [21]. Prior carbapenem exposure in the past 30 days is also a risk factor of MBL infection, but to a lesser extent than the risk of non-carbapenemase-producing carbapenem-resistant Enterobacterales [22].

Rapid molecular diagnostic tests are increasingly being developed to identify pathogens and antibiotic resistance patterns, but are expensive and not available everywhere [23,24]. They still require time for sample collection, lab delivery, and specimen analysis, and during this time, antibiotic therapy is usually not withheld.

There is probably room for developing artificial intelligence or machine-learning to help to bridge this time gap, e.g., by predicting antimicrobial resistance patterns. The first attempts at predicting carbapenem resistance provided encouraging results. In a recent analysis, McGuire and colleagues demonstrated that longitudinal clinical data could predict the risk of carbapenem resistance [25]. In this investigation, new carbapenem-resistant infections accounted for 1.6% of the population, yet the predictive model generated a sensitivity of 30%, a positive predictive value of 30% and a negative predictive value of 99% (AUROC 0.84).

5. Available Drugs

5.1. Ceftazidime-Avibactam/Aztreonam

MBL can hydrolyze all beta-lactams except aztreonam (ATM). However, in MBL-producing Enterobacterales, aztreonam is frequently hydrolyzed by other beta-lactamases that are frequently co-produced. In total, ATM alone remains active in no more than
one third of MBL isolates. The combination of ATM and a beta-lactam/beta-lactamase inhibitor such as ceftazidime avibactam (CZA) restores the intrinsic activity of ATM on MBL and is an attractive option for therapy. Indeed, CZA is active against Ambler A, C and D beta-lactamases including extended spectrum beta-lactamases such as CTX-M, AmpC and OXA-48. In a systematic review of in vitro data, MIC values ≤ 4 mg/L for ATM in combination with CZA have been described in 79.6% of the MBL-producing Enterobacterales [26].

The association was tested as a last-resort therapy and reported in a growing number of case-reports and cohorts [26]. In a multicenter cohort of 102 patients with BSI due to MBL-producing Enterobacterales (NDM n = 82, VIM n = 20), Falcone et al. compared the activity of CZA/ATM with other various combination therapies [27]. Of the 52 patients that received CZA/ATM, half were in ICU, 26% had septic shock and 30% received mechanical ventilation. The source of BSI was mainly urine (32%) and intravascular catheters (26.5%). Ten out of 52 died (19.2%), while clinical failure at day 14 was only diagnosed in 13 (25%) of them. After adjustment on SOFA score, chronic diseases, CZA/ATM use was associated with an improved survival rate (Hazard ratio 0.17 [95% Confidence Interval, 0.07–0.41]; p < 0.001). Among the patients not treated with CZA/ATM, the highest 30-day mortality was observed in patients treated with colistin-based regimens (59.3%).

Nagvekar et al. [14] reported 40 cases of severe infections due to Enterobacterales (Klebsiella n = 53, Escherichia coli n = 26) that carried either NDM alone or the combination of OXA-48 and NDM. The source of infection was intra-abdominal (32%), ventilator-associated pneumonia (26%), complicated urinary tract infections (9%) and bloodstream infections (9%). Seventy-two percent of the cases were hospitalized in ICU. CZA/ATM alone (n = 12) resulted in 11 clinical cure (92%). Combination with colistin (n = 21) or fosfomycin (n = 7) was associated with a clinical cure rate of 20 (71.4%).

We recently published the cases of two organ transplant recipients with septic shock due to NDM1-Klebsiella pneumoniae with ventilator-associated pneumonia and bloodstream infection; the clinical success was obtained after a 14-day CZA/ATM therapy [28]. In both cases, recurrences occurred within 30 days and were microbiologically and clinically controlled with the same antimicrobials. One of the patients subsequently died due to transplant rejection.

We treated nine patients with the combination therapy within the past 2 years for NDM-producing Enterobacterales in our ICU (Table 1), either after documentation or using the results of the multiplex polymerase chain reaction (mPCR) on respiratory secretions and previous known colonization. Infection was confirmed in seven cases (VAP, four; BSI of unknown origin, one; peritonitis, one; surgical site infection, one). The MIC of CZA/ATM was lower than 0.5 mg/L in all cases. Microbiological eradication was obtained in all but one case, and clinical cure was obtained in five out of seven cases. Four out of seven patients died; the death was probably related to NDM infection for two of them, and definitely unrelated for the remaining two others.

Even if clinical data are encouraging, many questions remain. The optimal dose of CZA/ATM is unknown. IDSA [29] recommends ceftazidime-avibactam 2.5 g IV q8h, infused over 3 h plus aztreonam: 2 g IV q8h, infused over 3 h, according to previous clinical studies [27]. A recent simulation model on hollow-fiber suggests that CZA 2 g every 8 h and ATM 2 g every 6 h over 2 h, or both agents administered in continuous infusions, yielded better bacterial killing with no emergence of resistance within 7 days [30]. Importantly, ATM and CZA should be given simultaneously. The combination of aztreonam and avibactam (AVI) is currently on phase III of the development process. The proposed dose is 500 mg ATM/167 mg AVI loading dose within 30 min followed by 1500 mg ATM/500 mg AVI over 3 h IV every 6 h [31].
## Table 1. Cases series of severe NDM infections treated with CZA/ATM in ICU patients—experience of Bichat-Claude Bernard hospital.

