

Ventilator associated Pneumonia due to Multi Drug Resistant, Colistin-S *Acinetobacter baumannii*: Successful Revival of Colistin, A Forgotten Drug

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ABSTRACT

Ventilator associated pneumonia (VAP) is one of the most dreadful complications that occurs in critical care setting and is associated with significant morbidity and mortality, especially when the episode of pneumonia is due to a multi drug resistant (MDR) pathogen. Due to its varied clinical presentations, and the involvement of MDR pathogens, disease poses a serious diagnostic and therapeutic challenge for clinicians, left with limited options. Such resistant strains have disseminated worldwide and often remain susceptible only to agents such as, tigecycline and polymyxins which are usually considered as treatment of 'last-resort'. The growing epidemic of infections in the intensive care units caused by such MDR strains has led clinicians to reconsider prescribing polymyxin antimicrobials [polymyxin B and polymyxin E (colistin)], that were removed from use in past because of the associated neurotoxicity and nephrotoxicity. Colistin, a polymyxin antibiotic appears as an appropriate therapeutic alternative. The available data on epidemiological and clinical characteristics of VAP, due to GNB susceptible only to colistin (col-S) is limited.

We here report a case of ventilator associated pneumonia caused by a multi drug resistant, but colistin-S strain of *Acinetobacter baumannii*, where the combined use of aerosolized and intravenous colistin led to the positive patient outcome.

Keywords: *Acinetobacter*, carbapenems, endo tracheal aspirate, mechanical ventilation, polymyxin

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INTRODUCTION

Ventilator associated pneumonia (VAP), specifically refers to pneumonia developing in a mechanically ventilated patient >48 hours after tracheal intubation or tracheostomy [1]. VAP is one of the most dreadful complications that occurs in critical care setting and is associated with significant morbidity and mortality with severe impact on the healthcare costs incurred by the society [2]. Due to its varied clinical presentations, disease is a challenge for clinician as well as for microbiologists, who needs to confirm bacteriological diagnosis as early as possible so that appropriate treatment can be initiated [3]. Studies have shown that the delayed antibiotic therapy in patients with VAP is associated with increased mortality,

especially when the episode of pneumonia is due to a multi drug resistant (MDR) pathogen [4].

Such resistant strains have disseminated worldwide and often remain susceptible only to agents such as, tigecycline and polymyxins which are usually considered as treatment of 'last-resort' [5,6]. Colistin, a polymyxin antibiotic appears as an appropriate therapeutic alternative. The available data on epidemiological and clinical characteristics of VAP, due to GNB susceptible only to colistin (col-S) is limited [7-9].

We here present the case of VAP caused by MDR, col-S strain of *Acinetobacter baumannii*, where the use of aerosolized

and intravenous (IV) colistin led to the positive outcome of the patient.

Case report

A 33 years old man was brought to the emergency department of our hospital, in a critical condition. He had a severe road traffic accident (hit and run case). On admission, he was unconscious, had multiple abrasions all over the body with left femur, left hip bone and vertebral fracture. Due to massive blood loss he was in hypovolemic shock, had hemoperitoneum, hemothorax, hypotension, decreased breathing sounds and had Glasgow coma scale (GCS) of nine. Patient was revived successfully with fluid

infusions, blood transfusions and exploratory laprotomy. Computed tomography scan of head was normal.

The patient required intubation and mechanical ventilation. Once stable, he was transferred to medical ICU (MICU). Surgical profile of the patient was requested and patient was started empirically on gentamicin (1g x BD, IV) and cefoperazone-sulbactam (1 g x BD IV). On day five of hospitalization patient developed a fever of 39°C, hypotension and deteriorating PaO₂ / FiO₂ (P/F) ratio. Chest radiograph (figure 1) revealed marked consolidation in the left lung.

