David Sweet, MD, Julian Marsden, MD, Kendall Ho, MD, Christina Krause, MSc, James A. Russell, MD

Emergency management of sepsis: The simple stuff saves lives

Research supports using protocols that include delivering antibiotics within minutes of identifying septic patients in the emergency department.

ABSTRACT: Many emergency departments have implemented sepsis protocols since the 2001 publication of results from the early goal-directed therapy trial, which showed early targeted resuscitation lowers mortality. As part of an attempt to improve clinical and operational outcomes for emergency departments across British Columbia, we reviewed sepsis management literature and considered sepsis protocol implementation in the province's emergency departments. During the literature review we found that many observational studies confirmed an association between implementation of emergency sepsis protocols and decreased mortality. The literature also confirmed that septic patients who have elevated serum lactate and do not clear serum lactate rapidly have increased mortality, and that delay in administration of antibiotics after onset of septic shock was associated with increased mortality. Two BC-based initiatives, the Evidence to Excellence Sepsis Collaborative and Clinical Care Management, support improvements in management of sepsis in BC emergency departments, which should include early identification of septic patients, rapid and appropriate fluid resuscitation, lab tests (serum lactate and blood cultures), antibiotic administration, and source control of infection. Close clinical monitoring and biomarker (lactate) monitoring are also necessary during resuscitation to optimize safety and efficacy.

In 2001 the *New England Journal of Medicine* published results of a randomized control trial by Rivers and colleagues of early goal-directed therapy (EGDT) that represented a significant advancement in the emergency department (ED) management of sepsis.[1] EGDT relies on invasive monitoring with arterial and central venous catheters that allows clinicians to normalize central venous pressure (CVP) with intravenous fluids and mean arterial pressure (MAP) with vasopressors. Blood transfusions and cardiac inotropes are also used in EGDT to ensure adequate oxygen delivery to peripheral tissues, as confirmed by normal central venous oxygen saturation ($ScvO_2$). This RCT showed that patients receiving EGDT after presenting to the emergency department with severe sepsis or sep-

Dr Sweet is a clinical assistant professor in the Department of Emergency Medicine at the University of British Columbia, and holds attending positions in emergency medicine and critical care medicine at Vancouver General Hospital and Surrey Memorial Hospital. He is also clinical lead for sepsis (clinical care management) with the BC Patient Safety and Quality Council. Dr Marsden is a clinical professor in the Department of Emergency Medicine at UBC and a physician in the emergency department at St. Paul's Hospital. Dr Ho is an associate professor in the Department of Emergency Medicine at UBC and a physician in the emergency department at Vancouver General Hospital. Ms Krause is executive director of the BC Patient Safety and Quality Council. Dr Russell is a professor in the Division of Critical Care Medicine at UBC, principal investigator of the James Hogg Centre for Cardiovascular and Pulmonary Research, and a member of the Division of Critical Care Medicine, St. Paul's Hospital and University of British Columbia.

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tic shock had an absolute mortality reduction of 16% compared with a control group. Although this single-centre study has been criticized, the findings were so dramatic that most members of the medical community endorsed the protocols recommended by Rivers soon after publication.[2]

Over the ensuing years, EDs around the world have implemented sepsis protocols, many with variations on the original EGDT, and two common themes have emerged in the subsequent evaluations. First, it is difficult to perform the full EGDT protocol in a busy emergency department[3-5] because of the time needed to place the various invasive catheters and perform the complex resuscitation, and because many departments are not set up to measure $ScvO_2$. Second, clinicians have found significant improvements in mortality of severely septic patients by implementing only key steps in the EGDT protocol rather than all steps.[6-9] These key steps are described below.[6,8-11]

Screening of septic patients

Timely recognition and management of trauma and myocardial infarction[12,13] have long been recognized as critical to optimal outcomes for these conditions; however, the evidence to support timeliness in sepsis management has only emerged over the last 10 years.[1,11] Once septic patients develop macrovascular shock (refractory hypotension) or microvascular shock (elevated lactate), they are on the steep part of the mortality curve and immediate identification and intervention is critical to avert rapid deterioration and death.[14-16] In order to screen a large volume of emergency department patients for sepsis in a timely manner, personnel require a high index of suspicion and an effective screening mechanism. Triage education and tools, such as sepsis posters and triage checklists, are needed to identify patients with severe sepsis or septic shock.

