

## Use of drotrecogin alfa (activated) in a severe acute respiratory syndrome patient with severe sepsis

*To the Editor:*

A 34-year-old female health care worker presented to our emergency department with a one-week history of fever, dyspnea, fatigue, arthralgia, myalgia and nonproductive cough. The previous week, our patient had been caring for a patient at the severe acute respiratory syndrome (SARS) index hospital in Toronto, Ontario. She had no significant medical history and was a nonsmoker. Her medications included acetaminophen, ibuprofen and guaifenesin.

On admission, she had a temperature of 36°C, a blood pressure of 107/74 mmHg, a heart rate of 144 beats/min and a respiration rate of 45 breaths/min. Her oxygen saturation was 86% on room air. She was alert but pale, and had one-to-two-word dyspnea. She had decreased air entry to the left lung base, decreased fremitus at the left lung base and crackles bilaterally to the apices. Her heart sounds and abdominal examination were unremarkable, and her neurological examination revealed diffuse weakness.

Over the next 12 h, the patient's condition progressively deteriorated. Her white blood cell count was  $9.9 \times 10^9/L$ , neutrophil count was  $8.5 \times 10^9/L$ , and prothrombin and partial thromboplastin times were 1.10 s and 33.5 s, respectively. Her kidney function was normal, and except for an elevated aspartate aminotransferase level (92 U/L), her liver enzymes were within normal range.

Despite 100% fraction of inspired oxygen by mask, the oxygen saturation fell to 90%. Her chest x-ray revealed bilateral interstitial infiltrates. The patient was intubated and mechanically ventilated. A dopamine drip was initiated (at 5 µg/kg/h), and she was transferred to the SARS intensive care unit. No immunological or serological assay was available at that early phase in the epidemic to assist in the diagnosis of SARS, so diagnosis was based on the existing World Health Organization criteria (1) – documented fever (temperature higher than 38°C), lower respiratory tract symptoms, and contact with a person believed to have had SARS or a history of travel to a geographical area where transmission of illness was documented. The patient was started on empirical treatment with an antiviral therapy (ribavirin) and antibiotics (Zithromax [Pfizer Canada Inc] 500 mg intravenously once a day, and Ceftriaxone [Sandoz Canada Inc] 2 g intravenously every 24 h).

Within 48 h after hospitalization, the patient had a fever of 38°C, a blood pressure of 105/70 mmHg with a

dopamine drip of 5 µg/h. Pressure control ventilation with positive end expiratory pressure was continued. Ceftriaxone was discontinued and piperacillin-tazobactam (4.5 g every 8 h) was started. Urine output was maintained at 100 mL/h to 200 mL/h.

Despite aggressive supportive therapy, the patient developed progressive multisystem organ dysfunction. In addition to the existing respiratory and cardiovascular dysfunctions, evidence of hepatic and hematological organ dysfunctions also developed – elevated aspartate aminotransferase level (155 U/L), alanine aminotransferase level (99 U/L) and alkaline phosphatase level (131 U/L), as well as elevated prothrombin and partial thromboplastin times (1.24 s and 68.7 s, respectively). Her creatinine level doubled to 92 µmol/L. There was no evidence of bacterial superinfection.

At this stage, the patient's condition met the established criteria for severe sepsis, and institutional and national guidelines for treatment with drotrecogin alfa (activated) (DrotAA) (2). A 96 h intravenous infusion of DrotAA at 24 µg/kg/h was initiated. This was performed because the SARS virus was proving to be very virulent and the patient was deteriorating, as evidenced by progressive organ dysfunctions, despite best standard of care. We also became aware of reports from Hong Kong of high mortality rates in otherwise healthy individuals with SARS (3).

Within two days after initiation of DrotAA, hepatic enzyme levels returned to normal, creatine kinase and lactate dehydrogenase levels decreased, and the patient became afebrile. By the end of the 96 h infusion, the patient's white blood count had decreased, creatinine levels returned to normal and metabolic acidosis reversed. Dopamine was discontinued the day after completing DrotAA. The patient continued to require ventilatory support and remained in the intensive care unit for three months until her respiratory symptoms resolved. The prolonged need for mechanical ventilation seen in our patient has been reported in other critically ill SARS patients (4-6).