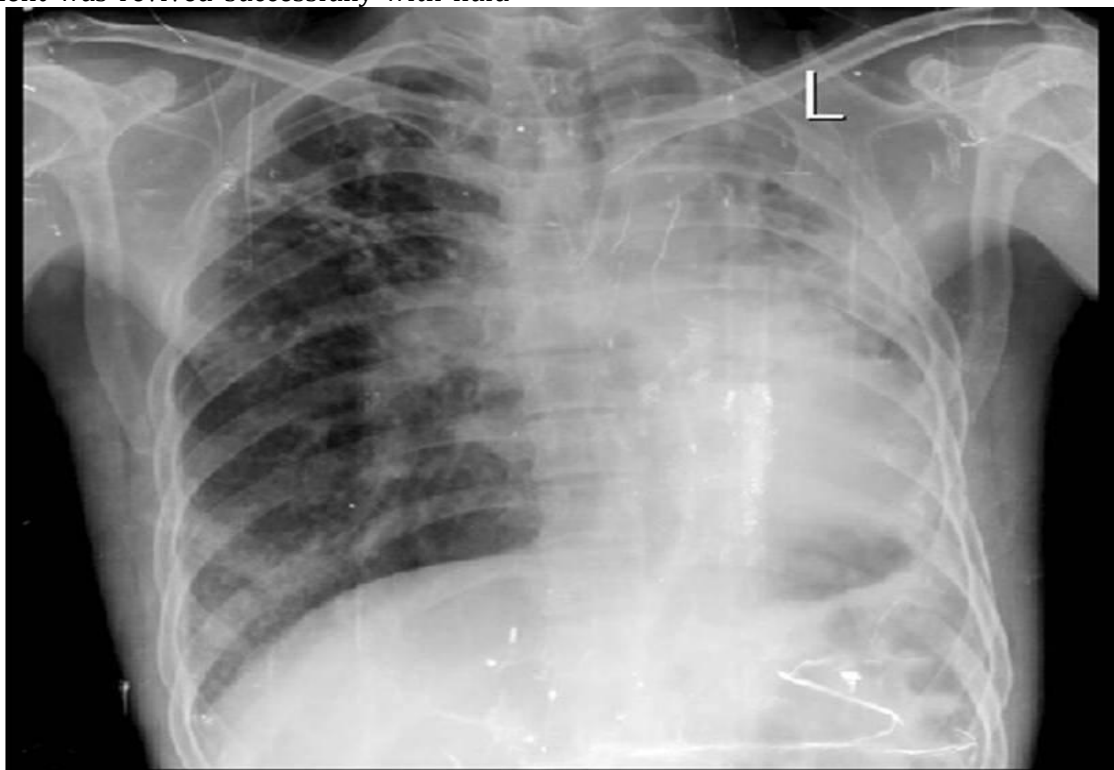


Figure 1: Chest X-ray showing marked consolidation in the left lung

Provisional diagnosis of late onset VAP was made with the Clinical Pulmonary Infection Score (CPIS) of 8. As the clinical condition of the patient did not improve, cefoperazone-sulbactam was replaced with piperacillin-tazobactam. Tracheostomy was done on day six and endotracheal aspirates (ETA) for gram staining, culture and sensitivity were received in microbiology laboratory. ETA sample received was thick, greenish yellow and mucopurulent. Gram staining showed plenty of pus cells and gram negative coccobacilli. Patient was already on broad spectrum antibiotics and

the same were continued. Later on day eight culture showed heavy growth of *A.baumannii* (figure 2a) which was resistant to all the routinely tested antibiotics (figure 2b) viz, quinolones, aminoglycosides, third generation cephalosporins and monobactams. The isolate was intermediately sensitive to carbapenems. With no clinical improvement, worsening pleural effusion and the available culture and sensitivity results, the antibiotic was again changed, this time to meropenem (1 g BD, IV). The clinical condition of patient still did not showed any improvement and the

same organism (with similar antibiogram) was recovered from the pleural fluid as well as the tracheal aspirate (TA) collected on day 13th.

At this point colistin and polymyxin-B were tested *in vitro*; and were found sensitive. The therapy was immediately switched to intravenous plus aerosolized colistin with the dosage of 1.5mg/kg/8 hrs and 40 mg/12 hrs respectively. The treatment was continued for next 14 days in combination with meropenem and drainage for pyopneumothorax. By day 6th of colistin therapy, remarkable clinical recovery was

seen in patient's condition. Temperature came down to normal and chest radiograph showed decrease in opacity. No bacterial growth was seen in TA collected on day 30th. The patient did not showed any signs of neuro and nephrotoxicity. He was in MICU for 45 days with ventilator and tracheostomy support. Due to prolonged hospital stay and immobilization for long duration he developed bedsores and nutritional insufficiency. He is on crutches, have spinal braces, and is admitted to physical rehabilitation department but is doing fine otherwise.