In screening for sepsis, two or more of a possible four criteria for systemic inflammatory response syndrome (SIRS) signify the presence of a potentially severe infection.[2] The four SIRS criteria are:

- Heart rate > 90 beats/min.
- Respiratory rate > 20 breaths/min.
- A high (≥ 38 °C) or low (< 36 °C) temperature.
- Abnormal white blood cell count ([> 12 000/cubic mm or < 4000/cubic mm]); several BC protocols substitute WBC with an altered level of consciousness as a marker of severity of illness at triage as a WBC is not initially available.

Furthermore, studies have consistently shown that even in the face of hemodynamic stability, elevated lactate levels are associated with an increased mortality, necessitating the need for early measurement of lactate levels.[14,15,17] Patients with a serum lactate level > 4.0 mmol/L have a sharp decline in survival, which is why EGDT and the majority of other sepsis protocols chose this value for entry into aggressive management algorithms.[1,15] These algorithms require centres to perform rapid lactate testing and deliver the results to the clinician.[1,18] The lactate readings can be obtained through either point-of-care testing devices or arterial/venous blood gas analysis.[19,20] Once identified in the emergency department, patients with severe sepsis or septic shock will require aggressive source control, fluid resuscitation, and antibiotic therapy.[21]

Identifying and controlling the source of sepsis

Source control dates back to the origins of medicine.[22] The need to drain abscesses and remove foreign bodies has been recognized since the fourth century BC, and the modern management of sepsis still relies on such surgical therapy. Identifying an infectious source and removing it, if possible, remains a core principle. The Surviving Sepsis Campaign guidelines recommend that a specific anatomic source diagnosis of infection be sought within 6 hours of presentation.[2] This requires blood cultures and often requires ultrasound or CT imaging; other cultures (e.g., urine, CSF, synovial fluid) may also be required.

Once identified, the focus of infection should be drained or removed with the least physiologic insult, such as through a percutaneously placed drain. Concurrent with surgical therapy, aggressive resuscitation, and early administration of antibiotics, samples should be taken from all potentially infected sites for cultures.

Fluid resuscitation

With the introduction of the Swan-Ganz pulmonary artery catheter in the 1970s, it became common to use fluid resuscitation to optimize a patient's hemodynamic status based on oxygen transport, even attempting supranormal oxygen delivery.[23] Although accepted by many clinicians at the time, studies since have produced conflicting results.[24-26] In 1995 Gattinoni and colleagues published the results of a well-designed, multicentre randomized control trial that concluded there was no benefit from supranormal oxygen delivery (although it is important to note that the patients entered in the trial were often enrolled relatively late into their disease process, even up to 72 hours after sepsis recognition).[26] A subsequent meta-analysis suggested that only early fluid resuscitation and normalization of hemodynamic parameters are associated with improved survival.[27]

These studies and an understanding of the cardiovascular pathophysiology of sepsis led Rivers to conduct his EGDT trial, which showed that beginning interventions as soon as severe sepsis is recognized is required to achieve favorable outcomes.[1] One key finding of this trial was that patients in the treatment arm received more intravenous fluids early in the course of their resuscitation. Numerous observational studies looking at the initiation of sepsis protocols in emergency departments[6-8,28-32] convincingly demonstrate that early aggressive resuscitation of the septic patient is associated with decreased mortality.[33]

Patients with sepsis and evidence of global hypoperfusion may require 6 to 10 L of crystalloid in their initial resuscitation.[34,35] Several recently published studies suggest that there is a danger of overresuscitation in this patient population, as there is with patients undergoing burn resuscitation.[36-38]Although some patients may require several litres of crystalloid early in their disease, it remains unclear at which point fluid administration may cause increased morbidity. Furthermore, optimal (meaning both safe and effective) fluid resuscitation may not require all of the invasive monitoring used in the original EGDT protocol. Accordingly, researchers and clinicians seek better targets for resuscitation that are less invasive than $ScvO_2$, such as circulating biomarkers to titrate resuscitation.

