

TRIMETHOPRIM - SULFAMETHOXAZOLE IN COMBINATION WITH MEROPENEM OR POLYMYXIN IS EFFECTIVE IN MANAGEMENT OF ACINETOBACTER BAUMANNII ASSOCIATED PNEUMONIA AND URINARY TRACT INFECTION

Keyal NK¹, Nepal N², Bhujel A¹

Affiliation

1. Department of Critical Care Medicine, B & C Medical College and Teaching Hospital and Research Center, Birtamode, Nepal.
2. Department of Anaesthesiology and Critical care, B & C Medical College and Teaching Hospital and Research Center, Birtamode, Nepal.

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* Corresponding Author

Dr Niraj Kumar Keyal

Lecturer

Department of Critical Care Medicine

B & C Medical College and Teaching Hospital and Research Center
Birtamode, Nepal

Email: nirajkumarkeyal@gmail.com

ORCID ID: <https://orcid.org/0000-0001-8587-1718>

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ABSTRACT

Acinetobacter baumannii is a common multidrug resistant bacteria that causes pneumonia and urinary tract infection in intensive care unit and requires dual antibiotic for effective management. There are limited expensive antibiotics that are active against Acinetobacter baumannii. Trimethoprim - Sulfamethoxazole is a cheap, older and easily available antibiotic that can be used in combination with Meropenem or Polymyxin for treatment to decrease antibiotic resistance. This case presentation of three patients describes the successful treatment of hospital acquired Pneumonia and Urinary Tract Infection by Acinetobacter baumannii with Trimethoprim - Sulfamethoxazole in combination with Meropenem and Polymyxin that lead avoidance of costly drugs and decrease in antibiotic resistance. Antibiotic resistance and lack of newer effective antibiotic against multidrug resistant bacteria like Acinetobacter baumannii is a common problem in intensive care unit. Trimethoprim -Sulfamethoxazole may help in combating this problem.

KEYWORDS

Acinetobacter baumannii, pneumonia, trimethoprim and sulfamethoxazole, urinary tract.



INTRODUCTION

Acinetobacter baumannii is a multidrug resistant (MDR) opportunistic gram negative coccobacilli that commonly causes hospital acquired^[1] but rarely it may also cause community acquired^[2] pneumonia, urinary tract infection, endocarditis, meningitis, wound infection.

It is MDR^[3] bacteria that is resistance to most of commonly used antibiotics therefore combination therapy is used to decrease antibiotic resistance and treatment failure.^[4] Drugs that are used treat in combination are Carbapenems, Beta lactamase inhibitor, Tigecycline, Aminoglycosides, Polymyxins, Rifampin and Fosfomycin.^[5-8] Studies have shown that sensitivity of Trimethoprim – Sulfamethoxazole (TMP-SMX) ranges from 0% to 73.2% for the treatment of *Acinetobacter baumannii*.^[9] Our case report describes successful treatment with Trimethoprim – Sulfamethoxazole and Polymyxin or Meropenem. This combination can become an excellent treatment option in this era of increasing antibiotic resistance and lack of newer antibiotic for MDR pathogen.

CASE PRESENTATION

Case 1

A 67 year old male, with past history of chronic obstructive airway disease, accompanied by his son, presented at the Emergency Department of General Superspeciality Hospital, Birtamode, Nepal. He had alleged history of trauma by car and sustained injury over face, chest, left upper and lower limb with Injury Severity Score of 35.

At the time of admission to the emergency department his GCS was 13/15, pulse rate 140 beats per min, blood pressure 80/60 mm Hg, respiratory rate 40 breaths/min and oxygenation saturation 82% on 10 liter of oxygen. Chest examination showed bilateral decrease air entry and crepitation. Abdominal examination showed generalized abdominal tenderness, with guarding and rigidity at left subcostal and lumbar region. Arterial blood gas analysis showed PH 7.21, partial pressure of oxygen (PaO₂) 56 mm Hg, partial pressure of carbon dioxide (PaCO₂) 38 mm Hg, lactate 8 mmol/L and bicarbonate 15 mEq/L.