| Age, (Year), Gender | Medical History | SAPS II | SOFA Score (Treatment) | Invasive Ventilation | Shock | HD/CVVH | Source | Germ/MIC of CZA/ATM | Treatment Duration (Days) | Combo | Clinical Cure | Microbiological Cure | Survival (Hospital) | Cause of Death |
|--------------------|----------------|---------|-------------------------|----------------------|-------|---------|--------|------------------|--------------------------|-------|---------------|-------------------|-----------------|---------------|
| 76, Female          | Obese; Diabetes; ARDS; SARS-CoV2 | 42      | 2                       | Yes                  | No    | No      | VAP    | Esherichia coli  | 1                        | Colistine | Yes           | Yes               | Alive           |               |
| 42, Male            | Obese; Diabetes; ARDS; SARS-CoV2 | 46      | 10                      | Yes                  | Yes   | Yes     | VAP    | Enterobacter cloacae; 0.064 mg/L | 6                        | Yes       | Yes           | Yes               | Coma            |               |
| 58, Male            | Endocarditis; mitral valve replacement | 53      | 4                       | Yes                  | Yes   | No      | Septic shock in NDM colonized patient | Citrobacter freundii | 2                        | Yes       | Yes           | Alive            |                |               |
| 67, Female          | renal transplant; hemorrhagic shock | 47      | 10                      | No                   | No    | No      | BSI    | Klebsiella pneumonia; 0.032 mg/L | 15                       | No           | Yes           | Alive            |                |               |
| 44, Female          | lung transplant; acute respiratory failure | 27      | 5                       | Yes                  | Yes   | No      | VAP    | Klebsiella pneumoniae; 0.064 mg/L | 52                       | Tigecycline | Yes           | Yes               | Alive           |               |
| 53, Male            | intraventricular communication/Endocarditis | 40      | 9                       | Yes                  | Yes   | Yes     | Petitionitis; cellulitis | Esherichia coli; 0.094 mg/L (+ESBLE Klebsiella pneumoniae); | 24                       | Colistine | Yes           | Yes               | Death           | Shock         |
| 40, Female          | Myocarditis, ECMO | 34      | 8                       | Yes                  | Yes   | Yes     | SSI (ECMO cannulas) | Klebsiella pneumoniae; 0.38 mg/L | 10                       | Yes           | Yes           | Death             | Shock           |               |
| 36, Male            | ARDS, SARS CoV2 | 23      | 3                       | Yes                  | No    | No      | VAP    | Klebsiella pneumoniae; 0.064 mg/L | 9                        | Yes           | Yes           | Alive             |                |               |
| 70, Male            | Chronic renal failure; Cardiac surgery (mitral valve replacement, tamponnade) | 54      | 6                       | Yes                  | Yes   | No      | VAP    | Enterobacter cloacae; 0.064 mg/L | 9                        | No            | Yes           | Death             | MOF            |               |

Abbreviations: VAP: ventilator-associated pneumonia; MOF: multiple organ failure; EBLSE: extended spectrum beta-lactamase Enterobacterales. ECMO: extra-corporeal membrane oxygenation; ARDS: acute respiratory distress syndrome; SSI: surgical site infection; BSI: bloodstream infection.
5.2. Cefiderocol

Cefiderocol is a novel siderophore cephalosporin with unique broad-spectrum activity and stability against all classes of carbapenemases, (KPC, OXA, NDM, VIM and IMP). It enters the bacterial cell through the iron transporters, shunting the need for porin channels. It is stable for hydrolysis by various beta-lactamases including MBLs. Using a breakpoint of 4 mg/L, MBL-producing Enterobacteriales are susceptible to more than 72% of NDM producers, 91.7% of VIM producers and 87% of IMP producers. However, for NDM producers, the MIC50 is 1 to 4 mg/L, i.e., very close to the breakpoint. Furthermore, it should be known that different testing modalities may lead to subsequent variation of MIC measurements in Enterobacteriales [32].

In the CREDIBLE-CR [33] and APEKS-NP [34] studies, cefiderocol monotherapy was effective against Gram-negative bacteria producing metallo-beta-lactamases. Overall, rates of clinical cure (70.8% (17/24)), microbiological eradication (58.3% (14/24)), and 28-day all-cause mortality (12.5% [3/24]) compared favorably with comparators of best available therapy and high-dose meropenem (40.0% (4/10); 30.0% (3/10); and 50.0% (5/10)), respectively. Clinical cure was lower for NDM (9/16, 56.2%) than for non-NDM (8/8, 100%) infections.

In an in vitro evolution experiment using clinical NDM-Enterobacter cloacae isolates via serial passaging, cefiderocol pressure leads to resistance acquisition. It was suggested that the presence of NDM facilitates the emergence of resistance via non-synonymous mutations of the CirA catecholate siderophore receptor [35].

In vivo acquired resistance to cefiderocol has been already reported [36] due to an increase in the copies of blaNDM5 gene of E. coli, resulting in a clinical failure to treat an intra-abdominal infection, which was eventually successfully treated by a combination of CZA/ATM.