The coagulopathy and inflammation associated with severe sepsis has been reported to be similar regardless of the causative microorganism, and the beneficial effects of DrotAA in treating severe sepsis have also been observed regardless of the infecting microorganism (7).

Recently, insights into the biological mechanisms of action of activated protein C have been elucidated, including in acute lung injury or acute respiratory distress syndrome (8,9). Most are thought to involve modulation of endothelial function, leukocyte activity or chemotaxis, and improvement of microvascular perfusion (mediated by interaction with protease-activated receptors, sphingosine-1 phosphate pathway, and protein C receptors on airway

*Continued on next page*

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epithelial cells and anti-apoptosis). These are in turn thought to improve organ dysfunction.

The present letter cannot establish that DrotAA, antibiotics or antivirals were helpful or harmful. According to current recommendations, however, DrotAA should be considered for patients with severe sepsis, at high risk of death and, putatively, regardless of the causative organism. The experience with our patient supports the further exploration of the use of DrotAA in

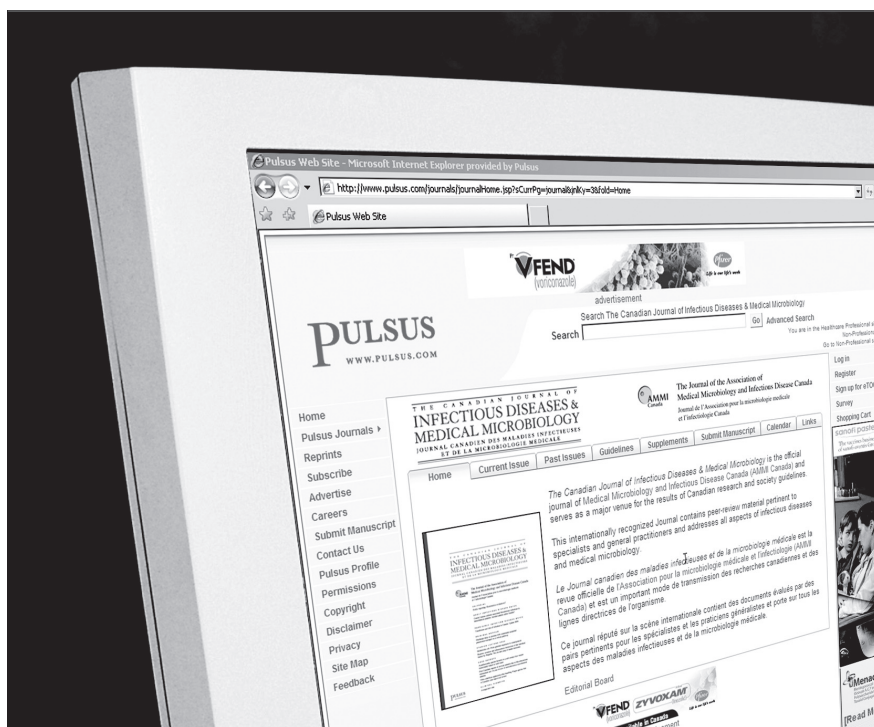
the treatment of severe sepsis of diverse etiologies in this context.

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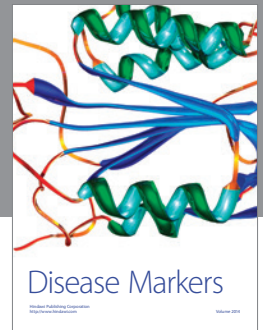
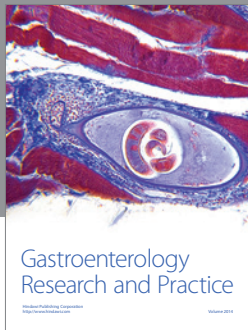
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