An emergency physician and paramedics immediately resuscitated him by inserting 16 gauge cannula, central venous catheter and giving two litres of balanced salt solution KabiLyte (Fresenius Kabi, Pune, India). Intubation was done with 7mm endotracheal tube.

Chest x-ray showed bilateral infiltrates, left hemothorax and left scapular fracture. Focused Assessment with Sonography for Trauma (FAST) was positive. Contrast enhanced computed tomography of chest and abdomen showed bilateral lung contusion with left sided hemothorax and grade 4 splenic injury with moderate hemoperitoneum respectively.

His investigation profiles were total leucocyte count (TLC)- 21000/mm³; platelets-90000/mm³; haemoglobin (Hb)-7 gm/dl; urea- 108 mg/dl; creatinine- 1.8 mg/dl. Sodium and

potassium was 138 mmol/ L and 4.9 mmol/L, respectively. Liver function test showed bilirubin- 4 mg/dl; Direct bilirubin- 1.6 mg/dl; Total protein 6.4- mg/dl; albumin- 2.8 mg/dl; alanine aminotransferase (ALT)-368 U/L; and aspartate aminotransferase (AST)- 561 U/L.

Emergency splenectomy and left chest tube insertion were performed and resuscitation was carried out with eight pint of whole and fresh blood and Noradrenaline at 0.1 µg/kg/min (Troikaa Pharmaceuticals Pvt. Ltd., Ahmedabad, India) was done. Patient was started on Piperacillin – Tazobactam 4.5 gram intravenous every eight hours (Aristo Pharmaceutical Pvt. Ltd., Mandideep, India) and Levofloxacin 750 mg intravenously once a day (Glenmark Pharmaceuticals Ltd. Baddi, India).

Patient was extubated on third day of admission. Patient developed shortness of breath, fever with maximum temperature of 102°F and cough after eighth day of admission. TLC was 23000/mm³. Chest x-ray showed bilateral chest infiltrate with right sided pleural effusion (Figure 1) and urine examination showed pus cell plenty. Patient was started on Meropenem 1 gram intravenously 8 hourly (Sun Pharmaceutical Industries Ltd. Mumbai, India) and Doxycycline 100 mg every 12 hours (Gufic Biosciences Limited, Mumbai, India). There was no improvement in patient. Culture report of sputum and urine both showed *Acinetobacter baumannii* sensitive to Polymyxin B, Colistin and TMP-SMX. Patient was started on Polymyxin B 1.5 million units intravenously stat and 1 million units intravenously 2 times a day (Bharat Serums And Vaccines Limited, Mumbai, India) and TMP-SMX (160 + 800 mg) 2 tablet per oral 12 hourly (Medico Remedies Ltd, Mumbai, India) for 10 days. He was discharged from hospital on the twenty second hospital day.

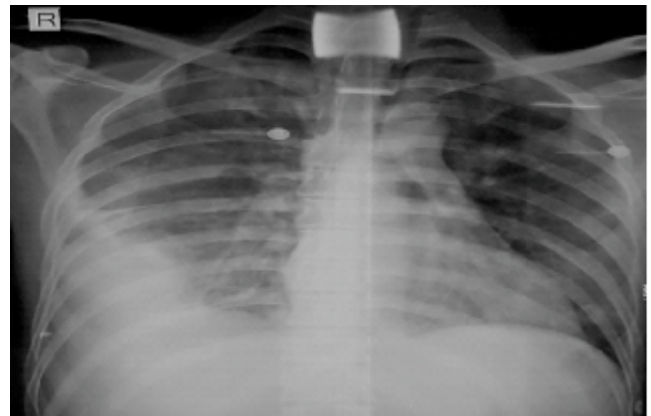


Figure 1: Chest X-ray anteroposterior view showing bilateral infiltrates with right sided pleural effusion

One week following discharge, he presented at the outpatient department for a follow up. His urine and chest-ray was normal.

