

Successful treatment of life-threatening melioidosis with activated protein C and meropenem

Che-Kim Tan, Khee-Siang Chan, Wen-Liang Yu, Chin-Ming Chen, Kuo-Chen Cheng

Department of Intensive Care Medicine, Chi-Mei Medical Center, Tainan, Taiwan

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Melioidosis is an endemic disease in southeast Asia and northern Australia, caused by *Burkholderia pseudomallei*. A typhoon-related outbreak occurred in southern Taiwan in July 2005. High mortality in melioidosis associated with bacteremic pneumonia and septic shock. We report a patient with life-threatening melioidosis who developed rapid progression of bacteremic pneumonia with acute respiratory distress syndrome, septic shock and multiple organ dysfunction and was successfully treated with recombinant human activated protein C (rhAPC) and meropenem. Although rhAPC has been reported to reduce the mortality of severe septic shock caused by various pathogens, to our best knowledge, this is the first reported case of rhAPC application in life-threatening melioidosis.

Key words: *Burkholderia pseudomallei*; Melioidosis; Pneumonia; Recombinant proteins; Respiratory distress syndrome, adult; Shock, septic; Thienamycins

Introduction

Melioidosis is an endemic disease in southeast Asia and northern Australia, caused by *Burkholderia pseudomallei*, which spreads mainly via inoculation of the wound by contaminated soil or water [1]. In addition, heavy rainfall has been assumed to be responsible for the increasing occurrences of pneumonia and severity of this disease, via inhalation-related transmission [2]. The overall mortality of melioidosis is about 19-40% [3]; however, the mortality for bacteremic pneumonia with septic shock is reported to be 80-100% [3,4].

The increasing number of clinical isolates of *B. pseudomallei* in recent years has made melioidosis an emerging disease in Taiwan [5]. Although typhoons accompanied by heavy rainfall in the summer and/or autumn seasons occur every year in Taiwan, melioidosis remains sporadic with a reported case number of <15 each year [6]. However, for the first time, an outbreak of melioidosis was reported in southern Taiwan about 10 days after a typhoon-related flood. According to the reports of the Taiwan Center for Disease Control [6],

from July 11 to August 9, 2005 (peak of onset between July 24-27), there were 24 confirmed cases related to the flood, resulting in 6 deaths. We report a critically ill patient, who was successfully treated with the use of recombinant human activated protein C (rhAPC) and meropenem.

Case Report

A 57-year-old man without any medical history presented with fever, productive cough, headache and general soreness for three days. Upon visiting our outpatient clinic, chest X-ray revealed a consolidation over the left upper lobe (Fig. 1A). The patient was prescribed oral amoxicillin-clavulanate. Six h later, the patient revisited the emergency department with shortness of breath. The condition rapidly progressed into acute respiratory distress syndrome within 4 h, requiring endotracheal intubation (Fig. 1B). He was then admitted to the intensive care unit (ICU).

The initial white blood cell count was 8800/ μ L with 27% band form. The C-reactive protein was >250 mg/L (normal, <6 mg/L) and blood glucose was 387 mg/dL. The lowest oxygenation ratio (arterial partial pressure of oxygen/fraction of inspired oxygen [P/F]) was 71 with the chest X-ray showing diffuse bilateral infiltrates

Corresponding author: Wen-Liang Yu, MD, Department of Intensive Care Medicine, Chi-Mei Medical Center, 901, Chunghua Rd., Yungkuang City, 710 Tainan County, Taiwan.
E-mail: yuleon_md@yahoo.com.tw