To conclude, if a metallo-beta-lactamase (i.e., NDM, VIM, or IMP) is identified, preferred antibiotic options include ceftazidime-avibactam plus aztreonam, or cefiderocol monotherapy. Clinical outcome data comparing these two treatment strategies are not available [29,37].

5.3. Carbapenems

In vitro activity of carbapenem has been reported in up to 60% of VIM-positive Enterobacteriales [38]. However, CRE with borderline susceptibility to carbapenem exhibits a marked inoculum effect, with a more than 8-fold increase in the MIC for inoculums between $10^4$ and $10^{5-6}$ cfu/mL [39]. The use of carbapenem monotherapy in carbapenemases-producing Klebsiella pneumoniae is limited, and resulted in a rate of clinical failure of 25% [40]. It should be discussed when meropenem MIC is $\leq$ 8 mg/L [37]. Data on carbapenem use in MBL infections are limited [41]. Considering the in vitro data, the absence of strong clinical evidence, and the available alternative antibiotics, the use of carbapenem in susceptible strains should be discouraged [29].

5.4. Tetracyclines

Tetracyclines such as tigecycline are active against most cases of blaNDM Enterobacteriales [42], but stable plasmidic resistance has been described. Tigecycline also remains active in vitro against most parts of other MBL-producing Enterobacteriales [43,44]. One animal model suggested that tigecycline alone at 50 mg bid or 100 mg bid is not sufficient to control pneumonia due to NDM-producing Enterobacteriales [45]. Indeed, administered in monotherapy at such humanized doses, it resulted in bacterial regrowth.

5.5. Fosfomycin

Fosfomycin is a broad-spectrum antimicrobial. It is active against Enterobacteriales including MBL producers [46], but with a high risk of acquired resistance. Fosfomycin diffusion in body tissues is excellent. In a neutropenic murine thigh infection model due to NDM K. pneumoniae, the AUC/MIC ratio needed to achieve one log kill was 22 [47].
It is also active against more than 90% of MBL-producing *Enterobacterales* [48,49]. With a dose of 6 g IV every 8 h, the AUC is about 715 mg.h/L [50]. Therefore, bacterial killing should be obtained if MICs are not higher than 8 mg/L. Monotherapy with fosfomycin should not be used to treat MBL-producing *Enterobacterales* infections, due to baseline hetero-resistance and frequently observed regrowth. The place of fosfomycin, always in combination therapy, especially to optimize the treatment of infected tissues, remains to be evaluated. Fosfomycin may display synergy with carbapenems and/or colistin against NDM-producing *K. pneumoniae*, but resistance via metallo-enzymes has been described and the intravenous formulation is not available in the U.S.

5.6. Polymixins

Polymixins are active in more than 90% of the cases against MBL-producing *Enterobacterales*, with an MIC90 of 1 mg/L [48]. It should be kept in mind that it is naturally inactive against *Proteus, Morganella, Providencia* and *Serratia* spp. It was one of the pivotal drugs used for treating MBL infections before 2015 [51]. In ICU, intravenous colistin should be given at high doses (i.e., 75 à 150,000 U/Kg/d with a maximal dose of 12 MUI per day). The therapeutic margin of colistin is narrow, and high concentrations are associated with increased renal and neurological toxicity. In the past few years, many studies have suggested not using colistin in difficult-to-treat Gram-negative infections when an alternative exists. A colistin-based regimen was associated with an increased risk of acute kidney injury [52–56]. In a systematic review, Wagenthaler et al. estimated the rate of nephrotoxicity of polymixins to be as high as 39% [57]. The odds of nephrotoxicity were greater with polymyxin-based therapies compared to non-polymyxin-based regimens (odds ratio 2.23 (95% CI 1.58–3.15); *p* < 0.001). Cohort studies suggest that colistin monotherapy is less effective than in combination in treating CRE infections [58,59].

5.7. Aminoglycosides

Aminoglycosides are rapidly bactericidal. Resistance, due to aminoglycosides-modifying enzymes, is common in MBL strains [60]. In a recent study from Greece, MBL-producing *Enterobacterales* were susceptible to gentamicin in one-third of the strains, but rarely susceptible to amikacin. Plazomycin is able to evade to enzymes and is active in more than 80% of the VIM and around half of the NDM-producing *Enterobacterales* [44,60,61]. The drug has been successfully tested in combination in CRE infections (mainly KPC) [62], and was approved by the FDA in 2018. Unfortunately, it is not commercialized yet. Overall, the high resistance rate precludes the use of aminoglycosides as empiric therapy. It may be used in association with other antibiotic therapies based on documented infections.

6. A Place for Nebulized Antimicrobials in MBL-Producing *Enterobacterales* Pneumonia

Despite appropriate parenteral antimicrobial therapy, VAP remains associated with a substantial risk of therapeutic failure. Potential causes of failure are a high bacterial inoculum, poor lung diffusion of antibacterial agents, reduced bronchial bacterial clearance by the alteration of the mucus layer, altered bacterial mechanical clearance and impaired local immunity. Of course, the situation is even more complex when pathogens are poorly susceptible to available antibacterial agents and when the minimum inhibitory concentration (MIC) is close to or beyond the resistance breakpoint. Nebulization of antimicrobials is feasible and widely used [63] in mechanically ventilated patients. It allows the delivery of extremely high concentrations of antimicrobials directly to the targeted tissue. It is especially interesting for MBL-producing organisms and for molecules with reduced lung diffusion and high dose-dependent systemic toxicity when administered parenterally, such as aminoglycosides and polymixins.