Monitoring serum lactate clearance

Currently, serum lactate clearance shows the most promise as a reasonable biomarker alternative to invasive resuscitation monitoring. Studies have found that septic patients who do not clear serum lactate by 10% in the first 2 to 6 hours have an increased mortality.[39,40] Two recently published studies examined the association of targeting lactate clearance as a resuscitation goal with mortality. In 2010 Arnold and colleagues published results of a multicentre trial in which patients were randomized to conventional invasive monitoring (EGDT) or a therapy target guided by serial lactate clearance of 20% every 2 hours in addition to conventional invasive monitoring.[39] They found a significantly reduced ICU length of stay and both ICU and hospital mortality in the lactate clearance group when adjusting for predefined baseline mortality risk factors. Also in 2010, Jones and colleagues published results of a multicentre noninferiority trial comparing two groups of patients: one assigned to normalization of CVP, MAP, and $ScvO_2$ according to EGDT protocols, and one to normalization of CVP, MAP, and a lactate clearance of 10% in the first 6 hours.[41] Although the authors found no significant difference in in-hospital mortality rates between the groups (i.e., noninferiority), suggesting that lactate clearance may be used instead of central venous oxygen saturation as a resuscitation target in severe sepsis, the study had two limitations. First, caregivers could not be blinded to the treatment groups of patients. Second, after normalization of CVP and MAP, very few patients required further therapy to normalize their $ScvO_2$ or to clear their lactate—that is, the planned intervention was not much different between treatment groups, which could explain why outcomes did not differ between groups. While there is growing evidence for resuscitation with a target of lactate clearance, and the use of this biomarker is simple and appealing, further research needs to be conducted before lactate clearance can be recommended as a resuscitation biomarker in severe sepsis.

Three large government-funded RCTs are now underway and each is designed to determine the ideal method of sepsis resuscitation: ProCESS (Protocolized Care for Early Septic Shock, NCT00510835 at www.clinicaltrials.gov), a US trial; ARISE (Australasian Resuscitation in Sepsis Evaluation, NCT00975793 at www.clinicaltrials.gov); and ProMISe (Protocolised Management in Sepsis), a UK trial. These trials will be performed in different countries, but the groups have planned for a prospective combined meta-analysis that they hope will provide a final answer to this hotly debated question.

Antibiotic administration

The importance of rapid initiation of antibiotic therapy for life-threatening infections has become increasingly apparent in the last few decades, as demonstrated by improved outcomes in patients with meningitis and community-acquired pneumonia who receive antimicrobials early rather than later in the course of their disease.[42,43] In the last 6 years several retrospective studies have shown a strong positive relationship between prompt antimicrobial administration and improved outcome in severe sepsis or septic shock.[44-46] The most commonly quoted study shows that in the first 6 hours after development of septic shock every hour of delay in initiating antibiotic therapy was associated with a 7.6% increase in mortality.[44] This led the international Surviving Sepsis Campaign to recommend that patients with severe sepsis and septic shock receive rapid initiation (beginning in less than 1 hour) of antimicrobials.[2]

One prospective study evaluated the individual components of the Surviving Sepsis Campaign "bundle" or group of therapies and their association with survival in 316 patients with severe sepsis or septic shock. Early ad-

ministration of antimicrobials (i.e., after less than 120 min from identification) and early collection of blood for cultures were the only interventions associated with lower mortality.[47] Another prospective observational study examined the relationship between components of the Surviving Sepsis Campaign bundle and outcome.[48] In a study of 2796 severe sepsis or septic shock patients they found that early administration of antimicrobials was one of only two interventions associated with significantly reduced mortality.