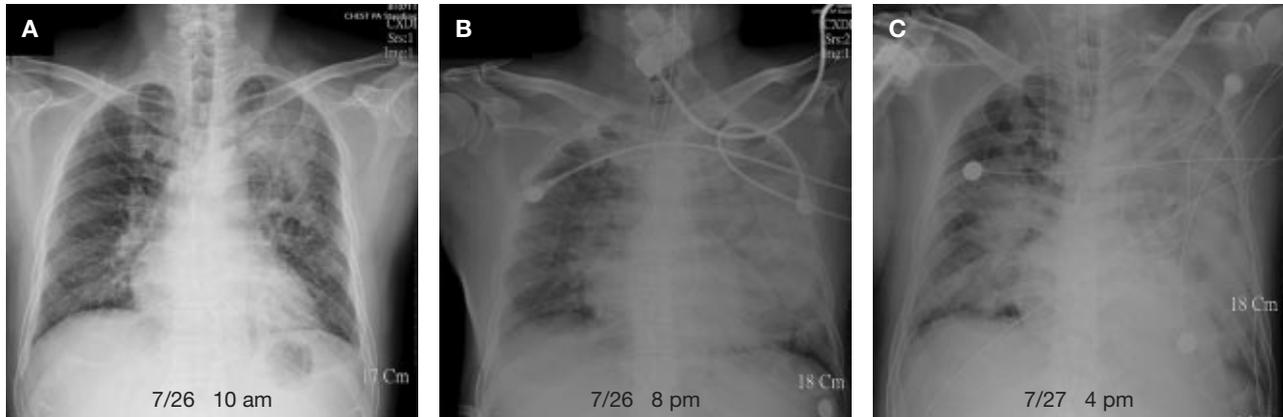


Fig. 1. Rapid progression of left upper lobe consolidation (A) into bilateral diffuse infiltrate (B) within 10 h. Recombinant human activated protein C was administered at the time of the most adverse chest X-ray findings (C).

(Fig. 1C). Disseminated intravascular coagulopathy (prolonged prothrombin time, 19.1 sec [control, 11.6 sec] and elevated D-Dimer), acute renal dysfunction (creatinine, 2.5 mg/dL), metabolic acidosis (base excess, -12.3 mmol/L; lactate, 4.6 mEq/L [normal, 0.4-2.0 mEq/L]) and hepatic dysfunction (aspartate aminotransferase, 224 IU/L; alanine aminotransferase, 195 IU/L) were also noted. Shock persisted after the early goal-directed fluid resuscitation and high-dose dopamine (15 $\mu\text{g}/\text{kg}/\text{min}$) was required to maintain a mean arterial pressure above 65 mm Hg.

Community-acquired pneumonia with septic shock, acute respiratory distress syndrome and multiple organ dysfunctions were diagnosed with a newly diagnosed type 2 diabetes mellitus (glycosylated hemoglobin, 10%). The guidelines of Surviving Sepsis Campaign were strictly followed [7]. Low-dose

corticosteroid, tight glycemic control, lung protective strategy of mechanical ventilation, protocol-driven analgesia/sedation with daily interruption and stress ulcer prophylaxis were implemented. Parenteral amoxicillin-clavulanate was used initially. However, his condition deteriorated rapidly after admission to ICU, and the antibiotic was then changed to meropenem plus minocycline for better coverage of some rare pathogens that cause life-threatening community-acquired pneumonia.

The shock status persisted and a high Acute Physiology and Chronic Health Evaluation II score (28) was noted with multiple organ dysfunction. rhAPC (drotrecogin alfa) 24 $\mu\text{g}/\text{kg}/\text{h}$ was given for 96 h, initiated at 20 h after ICU admission. The inotropic agent was discontinued the next morning (Fig. 2). The general condition, chest X-ray (Fig. 3) and disease parameters

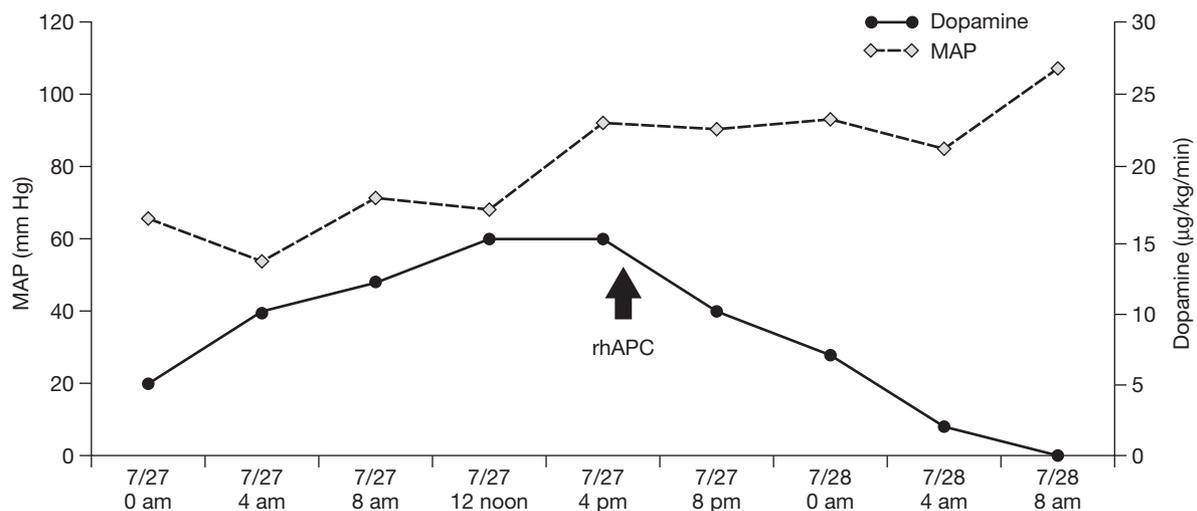


Fig. 2. Initially dopamine was required to maintain a mean arterial pressure (MAP) of 65 mm Hg or greater. After the administration of recombinant human activated protein C (rhAPC; arrow), dopamine was tapered-off the next morning.