Case 2

A 56 year old male, chronic alcoholic, smoker, diabetic accompanied by his son, presented at the Emergency Department of General Superspeciality Hospital, Birtamode, Nepal. He presented with complains of fever, cough, shortness of breath and abdominal distension for 4 days.

At the time of admission to the emergency department his GCS was 14/15, pulse rate 136 beats per min, blood pressure 84/56 mm Hg, respiratory rate 48 breaths/ min and oxygenation saturation 92% on 15 liter of oxygen. Chest examination showed bilateral crepitation. Abdominal examination showed generalized distension of abdomen with hepatosplenomegaly and shifting dullness. Arterial blood gas analysis showed PH 6.78, partial pressure of oxygen (PaO₂) 58 mm Hg, partial pressure of carbon dioxide (PaCO₂) 21 mm Hg, lactate 14 mmol/L and bicarbonate 5 mEq/L.

An emergency physician and paramedics immediately resuscitated him by inserting 16 gauge cannula, central venous catheter and giving two litres of balanced salt solution Kabilyte (Fresenius Kabi, Pune, India), Noradrenaline (Troikaa Pharmaceuticals Pvt, Ltd., Ahmedabad, India) and Sodium bicarbonate at 25ml per hour. Intubation was done with 7.5mm endotracheal tube.

Patient was started on Piperacillin–Tazobactam 4.5 gram intravenous every eight hours (Aristo Pharmaceutical Pvt.Ltd., Mandideep, India) and Levofloxacin 750 mg intravenously once a day (Glenmark Pharmaceuticals Ltd. Baddi, India)

His investigation profiles were total leucocyte count (TLC) - 3100/mm³; platelets- 60000/mm³; haemoglobin (Hb)-8 gm/dl; urea- 276 mg/dl; creatinine- 5.7 mg/dl. Sodium and potassium was 130 mmol/ L and 5.3 mmol/L respectively. Liver function test showed bilirubin- 6.4 mg/dl; Direct bilirubin- 4.1 mg/dl; Total protein 6.4- mg/dl; albumin- 2.6 mg/dl; alanine aminotransferase (ALT)- 1564 U/L; and aspartate aminotransferase (AST)- 1867 U/L.

Blood investigation IgM /IgG for malaria, dengue, scrub typhus, enteric fever and leptospira were normal. Ultrasound of abdomen and pelvis showed hepatosplenomegaly, bilateral enlarged kidney, ascites and pneumonia. Patient was extubated on second day of admission.