It should be kept in mind that the ECCMID task force recommends avoiding nebulized antimicrobials in patients with severe hypoxemia (PaO2/FiO2 < 200 mmHg) or in patients that have shown signs of poor pulmonary reserve or tending to rapid lung derecruitment.
This condition is frequent in all patients with moderate to severe acute respiratory distress syndrome [64].

In a recent meta-analysis of cohort studies, the use of adjunctive nebulized antibiotics in VAP improved the rates of clinical cure (relative risk (RR) 1.13, 95% CI (1.02, 1.26)) and microbiological eradication (RR 1.45, 95% CI (1.19, 1.76)) but had no impact on mortality (RR 1.00, 95% CI (0.82, 1.21)) [65]. Inhaled antibiotic therapy was associated with an increased risk of bronchospasm (RR 2.74, 95% CI (1.31–5.73)) [65]. Adjunctive nebulized antibiotics had no effect on the duration of mechanical ventilation and on the ICU length of stay.

A single-center double-blind trial compared an adjunctive therapy of 7 days of aerosolized amikacin (400 mg tid) versus placebo administered via a jet nebulizer on VAP due to resistant Gram-negative bacteria (Acinetobacter baumannii \(n=16\), P. aeruginosa \(n=15\), Enterobacterales \(n=22\)) and other non-fermentative bacteria \(n=7\)). Adjunctive nebulized antibiotic resulted in a quicker clinical improvement without effects on the delay in successful ventilator weaning or 28-day mortality. Bacterial eradication was more frequently obtained at the end of treatment with adjunctive nebulized amikacin (13/32 vs. 4/28, \(p=0.024\)) without the emergence of amikacin resistance during the 28-day follow up [66]. Two other randomized double-blind studies, using adjunctive inhaled amikacin combined with fosfomycin [67] or amikacin [68], also suggested that adjunctive inhaled antibiotics may lead to a higher bacterial eradication in extensively and pan-drug resistant Gram-negative pneumonia with no significant impact on clinical cure or mortality.

A positive effect of adjunctive antimicrobial nebulization was also suggested by a single-center double-blind RCT in chronically intubated critically ill patients at risk of infections with multidrug-resistant organisms (MDRO). Inhaled antibiotics for 14 days (mainly aminoglycosides) resulted in more bacterial eradication at the end of treatment (14 out of 16 patients compared with 1 of 11 for placebo (\(p<0.001\)). New resistance was less common when an adjunctive inhaled antibiotic was used (2/16 vs. 6/11, \(p=0.03\)) [69].

In the IDSA guidelines, for patients with VAP due to Gram-negative bacilli that are susceptible to only aminoglycosides or polymyxins (colistin or polymyxin B), the experts suggested combining both inhaled and systemic antibiotics, rather than systemic antibiotics alone (weak recommendation, very low-quality evidence). It is reasonable to consider adjunctive inhaled antibiotic therapy as a last-resort treatment for patients who are not responding to intravenous antibiotics alone, whether the infecting organism is a MDRO or not [70].

Importantly, the small benefit observed in bacterial clearance of MDR/PDR GNB does not automatically translate into improved clinical outcomes and may be counterbalanced by poor tolerance, especially in patients with severe alteration of oxygenation. Its use should be limited to units experienced in nebulization, using checklists and specific surveillance [71] in order to reduce the risk of misuse and adverse effects.

### 7. Monotherapy or Combination in Critically Ill Patients

There are some indirect data suggesting that combination therapy is preferable for severe infections due to CRE. This is especially the case when strains are not treated with new beta-lactams antimicrobials [72]. The INCREMENT cohort compared monoactive and dual active antibiotic therapy for CRE (almost exclusively KPC and OXA-48) [59]. In the most severe patients, combination therapy was associated with lower mortality than monotherapy was (30 (48%) of 63 vs. 64 (62%) of 103; adjusted HR 0.56 (0.34–0.91); \(p=0.02\)). It should be kept in mind that available clinical data on this topic are scarce and associated with important limitations. Indeed, randomized control trials have never been performed. Published cohort studies only referred to targeted therapy and did not consider the potential benefit of a combination therapy for treatment started empirically, leading to an important risk of immortal time bias.

Moreover, in infections due to MBL-producing strains, the presence of co-existing resistance mechanisms leaves very few therapeutic options for combinations.
The combination of a pivotal beta-lactam and one of the possible therapeutic alternatives is not usually recommended for MBL infections [37,73]. However, combination therapy might be considered for the empirical therapy of patients previously colonized with MBL producers. Combination may also be considered when the initial bacterial inoculum is very high, such as in hospital-acquired pneumonia and VAP. In pneumonia, if there is no severe hypoxemia, nebulization of colistin of aminoglycosides might be considered.

