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Double carbapenem regimen used as salvage therapy to treat multidrug-resistant *Klebsiella pneumoniae* causing ventilator-associated pneumonia

Abstract

Carbapenemase-producing *Klebsiella pneumoniae* is an emerging threat worldwide. The appropriate therapy for infections due to these multidrug-resistant pathogens is not well defined and depends upon the susceptibilities of individual isolates, and the choices are often severely limited. We report a case of a 8-year-old male child with ARDS with left-sided tubercular pleural effusion who developed ventilator-associated pneumonia due to multidrug-resistant *Klebsiella pneumoniae* treated successfully with a regimen comprising a combination of colistin and double carbapenem.

Key words: double carbapenem, ventilator-associated pneumonia, *Klebsiella pneumoniae*

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Introduction

Klebsiella pneumoniae is a frequent cause of nosocomial infections [1]. A rise of antimicrobial drug resistance in *Klebsiella pneumoniae* raises serious therapeutic challenges [2]. Among several mechanisms of drug resistance in *Klebsiella pneumoniae*, carbapenemases are increasingly recognized worldwide. They are particularly prevalent in *Klebsiella pneumoniae* from several geographic areas, including the Indian subcontinent and the Mediterranean countries [3]. New antibiotic options are urgently needed for the treatment of carbapenem-resistant *Enterobacteriaceae* infections. We report a case of a 8-year-old male child with ARDS with left-sided tubercular pleural effusion who developed ventilator-associated pneumonia due to multidrug-resistant *Klebsiella pneumoniae* treated successfully with a regimen comprising a combination of colistin and double carbapenem.

Case report

A 8-year-old male child on mechanical ventilation was shifted to our hospital from another hospital with a history of increasing oxygen requirement and radiological deterioration. He presented to the previous hospital with one-week history of cough, fever and breathlessness. Pleural tap was done at the previous hospital, which was positive for *Mycobacterium tuberculosis* on gene xpert. On presentation, the child was already on meropenem, vancomycin and antitubercular medication for the past 3 days. In spite of treatment, the general condition of the patient was deteriorating, thus he was shifted to our setup. On admission to our hospital, the patient was febrile, on mechanical ventilation with oxygen requirement of 70%, end expiratory pressure of 7 mm Hg and inspiratory pressure of 26 mm Hg. He was generating tidal volumes of around 200 mL. On suctioning of the endotracheal tube blood

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clots were seen. His laboratory investigations revealed raised serum bilirubin of 2.1 mg/dL, aspartate aminotransferase of 313 U/L, alanine aminotransferase of 667 U/L, international normalized ratio — 1.5, total leukocyte count of 15 × $10^3/\mu$L and raised C-reactive protein of 23.9 mg/L. Endotracheal secretions showed the growth of *Acinetobacter baumannii* with colony count: > 100000, colony-forming units/ml which was sensitive to colistin, fosfomycin, minocycline and ceftriaxone EDTA sulbactum (Figure 1). The antibiotics and antitubercular therapy were changed to ceftriaxone EDTA sulbactum 1.5 mg 12 hourly, vancomycin 500 mg 8 hourly and levofloxacin 500 mg once daily, amikacin 500 mg once daily, ethambutol 600 mg once daily.

There was sudden worsening of respiratory pattern on the third day of presentation with subcutaneous emphysema. Computed tomography of the chest was done (Figure 2, 3), which showed bilateral patches of consolidation with crazy paving in both the lungs, along with pulmonary interstitial emphysema with extensive pneumo-mediastinum, minimal left pneumothorax and subcutaneous emphysema.

Intercostal chest drain was inserted on the left side. The child was not relieved of fever even after three days of changing antibiotics. Blood, pleural fluid and urine cultures were sterile. Bronchial lavage revealed the growth of multidrug-resistant *Acinetobacter baumannii* which was sensitive to colistin, ceftriaxone EDTA sulbactum and fosfomycin. Then colistin (loading dose of 6000000 IU, then 3000000 IU every 12 hours) was started, and ceftriaxone EDTA sulbactum (1.5 mg every 12 hours) was continued. As liver functions improved, isoniazid 300mg was started and aminoglycoside stopped due to risk of significant side effects in combination with collistin. The patient became afebrile after 48 hours of revising the antibiotics. Subsequently, rifampicin was re-introduced. After two doses of rifampicin 450 mg, the boy started having bleeding through the endotracheal tube, and repeated liver functions showed deterioration (international normalized ratio — 1.8, platelet count — 110000, serum bilirubin — 2.1 mg/dL, alanine aminotransferase — 209 U/L, aspartate aminotransferase- 45 U/L). On ultrasound of the whole abdomen, hepatomegaly with minimal ascites was present. Rifampicin was stopped and fresh frozen plasma was given to control bleeding. As there was a problem with ventilation, therapeutic bronchoscopy was done to remove the clots. Bleeding tendency on re-introducing rifampicin could be due to part of sepsis induced by disseminated intravascular coagulation or some idiosyncratic reaction. There was a gradual improvement in the patient's general condition. Percutaneous tracheostomy was done.