A more recent study of septic shock found there was no association between each hour delay in initiating antibiotic therapy and mortality. However, patients who had antimicrobials administered after onset of hypotension had higher mortality than did patients who had antimicrobials given before hypotension.[49]

Thus, there has been some controversy about these guidelines because of the retrospective nature of the research from which they are derived. Fortunately, interventional studies supporting early administration of antimicrobials have recently been published.[50] To our knowledge, there is only one preliminary report of a randomized control trial of early versus later initiation of antibiotic therapy in severe sepsis.[51] This Australian study examined the benefit of prehospital administration of antimicrobials in 198 septic shock patients, all of whom required long transport times from rural areas. They showed that administering antimicrobials 3.4 hours earlier, on average, resulted in an absolute risk reduction of 28-day mortality of 14.3% ($P = .049$). It should be noted that this study has not been peer reviewed.

Although there are several key components to the early management of septic patients, none may be as simple or as important as early initiation of antibiotics. The development of systems that allow clinicians to deliver antimicrobials within minutes of identifying septic patients is likely the single greatest lifesaving improvement that many emergency departments can implement.

Sepsis best practices in BC

In 2008, the BC Ministry of Health funded Evidence 2 Excellence, an academic emergency health care initiative to establish interprofessional collaboration that supports improvements in emergency department management of sepsis. Evidence 2 Excellence employs an electronic community of practice, popularized by Wenger and colleagues,[52] to engage stakeholders across the province in networking to deepen their knowledge and skills.[53] Inspired by the Institute for Healthcare Improvement's Breakthrough Series collaborative model,[54,55] Evidence 2 Excellence partnered with the UBC eHealth Strategy Office and the BC Patient Safety and Quality Council to conduct two Sepsis Collaboratives for clinical and operational improvement, the first in 2008–2009 involving 20 emergency departments, and the second in 2009–2010 involving another 18 teams throughout BC. Research funding from the Canadian Institutes of Health Research is being used for a 3-year study to examine how to introduce best practices in sepsis provincially into different emergency departments with a variety of locations, patient mixes, case volumes, staffing and trainee arrangements, resources, and other aspects of practice. Thus, a critical strength of this study is that it is "real world" and therefore highly generalizable. While this study will not finish until later this year, early results suggest that even though the evidence for sepsis care is straightforward to understand, using the evidence in different, highly varied clinical contexts is difficult.

Following the initial success of Evidence 2 Excellence, the BC Ministry of Health made sepsis one of nine topics in its Clinical Care Management initiative. The purpose of Clinical Care Management is to improve the quality of patient care in BC through a well-supported system-wide approach that promotes implementation of evidence-based clinical best practices and reports on the results. The BC Patient Safety and Quality Council is mandated to support implementation across the province, and is partnering with Evidence 2 Excellence to continue the improvement work in sepsis care.

One of the first steps in the process was the development of new provincial guidelines for sepsis care (see **Figure** on next page). These guidelines were developed and approved by Evidence 2 Excellence faculty and the Sepsis Care Clinical Expert Group, which has the knowledge and peer credibility to make these recommendations. In addition to following the sepsis guidelines, emergency departments are required to collect data and report on key process and outcome measures to ensure that BC residents are receiving optimal sepsis care. BC Patient Safety and Quality Council has appointed a clinical lead, Dr David Sweet, to provide the clinical expertise and to support health authorities with their improvement work. Support is tailored to the needs of individual sites and entails ongoing assessment and feedback. The BC Patient Safety and Quality Council has designed implementation tools for clinicians interested in initiating sepsis protocols in their departments. These tools include improvement guides, examples of sepsis protocols, posters, and data collection tools, all available at www.clinical

All patients > 18 years of age with 2 of 4 criteria for systemic inflammatory response syndrome (SIRS)* and suspected infection and one of the following will be classified as level 2 on the Canadian Triage and Acuity Scale (CTAS):

- Looks unwell
- Age > 65
- Recent surgery
- Immunocompromised (AIDS, chemotherapy, neutropenia, asplenia, transplant, chronic steroid use)
- Chronic illness (diabetes, renal failure, hepatic failure, cancer, alcoholism, IV drug use)

All patients with 2 of 4 criteria for SIRS, suspected infection, and one of the above risk factors should receive:

- Blood cultures.
- Venous lactate measurement within 30 min of presentation to triage, ideally with initial blood draw; results should be available to clinician within 30 min of collection.
- If initial lactate is elevated, patient should have repeat venous lactate measurement in next 2–4 hours.