8. Therapeutic Rules

Some rules should be taken into account when deciding and implementing the therapy of patients with suspected or proven MBL infections [16,74]. Antimicrobial stewardship programs have a crucial role in limiting excess antibiotic use and providing expertise on extensively drug-resistant infections; however, the treatment of class B MBLs remains challenging.

In critically ill patients with sepsis, the pharmacokinetics (PK) is severely altered and leads to high inter- and intra-patient variability in dosing requirements. The PK of hydrophilic antibiotics such as β-lactams, aminoglycosides, or colistin is particularly impaired, as their volumes of distribution (Vd) are greatly increased in sepsis and septic shock [75]. Hypoalbuminemia is frequent and may increase the clearance of highly bounded antibiotics by increasing their unbound fraction. Consequently, antibiotic treatment underdosing is frequent, with up to 65% of critically ill patients receiving β-lactams not achieving maximal bacterial killing [76].

That is why the optimization of PK is instrumental, especially at the beginning of therapy. Some simple rules displayed in Table 2 favor an appropriate initial therapy. The glomerular hyperfiltration, common during the first phase of infection, should be taken into account. It should be kept in mind that traditional formulas for the estimation of creatinine clearance are not appropriate for critically ill patients, and thus the measurement of urine output and urine creatinine is required for an appropriate evaluation. The variability of volume of distribution and of clearance is important in the most severe patients, and therapeutic drug monitoring is probably preferable to optimize therapy [77].

In the fight against antimicrobial resistance, interventions to limit antibiotic exposure target the inappropriate use of antimicrobials, including excessive treatment duration. An unjustified prolonged antibiotic course also leads to higher health costs and a higher risk of antibiotic-related adverse events. On the other hand, inappropriate shortening of antibiotic therapy may be associated with a higher risk of treatment failure, especially if pharmacokinetic targets are difficult to reach, such as the treatment of challenging organisms. The appropriate treatment duration of MBL infections is not known [78]. Some simple rules may be helpful to individualize the duration of therapy in MBL infections. First of all, infection with a MBL-producing Enterobacterales is not a reason per se to prolong the duration of antibiotic therapy [79]. Second, although short therapy (5–7 days) is always preferable, it has been safely used only in the absence of underlying immune suppression, and requires an appropriate source control. Third, a short therapy should be safely used only if the clinical situation is stabilized with an improvement of signs of infections and the recovery of organ dysfunctions. Fourth, if bactericidal beta-lactam pivotal therapy is not an option, and therapy is based on colistin- or tigecycline-based regimens, available data may suggest that a short course is associated with more therapeutic failures [80].

Adapting antibiotic treatment duration based on the patient’s status could be a way to decrease overall antibiotic use, without compromising the safety of each individual treatment. Such algorithms for individualized treatment interruption have been evaluated, based on the evolution of clinical and biological variables. In a randomized trial on patients with GNB bloodstream infection, a C-reactive protein (CRP)-guided treatment was non-inferior to a 7-day or 14-day fixed treatment in terms of clinical failure rate [81]. The decrease in procalcitonin levels has also been successfully used to reduce antibiotic exposure in severe ICU patients [82].
Table 2. Appropriate therapy of severe MBL infections: the 12 labors of physicians.

1. Do not treat simply colonized patients.

2. Use a pivotal beta-lactam antibiotic therapy with either the combination of aztreonam and ceftazidime-avibactam or cefiderocol.

3. A combination with another effective antimicrobial (Colistine, tigecycline, aminoglycoside, fosfomycin) is preferable before the knowledge of the susceptibility profile.

4. Ask the microbiological lab for MICs for the susceptible micro-organism.

5. A prolonged dual active antibiotic therapy is not recommended unless the use of a pivotal beta-lactam antibiotics is not possible. For colistin based antimicrobial regimen a combination therapy with another effective antibiotic is recommended.

6. The initial antibiotic dose should not be adapted to the renal clearance during the first 24 to 48 h of therapy.

7. For beta-lactam antibiotics, prolonged or continuous infusion should be used to improve the PK/PD.

8. In pneumonia, adjunctive nebulized antibiotic may be considered if not contra-indicated.

9. Monitor the creatinin clearance during therapy.

10. Therapeutic drug monitoring is important to optimize therapy and avoid over and under-dosage.

11. The duration of therapy should follow the guidelines for each infection. The individualization of the duration of therapy should depend on underlying illness, source control, the bactericidal nature of the pivotal antimicrobial and the improvement of clinical and biological parameters.

12. Protect the other patients. Antibiotic stewardship should be combined with strict infection control practices to avoid cross-transmissions of MBL Enterobacterales.

9. Conclusions

MBL infections are increasingly common, even in non-endemic areas. The treatment should follow simple rules of antibiotic stewardship. Bactericidal therapy including new agents such as CZA/ATM or cefiderocol is effective. The treatment should be optimized through close collaboration with microbiologists and pharmacists, with determination of MICs to the available antimicrobials and a thorough therapeutic drug monitoring.

Author Contributions: Conceptualization, J.-F.T., P.-H.W. and E.d.M.; methodology, J.-F.T., P.-H.W. and E.d.M.; investigation, J.-F.T., P.-H.W. and E.d.M.; resources, J.-F.T., P.-H.W. and E.d.M.; data curation, J.-F.T., P.-H.W. and E.d.M.; writing—original draft preparation, J.-F.T., P.-H.W. and E.d.M.; writing—review and editing, J.-F.T., P.-H.W. and E.d.M.; All authors have read and agreed to the published version of the manuscript.