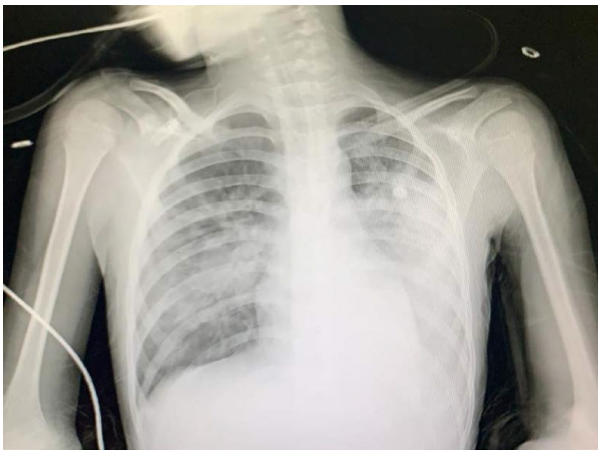

Figure 1. Chest radiography (anterior-posterior view) showing bilateral consolidation

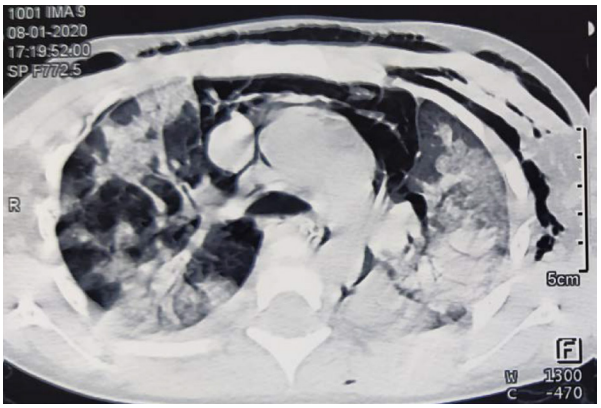

Figure 2. High resolution computed tomography of the chest showing bilateral patches of consolidation

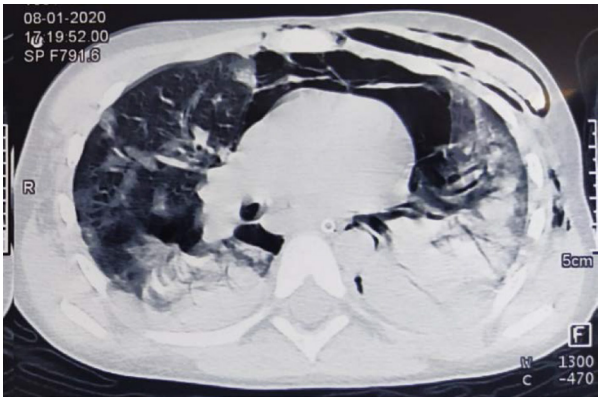

Figure 3. High resolution computed tomography of the chest showing bilateral patches of consolidation with pneumomediastinum, pneumothorax and subcutaneous emphysema

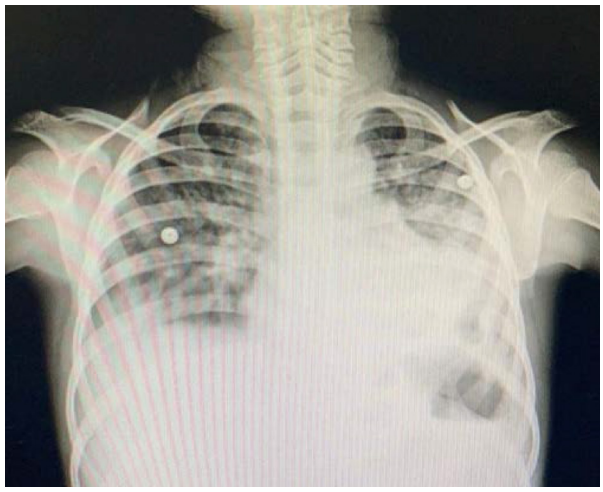

Figure 4. Chest radiography showing an increase in left lower zone infiltrates

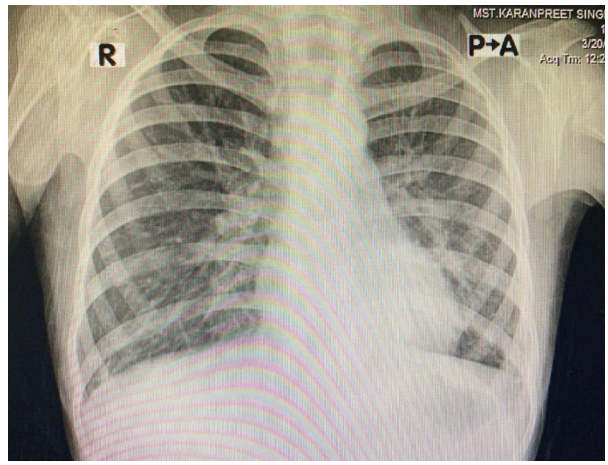

Figure 5. Follow-up chest radiography showing complete resolution of opacities

The boy started improving clinically and radiologically. In due course, pyrazinamide 750 mg once daily was started. Again, after 12 days of ceftriaxone EDTA sulbactum and colistin combination, the patient started having high-grade fever upto 104°F and oxygen requirement increased. There was worsening in inflammatory markers and on radiology (Figure 4) with an increase in left lower zone infiltrates.