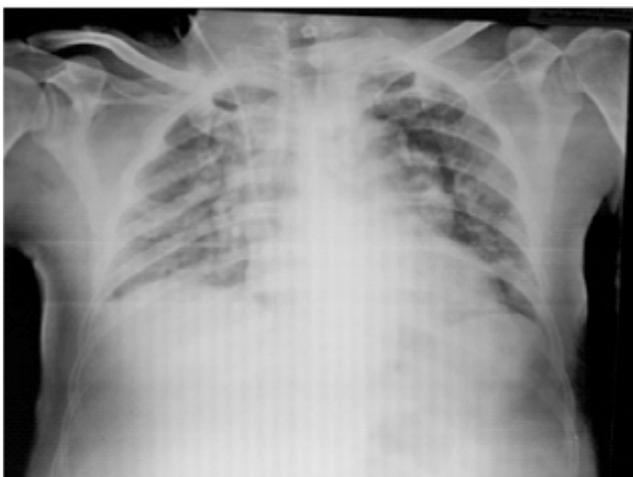


Figure 2: Chest X-Ray anteroposterior view showing bilateral infiltrates

Patient developed fever with maximum temperature of 102.5°F, cough and burning micturition on fifth day on admission in ICU. Blood investigations showed TLC of 18000/mm³ with neutrophil predominance and creatinine - 8 mg/dl. Sputum and urine culture report showed *Acinetobacter baumannii* sensitive to Meropenem and TMP-SMX. Patient was started on Meropenem 500 mg intravenously two times a day (Sun Pharmaceutical Industries Ltd. Mumbai, India) and TMP-SMX (160+800 mg) 1 tablet per oral 12 hourly (Medico Remedies Ltd, Mumbai, India) for 10 days. Serum creatinine was monitored daily and was noted to be in decreasing trend until it became normal on the fifteenth day of admission (Figure 3). He was discharged from hospital on the twenty eighth hospital day.

One week following discharge, he presented at the outpatient department for a follow up. His urine routine examination and chest x-ray were normal.

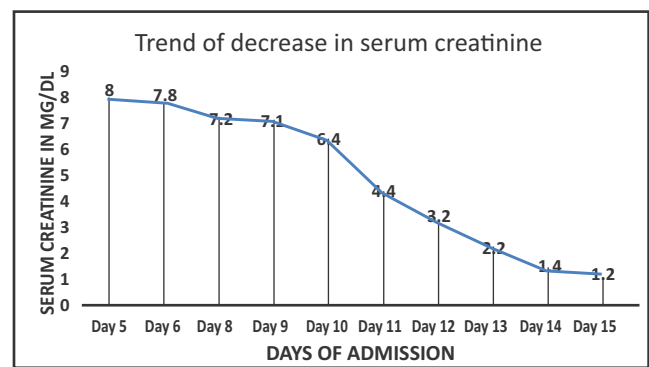


Figure 3: Line graph showing trend in decrease in serum creatinine

Case 3

A 21 year old male, without any significant past history, presented at the Emergency Department of General Superspeciality Hospital, Birtamode, Nepal. He had alleged history of trauma by truck and sustained injury over head, face and chest with Injury Severity Score of 40.

At the time of admission to the emergency department his GCS was 3/15, and his pupils were not reactive to light, pulse rate 160 beats per min, blood pressure 70/60 mm Hg, respiratory rate 40 breaths/ min and oxygenation saturation 72% on 10 liter of oxygen. Chest examination showed bilateral decrease air entry and crepitation. Abdominal and cardiovascular examination was normal. Arterial blood gas analysis showed PH 7.11, partial pressure of oxygen (PaO₂) 58 mm Hg, partial pressure of carbon dioxide (PaCO₂) 26mm Hg, lactate 10mmol/L and bicarbonate 21mEq/L.

An emergency physician and paramedics immediately resuscitated him by inserting 16 gauge cannula, central venous catheter and giving two liters of balanced salt solution Kabilyte (Fresenius Kabi, Pune, India). Intubation was done with 7mm endotracheal tube.

Chest x-ray showed bilateral infiltrates, hemopneumothorax. Extended Focused Assessment with Sonography for Trauma (FAST) was positive. Contrast enhanced computed tomography

of head and chest showed bilateral subdural hematoma with subarachnoid hemorrhage and bilateral lung contusion with hemopneumothorax respectively.

His investigation profiles were total leucocyte count (TLC) - 11000/mm³; platelets- 750000/mm³; haemoglobin (Hb)- 9 gm/dl; urea- 108 mg/dl; creatinine- 2.8 mg/dl. Sodium and potassium was 138 mmol/ L and 4.9 mmol/L, respectively. Liver function test showed bilirubin-1.8mg/dl; Direct bilirubin- 1.2 mg/dl; Total protein 6.4- mg/dl; albumin- 3.8 mg/dl; alanine aminotransferase (ALT)- 168 U/L; and aspartate aminotransferase(AST)- 68 U/L.