Funding: J.-F.T. was supported in part by the Innovative Medicines Initiative Joint Undertaking under grant agreement no. [115737-2–COMBACTE-MAGNET], resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies.
Acknowledgments: The authors thank Céline Féger (EMIBIOTECH TM) for her editing support in writing the manuscript.

Conflicts of Interest: J.-F.T. reports advisory board participation for Pfizer, Shionoghi, Gilead, Beckton-Dickinson, Merck.

References

1. Polemis, M.; Mandilara, G.; Pappa, O.; Argyroupoulou, A.; Perivolioti, E.; Kouroumniakis, N.; Pournaras, S.; Vasilakopoulou, A.; Vourli, S.; Katsifa, H.; et al. COVID-19 and Antimicrobial Resistance: Data from the Greek Electronic System for the Surveillance of Antimicrobial Resistance-WHONET-Greece (January 2018–March 2021). Life 2021, 11, 996. [CrossRef] [PubMed]

2. Kazmierczak, K.M.; Karlowsky, J.A.; de Jonge, B.L.M.; Stone, G.G.; Sahm, D.F. Epidemiology of Carbapenem Resistance Determinants Identified in Meropenem-Nonsusceptible Enterobacteriaceae Collected as Part of a Global Surveillance Program, 2012 to 2017. Antimicrob. Agents Chemother. 2021, 65, e020002. [CrossRef] [PubMed]

3. Sader, H.; Mendes, R.E.; Streit, J.M.; Carvalhaes, C.G.; Castanheira, M. Antimicrobial susceptibility of Gram-negative bacteria from intensive care unit and non-intensive care unit patients from United States hospitals (2018–2020). Diagn. Microbiol. Infect. Dis. 2022, 102, 115557. [CrossRef] [PubMed]

4. Babiker, A.; Clarke, L.G.; Saul, M.; Gealey, J.A.; Clancy, C.J.; Nguyen, M.H.; Shields, R.K. Changing Epidemiology and Decreased Mortality Associated With Carbapenem-resistant Gram-negative Bacteria, 2000–2017. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 2021, 73, e4521–e4530. [CrossRef] [PubMed]

5. Babiker, A.; Clarke, L.G.; Saul, M.; Gealey, J.A.; Clancy, C.J.; Nguyen, M.H.; Shields, R.K. Changing Epidemiology and Decreased Mortality Associated With Carbapenem-resistant Gram-negative Bacteria, 2000–2017. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 2021, 73, e4521–e4530. [CrossRef] [PubMed]

6. Brolund, A.; Lagerqvist, N.; Byfors, S.; Struelens, M.J.; Monnet, D.L.; Albiger, B.; Kohlenberg, A. Worsening epidemiological situation of carbapenemase-producing Enterobacteriaceae in Europe, assessment by national experts from 37 countries, July 2018. Euro Surveill. Bull. Eur. Mal. Transm. Eur. Commun. Dis. Bull. 2019, 24, 1900123. [CrossRef] [PubMed]

7. Bush, K.; Bradford, P.A. Epidemiology of beta-Lactamase-Producing Pathogens. Clin. Microbiol. Rev. 2020, 33, e00047-19. [CrossRef]

8. Lopez, C.; Ayala, J.A.; Bonomo, R.A.; Gonzalez, L.J.; Vila, A.J. Protein determinants of dissemination and host specificity of metallo-beta-lactamases. Nat. Commun. 2019, 10, 3617. [CrossRef]

9. Palacios-Baena, Z.R.; Giannella, M.; Manissero, D.; Rodriguez-Bano, J.; Viale, P.; Lopes, S.; Wilson, K.; Mccool, R.; Longshaw, C. Risk factors for carbapenem-resistant Gram-negative bacterial infections: A systematic review. Clin. Microbiol. Infect. Off. Publ. Eur. Soc. Clin. Microbiol. Infect. Dis. 2021, 27, 228–235. [CrossRef] [PubMed]

10. Snyder, B.M.; Montague, B.T.; Anandan, S.; Madabhushi, A.G.; Pragasam, A.K.; Verghese, V.P.; Balaji, V.; Simoes, E.A.F. Risk factors and epidemiologic predictors of blood stream infections with New Delhi Metallo-b-lactamase (NDM-1) producing Enterobacteriaceae. Epidemiol. Infect. 2019, 147, e137. [CrossRef]

11. Daikos, G.L.; Petrikkos, P.; Psychogiou, M.; Kosmidis, C.; Vryonis, E.; Skoutelas, A.; Georgousi, K.; Tzouvelekis, L.S.; Tassios, P.T.; Mamoulaki, A.; Vasilakis, C.; Pournaras, S.; Vasilakopoulou, A.; Vourli, S.; Katsifa, H.; et al. COVID-19 and Antimicrobial Resistance: Data from the Greek Electronic System for the Surveillance of Antimicrobial Resistance-WHONET-Greece (January 2018–March 2021). Life 2021, 11, 996. [CrossRef] [PubMed]