If systolic blood pressure is < 90 mm Hg at triage, patient should be classified as CTAS level 1 and should receive:

- Broad-spectrum intravenous (IV) antibiotics within 1 hour of presentation to triage, ideally **after** blood cultures drawn.
- Second litre of IV crystalloid starting within 1 hour of presentation to triage.

If initial venous lactate result is > 4.0 mmol/L, patient should receive:

- Broad-spectrum IV antibiotics within 1 hour of lactate blood draw, ideally **after** blood cultures drawn.
- Second litre of IV crystalloid starting within 1 hour of lactate blood draw.

If systolic blood pressure is > 90 mm Hg at triage and initial lactate is < 4 mmol/L but patient is admitted to the hospital and given IV antibiotics:

- IV antibiotics administered within 3 hours of presentation to triage.
- Blood cultures taken before IV antibiotics administered.

If patient is hypotensive despite fluid bolus (20–30 mL/kg) or lactate fails to improve by 10% after second measurement (at least 2 hours after initial), consider:

- Placing central venous catheter and arterial catheter, continuing fluid resuscitation, and initiating norepinephrine or dopamine to maintain MAP > 65 mm Hg.
- Consultation with ICU in your facility.
- Contacting BC Bedline for critical care consultation/transfer to ICU.

Figure. Sepsis care in the emergency department: Guidelines.

*Heart rate > 90 beats per minute, respiratory rate > 20 breaths per minute, Temperature ≥ 38 °C or < 36 °C, altered LOC)

Adapted from guidelines on the BC Patient Safety and Quality Council website: www.bcpsqc.ca/quality/sepsisguidelines.html

caremanagement.ca. It is expected that within 1 year all emergency departments in BC seeing over 10 000 patients annually will be engaged in sepsis improvement and will be actively reporting process and outcome measurements for septic patients to the Ministry of Health, including the following:

- Percentage of patients who received antibiotics by time goal.
- Percentage of patients who had blood drawn for cultures before IV antibiotic therapy was initiated.
- Percentage of patients who received initiation of a second litre of crystalloid by time goal.
- Percentage of patients who had appropriate lactate measurements by time goals.
- Mortality.

Conclusions

The identification and management of patients with sepsis has evolved since the landmark study by Rivers and colleagues[1] 10 years ago and will continue to evolve. A literature review indicates that key steps to optimize outcome when managing sepsis in the emergency department include:

- Early triage and identification of patients.
- Rapid and appropriate fluid resuscitation.
- Lab testing (blood cultures), antibiotic administration, and source control of infection.
- Close clinical and biomarker (lactate) monitoring.

The evidence for making dramatic improvements in outcomes for septic patients is compelling; however, we continue to have a gap in care for these patients in our province because of the difficulty of safely and effectively applying evidence to clinical practice. The reasons for this difficulty are multifactorial and involve the core challenges of knowledge translation: clinician engagement, availability of resources, and capacity for measurement and data collection. Great strides have been made in sepsis care across BC as a result of the commitment and dedication of health care providers working in EDs across the province and through the support provided by Evidence 2 Excellence and the Clinical Care Management initiative. Sepsis care will continue to improve and be sustained across the province and beyond as we meet the challenges of knowledge translation. To learn more and get involved in improving BC sepsis care we invite you to join the BC Sepsis Network at www.BCPSQC.ca.

Competing interests

Dr Russell holds stock in Sirius Genomics Incorporated, which has submitted patents related to the genetics of sepsis and its

treatment that are owned by the University of British Columbia and licensed to Sirius Genomics. The University of British Columbia has also submitted a patent related to the use of vasopressin in septic shock. Dr Russell is named as an inventor on these patents. Dr Russell has received consulting fees from Ferring Pharmaceuticals (which manufactures vasopressin and is developing a selective V1a agonist), from AstraZeneca (which is developing an anti-TNF-alpha product), from BioCritica (which sells activated protein C in the US), and from Sirius Genomics. Dr Russell has received grant support from Sirius Genomics, Ferring Pharmaceuticals, AstraZeneca, and Eli Lilly, and speaking honoraria from Pfizer and Eli Lilly.

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