Repeat tracheal aspirates showed carbapenemase-producing multidrug-resistant *Klebsiella pneumoniae* which was sensitive only to colistin (minimum inhibitory concentration ≤ 0.5 μg/mL), which was already going on. The patient was started on combination of imipenem (MIC ≥ 16μg/mL) in extended infusion, ertapenem (MIC ≥ 8 μg/mL), and colistin was continued. Fever subsided within 48 hours of starting the combination with gradual normalization of inflammatory markers. In due course, the patient was de-cannulated. Colistin and double carbepenem regimen was continued for 14 days and the child was discharged in good clinical condition. Chest radiograph done at follow-up showed almost complete clearance of infiltrates (Figure 5). Follow-up chest radiographs showed almost complete clearance of the infiltrates.

Discussion

The increasing global prevalence of carbapenem-resistant *Enterobacteriaceae* (CRE) combined with the decline in effective antimicrobial therapies is a serious public healthcare problem. According to CDC, CRE is defined as *Enterobacteriaceae* that are resistant to any carbapenem antimicrobial (i.e., minimum inhibitory concentration of ≥ 4 mcg/mL for doripenem, meropenem or imipenem OR ≥ 2 mcg/mL for ertapenem) or documented to produce carbapenemase [4]. Infections caused by these Gram-negative multidrug-resistant organisms resulted in high mortality rates, prolonged hospitalization and increased cost of care [5]. Currently, the available antibiotic options to combat these organisms are limited. So, new therapeutic approaches against these burgeoning organisms are needed. Recently, the double carbapenem regimen has been come up as a valid therapeutic option in severe infections due to pandrug-resistant *Klebsiella pneumonia* [6].

This case confers how the combination of colistin with ertapenem plus imipenem was effective and synergistic against a multidrug-resistant *Klebsiella pneumoniae* causing ventilator-associated pneumonia, even in the presence of high MIC values. The rationale for this combination has not been extensively explored, it is hypothesized that one of the carbapenem compounds distracts the carbapenemase enzyme acting as a suicide inhibitor, thus allowing and preserving the other carbapenem's activity [7]. Carbapenemase enzyme has preferential affinity for ertapenem, due to the ease of hydrolysis versus that of imipenem. Since enzyme is consumed during this interaction with ertapenem, higher concentrations of imipenem are present in the vicinity of the organism that would otherwise be recognized if copious amounts of enzyme were freely available to degrade imipenem. After that disruption caused to the outer bacterial cellular membrane by colistin allowing other drugs to reach adequate intracellular concentrations. Despite hydrolysis of carbapenems by the carbapenemase enzyme, these compounds perpetuate their bactericidal

effect. This has been demonstrated both in vitro and in animal models [8, 9].

A study was conducted to determine therapeutic strategy for pandrug-resistant *Klebsiella pneumoniae* severe bloodstream infection by Oliva *et al.*; it showed combination of colistin with ertapenem plus meropenem manifest rapid bactericidal activity, even at subinhibitory concentrations. Therefore, given the potent in vitro effect and the good clinical outcome of the patient, it suggested that colistin might be useful as an initial therapeutic add-on against pandrug-resistant organisms, rapidly decreasing the bacterial amount and limiting drug toxicity [10].

Another combination, colistin-rifampin may have a role in the treatment of multidrug-resistant *Klebsiella pneumoniae* and may possibly slow the selection of hetero-resistant subpopulations during colistin therapy. A study conducted to determine synergistic activity of colistin plus rifampin against colistin-resistant KPC-producing *Klebsiella pneumonia* by Tascini *et al.* showed that colistin plus rifampin is the most consistently synergistic combination against KPC-producing *Klebsiella pneumoniae* isolates, including colistin-resistant strains [11]. Combination is based on the principle that perturbation of the outer bacterial cellular membrane by colistin may favor the uptake of rifampin, allowing the drug to reach sufficient intracellular concentrations to inhibit protein synthesis. But in our case, we were not able to use this regimen due to rifampicin-induced hepatotoxicity and bleeding tendencies.

A source of these multidrug-resistant organisms could be a prolonged stay in hospital, and in addition, on mechanical ventilation. We treated our patient with colistin and double carbapenem regimen for 14 days, but we stopped colistin 6 days before the completion of regimen as the patient was already on colistin for the previous 8 days and he recovered clinically as well as radiologically.

Conclusions

In conclusion, this case indicates that this regimen is a valid and effective therapeutic strategy in treating severe infections caused by carbapenemase-producing *Klebsiella pneumonia*. Contact precautions and active surveillance are common measures that should be employed for controlling the spread of these microorganisms in hospitals.

Conflict of interest

None declared.

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