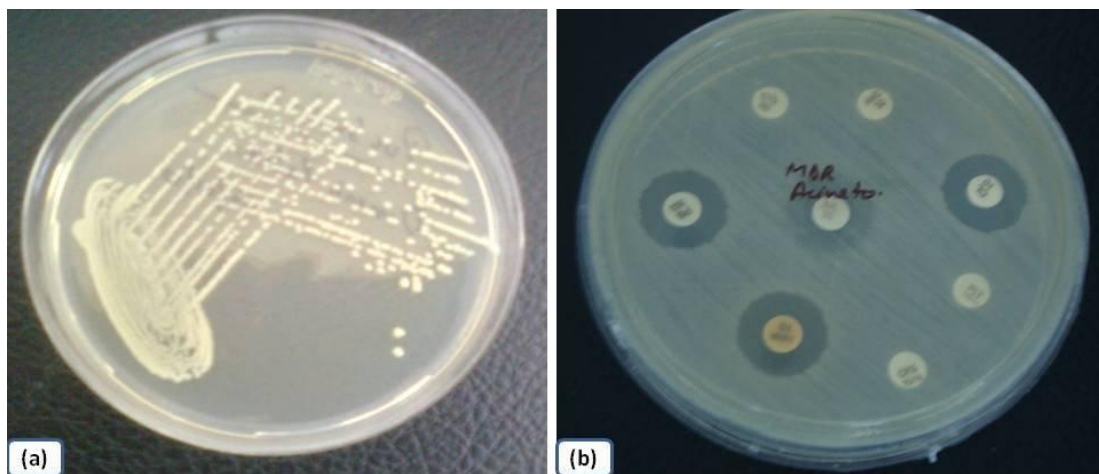


Figure 2: (a) Growth of *Acinetobacter baumannii* on nutrient agar; (b) Antimicrobial sensitivity plate (Kirby-Bauer disc diffusion method) showing isolate sensitive to colistin and polymyxin only.

DISCUSSION

Ventilator associated pneumonia is one of the most frequent nosocomial infections in the ICU and effects upto 27% of patients undergoing mechanical ventilation with the crude mortality rates of >50% [10]. VAP presents to the clinician along with diagnostic dilemmas, difficulties in the ventilatory management of the patient as the source of the disease is the ventilator itself.

It has been acknowledged that VAP episodes caused by 'high-risk pathogens' particularly the non fermenting, gram negative bacilli (NFGNB); *Acinetobacter* spp., and *Pseudomonas aeruginosa* are associated with higher mortality than with other organisms [9]. Over the last decade, *A.baumannii* has emerged as one of the most problematic nosocomial pathogens,

particularly in VAP. The epidemic potential and the clinical severity of *A.baumannii* infections are particularly related to MDR and pan drug resistant (PDR) strains [6]. The growing epidemic of infections in the intensive care units (ICUs) caused by such MDR/PDR strains has led clinicians to reconsider prescribing polymyxin antimicrobials (polymyxin B and polymyxin E [colistin]), that were removed from use in past because of the associated neuro and nephrotoxicity [10].

This was a typical case of late onset VAP with no clinical response to broad range of antibiotics (cefoperazone-sulbactam, piperacillin-tazobactam, gentamicin, meropenem), a CPIS score of 8 and the causative agent involved was a MDR strain of *A.baumannii*. The organism is known to rapidly develop resistance to majority of

antibiotics including carbapenems; currently the drug of choice for VAP due to *A. baumannii*. Most important associated risk factors for development of VAP due to MDR organisms are mechanical ventilation for >7 days duration and use of broad spectrum antibiotics [10].

Intravenous formulations of colistin were widely used in 1950's but were gradually abandoned worldwide in early 1970's because of the severe toxicities associated with their use [11], also the clinical experience with this antibiotic was poor [12]. But recently pharmacodynamic properties of colistin against MDR gram negative bacilli such as *A.baumannii*, *P.aeruginosa* and *Klebsiella pneumoniae* have been studied, based on which colistin seems to be very active in initial killing of *A.baumannii* [13, 14].

This case highlights the timely susceptibility testing for colistin and its combined administration as aerosolized and IV form for the treatment of VAP. As inhaled antibiotics deliver high drug concentrations at the site of infection with ignorable systemic absorption and toxicity, aerosolized colistin combined with IV administration can be considered as suitable option for treatment of patients with VAP due to MDR pathogens. There are recommendations to begin colistin as empiric antibiotic in VAP, but we consider it as a drug of 'last-resort' and to be started only in VAP cases due to MDR strains. Also microbiologists should always consider susceptibility testing of colistin against such resistant strains, as delay in antimicrobial therapy increases VAP mortality rate.

CONCLUSION

With the emergence of MDR and PDR bacterial strains, particularly in ICUs and lack of any new broad spectrum antimicrobial in the pipeline we should realize the possible therapeutic limitations with such isolates. Parenteral colistin combined with the aerosolized form can be considered as a promising option to achieve a satisfactory clinical response in a patient suffering with VAP due to multi drug resistant strain.

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