Chest tube was inserted bilaterally and resuscitation with two pint of whole and two pint fresh blood and noradrenaline at 0.1 µg/kg/min (Troikaa Pharmaceuticals Pvt, Ltd., Ahmedabad, India) was done. Patient was started on Piperacillin –Tazobactam 4.5 gram intravenous every eight hours (Aristo Pharmaceutical Pvt.Ltd., Mandideep, India) and Levofloxacin 750 mg intravenously once a day (Glenmark Pharmaceuticals Ltd. Baddi, India).

Chest tube was removed on the third day of admission. However, there was no improvement in GCS and he developed increased secretion and fever with maximum temperature of 101^oF on the fifth day of admission in ICU. Chest x-ray was done which showed bilateral infiltrate (Figure 4). Blood investigation showed TLC of 24,000/mm³. Tracheal aspirate showed *Acinetobacter baumannii* sensitive Polymyxin B, Colistin and TMP-SMX. Patient was started on Polymyxin B 1.5 million units intravenously stat and 1 million unit intravenously 2 times a day (Bharat Serums And Vaccines Limited, Mumbai, India) and TMP-SMX (160+ 800 mg) 2 tablet per oral 12 hourly (Medico Remedies Ltd, Mumbai, India) for 10 days. Tracheostomy was done on tenth day of admission. He was discharged from hospital to long term care facility on fifteenth day of hospital admission.



Figure 4: Chest X-Ray showing bilateral infiltrates, more on the right.

Summary of clinical and laboratory characteristics of all three cases are presented in table 1.

Table 1. Patients' characteristics – demographics, clinical and laboratory characteristics

	Case 1	Case 2	Case 3
Age (Years)	67	56	21
Gender	Male	Male	Male
Fever (Max)	102 ^o F	102.5 ^o F	101 ^o F
Heart rate >90/minute	Yes	Yes	Yes
Respiratory rate > 20/minute	Yes	Yes	Yes
Cough	Yes	Yes	Intubated
Shortness of breath	Yes	No	Intubated
Burning Micturation	No	Yes	No
Total Leucocyte Count	23000/mm ³	18000/mm ³	24000/mm ³
New developed infiltrates on chest x-ray	Yes	Yes	yes

DISCUSSION

Gram negative infection is more common in developing country[10] ICU and incidence ranges from 47 to 84%. [10] *Acinetobacter baumannii* is a MDR bacteria and incidence ranges from 13 to 41% [11-13] and mortality is very high up to 81%.^[11-13]

Acinetobacter baumannii infection generally occurs in patient that have risk factor like recent hospitalization, poor general medical condition, mechanical ventilation, cardiac or respiratory failure, antibiotic therapy and presence of central venous or urinary catheter that leads to emergence of a multidrug resistant *Acinetobacter baumannii*. Meropenem, Imipenem, Doripenem, Polymyxin B, Colistin is used in combination with Rifampin, Tigecycline, Amikacin and fosfomycin for treatment of *Acinetobacter baumannii*.

Studies have shown that sensitivity of TMP- SMX is different from hospital to hospital; ranges from 0% to 73%.^[1,9,14] Dose of TMP- SMX is unclear in critically ill patients for susceptible organism despite being older antibiotic.^[15] It can be given in oral or intravenous form ; can be given two times in non-critical patients but three or four times to avoid toxicity in critically ill patients. In our patient we used oral form as intravenous was not available at our center.

Newer drugs that can be used in future for *Acinetobacter baumannii* are Siderophore cephalosporins, Eravacycline, Apramycin, phage therapy. This newer drugs are expensive and are still in clinical trial.^[16] Therefore, TMP-SMX can be used in combination for treatment of *Acinetobacter baumannii* based on sensitivity.^[17-19]

CONCLUSIONS

TMP-SMX is older, cheaper easily available antibiotic that is available at primary health care center that can be used in combination with Polymyxin or Carbapenem for treatment of *Acinetobacter baumannii*.

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