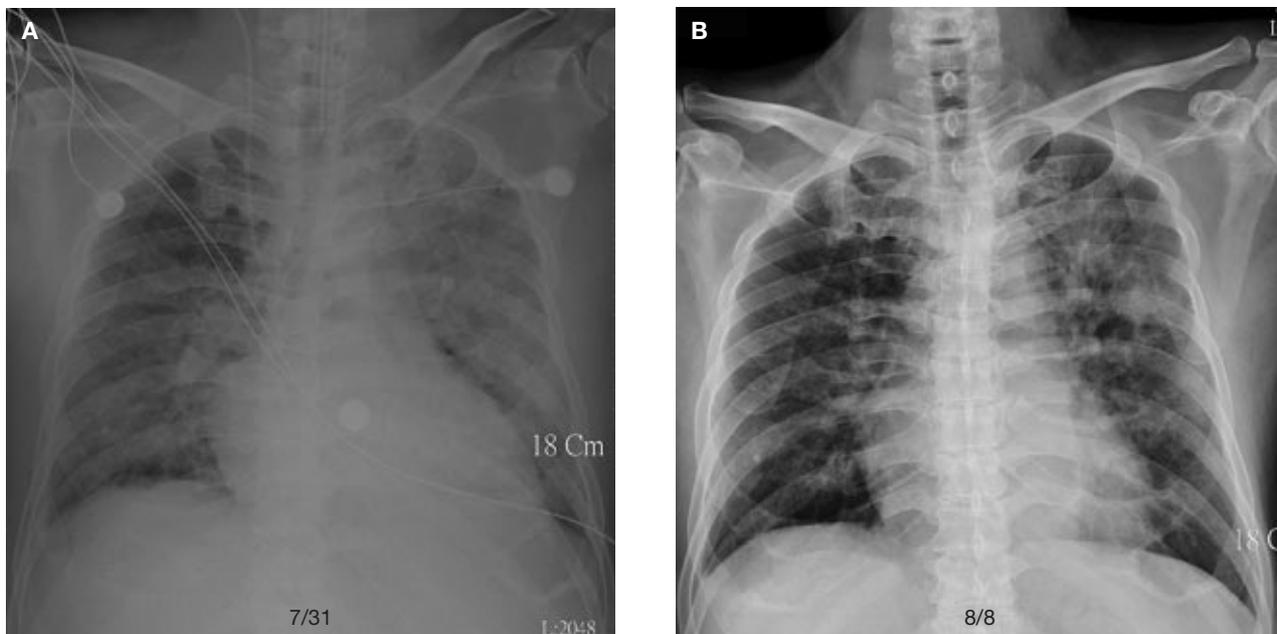


Fig. 3. Chest X-ray showing substantial improvement (A) with only residual left upper lobe consolidation after intensive care unit discharge (B).

including oxygenation (P/F ratio), lactic acidosis, C-reactive protein (Fig. 4) and other organ dysfunction also gradually improved. Both the sputum and blood cultures yielded *B. pseudomallei* on the sixth day of admission. The patient was successfully extubated

on the 10th ICU day, and was transferred to general ward the next day. He was discharged after 3 weeks' admission and received maintenance therapy at the outpatient department. In reviewing the patient's exposure history, it was noted that he lived in the area