12. Tischendorf, J.; de Avila, R.A.; Safdar, N. Risk of infection following colonization with carbapenem-resistant Enterobacteriaceae: A systematic review. Am. J. Infect. Control 2016, 44, 539–543. [CrossRef] [PubMed]

13. Dickstein, Y.; Edelman, R.; Dror, T.; Hussein, K.; Bar-Lavie, Y.; Paul, M. Carbapenem-resistant Enterobacteriaceae colonization and infection in critically ill patients: A retrospective matched cohort comparison with non-carriers. J. Hosp. Infect. 2016, 94, 54–59. [CrossRef] [PubMed]
20. Lin, Q.; Wang, Y.; Yu, J.; Li, S.; Zhang, Y.; Wang, H.; Lai, X.; Liu, D.; Mao, L.; Luo, Y.; et al. Bacterial characteristics of carbapenem-resistant Enterobacteriaceae (CRE) colonized strains and their correlation with subsequent infection. BMC Infect. Dis. 2021, 21, 638. [CrossRef]

21. Leibman, V.; Martin, E.T.; Tal-Jasper, R.; Grin, L.; Hayakawa, K.; Shefler, C.; Azouri, T.; Kaplansky, T.; Maskit, M.; Lazarovitch, T.; et al. Simple bedside score to optimize the time and the decision to initiate appropriate therapy for carbapenem-resistant Enterobacteriaceae. Ann. Clin. Microbiol. Antimicrob. 2015, 14, 31. [CrossRef] [PubMed]

22. Marimuthu, K.; Ng, O.T.; Cheng, B.P.Z.; Fong, R.K.C.; Pada, S.K.; De, P.P.; Ooi, S.T.; Smitasiri, N.; Thoon, K.C.; Krishnan, P.U.; et al. Antecedent Carbapenem Exposure as a Risk Factor for Non-Carbapenemase-Producing Carbapenem-Resistant Enterobacteriaceae. Antimicrob. Agents Chemother. 2019, 63, e00845-19. [CrossRef]

23. Kerneis, S.; Visseaux, B.; Armand-Lefevre, L.; Timsit, J.F. Molecular diagnostic methods for pneumonia: How can they be applied in practice? Curr. Opin. Infect. Dis. 2021, 34, 118–125. [CrossRef] [PubMed]

24. Renaud, C.; Kollef, M.H. Classical and Molecular Techniques to Diagnose HAP/VAP. Semin. Respir. Crit. Care Med. 2022. [CrossRef] [PubMed]

25. Mgueire, R.J.; Yu, S.C.; Payne, P.R.O.; Lai, A.M.; Vazquez-Guillamat, M.C.; Kollef, M.H.; Michelson, A.P. A Pragmatic Machine Learning Model To Predict Carbapenem Resistance. Antimicrob. Agents Chemother. 2021, 65, e006321. [CrossRef] [PubMed]

26. Mauri, C.; Maraolo, A.E.; Di Bella, S.; Luzzaro, F.; Principe, L. The Revival of Aztreonam in Combination with Avibactam against Metallo-beta-Lactamase-Producing Gram-Negatives: A Systematic Review of In Vitro Studies and Clinical Cases. Antibiotics 2021, 10, 1012. [CrossRef]

27. Falcione, M.; Tiseo, G.; Nicastro, M.; Leonilidi, A.; Vecchione, A.; Casella, C.; Forfori, F.; Malacarne, P.; Guarracino, F.; Barnini, S.; et al. Cefiderocol as Rescue Therapy for Acinetobacter baumannii and Other Carbapenem-resistant Gram-negative Infections in Intensive Care Unit Patients. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 2021, 72, 2021–2024. [CrossRef] [PubMed]

28. Benchetrit, L.; Mathy, V.; Armand-Lefevre, L.; Bouadma, L.; Timsit, J.F. Successful treatment of septic shock due to NDM-1-producing Klebsiella pneumoniae using cefazidime/avibactam combined with aztreonam in solid organ transplant recipients: Report of two cases. Int. J. Antimicrob. Agents 2020, 55, 105842. [CrossRef] [PubMed]

29. Tamma, P.D.; Aitken, S.L.; Bonomo, R.A.; Mathers, A.J.; van Duin, D.; Clancy, C.J. Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum beta-lactamase Producing Enterobacteriales (ESBLE), Carbapenem-Resistant Enterobacteriales (CRE), and Pseudomonas aeruginosa with Difficult-to-Treat Resistance (DTR-P. aeruginosa). Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 2021, 72, e169–e183. [CrossRef]

30. Lodise, T.P.; Smith, N.M.; O'Donnell, N.; Eakin, A.E.; Holden, P.N.; Boissonneault, K.R.; Zhou, J.; Tao, X.; Bulitta, J.B.; Fowler, V.G.; et al. Determining the optimal dosing of a novel combination regimen of cefazidime/avibactam with aztreonam in solid organ transplant recipients: Results from the REJUVENATE study. J. Antimicrob. Chemother. 2020, 75, 2622–2632. [CrossRef] [PubMed]