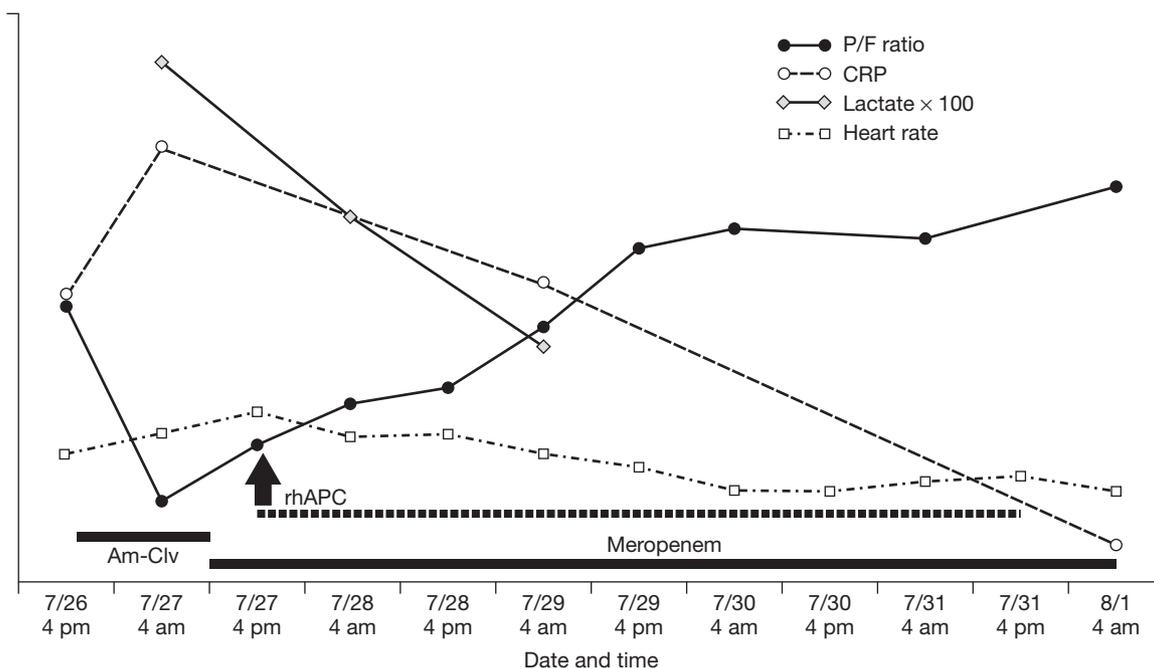


Fig. 4. Increased oxygenation ratio (arterial partial pressure of oxygen/fraction of inspired oxygen [P/F]), decreased C-reactive protein (CRP; mg/L) and lactate (mEq/L), and normalized heart rate (beats/min) were noted after the administration of meropenem (bold line) and recombinant human activated protein C (rhAPC; arrow and broken line). Lactate values are amplified 100 times for illustrative purposes. Am-Clv = amoxicillin-clavulanate.

of this outbreak and went out cycling the day after the strike of typhoon Haitang. There was no injury or wound noted. The possible route of transmission was inhalation, with an incubation period of 5 days.

Discussion

The overall mortality of melioidosis is about 19-40% [3]; however, the mortality for bacteremic pneumonia with septic shock is reported to be 80-100% [3,4]. The drug of choice for severe disease is ceftazidime or carbapenem [1]. A comparative study showed no difference in overall mortality rate between meropenem and ceftazidime, but the meropenem group had a lower mortality than ceftazidime in the subgroup with severe sepsis (25% vs 76%) [8]. In addition, meropenem has a lower intracellular minimum inhibitory concentration than ceftazidime, possibly with better intracellular killing of *B. pseudomallei* [9]. Besides, ceftazidime is associated with a higher rate of treatment failure, and thus a carbapenem is worthy of consideration as the first-line antibiotic to treat severe melioidosis [8,10].

We chose the carbapenem instead of ceftriaxone after the failure of amoxicillin-clavulanate to treat this life-threatening community-acquired pneumonia, in order to have a broader coverage of common pathogens (such as *Streptococcus pneumoniae* and *Klebsiella pneumoniae*) and some rare pathogens, such as *Acinetobacter baumannii* [11] and other drug-resistant pathogens. Additional minocycline was used to cover potential atypical pathogens in Taiwan, including *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, *Rickettsia tsutsugamushi* or even *Leptospira interrogans*. Recent guidelines suggested that the selection of antibiotics should take into consideration the local microbiological data for community-acquired pneumonia [12]. Hence, melioidosis should also be considered after an extreme weather event in an endemic area [13].

rhAPC has been reported to significantly reduce the mortality of patients with severe sepsis [14]. It is believed that rhAPC will be equally effective for severe sepsis in melioidosis, which is also caused by a Gram-negative bacillus. In addition, the evidence that activated protein C level is low in severe melioidosis [15] further supports the rationale of rhAPC usage in melioidosis with septic shock. However, its high cost will hinder regular usage in developing countries with endemic disease areas.

Fatal cases of severe melioidosis died rapidly in the ICU with a median survival of only 2 days [16]. Thus,

the prompt usage of effective antibiotic treatment is crucial when life-threatening melioidosis is suspected. Recent studies have reported the use of the carbapenem as first-line treatment in victims of the tsunami in southern Asia [17,18], who were suspected or confirmed to have melioidosis. However, the appropriateness of initial use of meropenem for suspected severe melioidosis after an extreme weather event deserves further study, both for its effectiveness and possible economical and ecological impacts.

Despite the introduction of ceftazidime- or carbapenem-based parenteral therapy, melioidosis with severe sepsis is still associated with significant mortality [6,7]. Apart from the prompt usage of meropenem, the implementation of the Surviving Sepsis Campaign guidelines and the early usage of rhAPC, might have contributed to the favorable outcome in this patient with life-threatening melioidosis.

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