31. Cornely, O.A.; Cisneros, J.M.; Torre-Cisneros, J.; Tallon-Aguilar, L.; Calbo, E.; Horcajada, J.P.; Queckenberg, C.; Zettelmeyer, U.; Arenz, D.; et al. Pharmacokinetics and safety of aztreonam/avibactam for the treatment of complicated intra-abdominal infections in hospitalized adults: Results from the REJUVENATE study. J. Antimicrob. Chemother. 2020, 75, 618–627. [CrossRef] [PubMed]

32. Albano, M.; Karau, M.J.; Schuetz, A.N.; Patel, R. Comparison of Agar Dilution to Broth Microdilution for Testing In Vitro Activity of Cefiderocol against Gram-Negative Bacilli. J. Clin. Microbiol. 2020, 59, e00966-20. [CrossRef] [PubMed]

33. Bassetti, M.; Echols, R.; Matsunaga, Y.; Ariyasu, M.; Doi, Y.; Ferrer, R.; Lodise, T.P.; Naas, T.; Niki, Y.; Paterson, D.L.; et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREBLE:CR): A randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. Lancet. Infect. Dis. 2021, 21, 226–240. [CrossRef]

34. Wunderink, R.G.; Matsunaga, Y.; Ariyasu, M.; Clevenbergh, P.; Echols, R.; Kaye, K.S.; Kollef, M.; Menon, A.; Pogue, J.M.; Shorr, A.F.; et al. Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): A randomised, double-blind, phase 3, non-inferiority trial. Lancet. Infect. Dis. 2021, 21, 213–225. [CrossRef]

35. Nurjadi, D.; Kocer, K.; Chanthalangsry, Q.; Klein, S.; Heeg, K.; Boutin, S. New Delhi metallo-beta-lactamase facilitates the emergence of cefiderocol resistance in Entorobacter cloacae. Antimicrob. Agents Chemother. 2021, AAC0201121. [CrossRef]

36. Simmer, P.J.; Mostafa, H.H.; Bergman, Y.; Ante, M.; Tekle, T.; Adebayo, A.; Beisken, S.; Dzintars, K.; Tamma, P.D. Progressive Development of Cefiderocol Resistance in Escherichia coli During Therapy Is Associated with Increased blaNDM-5 Copy Number and Gene Expression. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 2021, eia888. [CrossRef]

37. Paul, M.; Carrara, E.; Retamar, P.; Tøndén, T.; Bitterman, R.; Bonomo, R.A.; de Waale, J.; Daikos, G.L.; Akova, M.; Harbarth, S.; et al. European Society of clinical microbiology and infectious diseases (ESCMID) guidelines for the treatment of infections caused by Multidrug-resistant Gram-negative bacilli (endorsed by ESICM-European Society of intensive care Medicine). Clin. Microbiol. Infect. Off. Publ. Eur. Soc. Clin. Microbiol. Infect. Dis. 2021. [CrossRef]

38. Oteo, J.; Ortega, A.; Bartolome, R.; Bou, G.; Conejo, C.; Fernandez-Martinez, M.; Gonzalez-Lopez, J.J.; Martinez-Garcia, L.; Martinez-Martinez, L.; Merino, M.; et al. Prospective multicenter study of carbapenemase-producing Enterobacteriaceae from 83 hospitals in Spain reveals high in vitro susceptibility to colistin and meropenem. Antimicrob. Agents Chemother. 2015, 59, 3406–3412. [CrossRef]
79. Yahav, D.; Franceschini, E.; Koppel, F.; Turjeman, A.; Babich, T.; Bitterman, R.; Neuberger, A.; Ghanem-Zoubi, N.; Santoro, A.; Eliakim-Raz, N.; et al. Seven versus fourteen Days of Antibiotic Therapy for uncomplicated Gram-negative Bacteremia: A Non-inferiority Randomized Controlled Trial. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 2018, 69, 1091–1098. [CrossRef]

80. Zhou, C.; Jin, L.; Wang, Q.; Wang, X.; Chen, F.; Gao, Y.; Zhao, C.; Chen, H.; Cao, B.; Wang, H. Bloodstream Infections Caused by Carbapenem-Resistant Enterobacterales: Risk Factors for Mortality, Antimicrobial Therapy and Treatment Outcomes from a Prospective Multicenter Study. Infect. Drug Resist. 2021, 14, 731–742. [CrossRef]

81. von Dach, E.; Albrich, W.C.; Brunel, A.S.; Prendki, V.; Cuvelier, C.; Flury, D.; Gayet-Ageron, A.; Huttner, B.; Kohler, P.; Lemmenmeier, E.; et al. Effect of C-Reactive Protein-Guided Antibiotic Treatment Duration, 7-Day Treatment, or 14-Day Treatment on 30-Day Clinical Failure Rate in Patients With Uncomplicated Gram-Negative Bacteremia: A Randomized Clinical Trial. JAMA 2020, 323, 2160–2169. [CrossRef] [PubMed]

82. Bouadma, L.; Luyt, C.E.; Tubach, F.; Cracco, C.; Alvarez, A.; Schwebel, C.; Schortgen, F.; Lasocki, S.; Veber, B.; Dehoux, M.; et al. Use of procalcitonin to reduce patients’ exposure to antibiotics in intensive care units (PRORATA trial): A multicentre randomised controlled trial. Lancet 2010, 375, 463–474. [CrossRef]