



GUIDELINES FOR USE OF ACTIVATED PROTEIN C: NICE GUIDELINES SUPERSEDE SICS GUIDELINES OF NOVEMBER 2002

Introduction

Sepsis and septic shock are relatively common syndromes occurring in an Intensive Care Unit and are associated with a high mortality. The initial infective insult triggers the host defence system and initiates a complex cascade of enzyme activation that results in the production of both inflammatory and counter inflammatory molecules. In many cases there is a predominance of inflammation leading to the syndromes of SIRS, sepsis and septic shock.

The license for drotrecogin alfa (activated) in Europe is for use *in adult patients with severe sepsis with multiple organ failure when added to best standard care.*

The Scottish Intensive Care Society issued guidelines for the use of drotrecogin in November 2002 when the Scottish Medicines Consortium approved the use of the drug in the NHS in Scotland. In September 2004 the National Institute for Clinical Excellence (NICE) issued guidance and NHS Quality Improvement Scotland (NHS QIS) has subsequently endorsed these as being applicable to Scotland. This guidance supersedes the SICS guidelines of 2002. The main difference is that the use of the APACHE II score to select patients for treatment is NOT recommended.

The NICE guidance is available from their website www.nice.org.uk. The most relevant parts are Section 1 and Section 7. In its guidance NICE states that intensive care units should define clinical circumstances in which drotrecogin alfa (activated) should be used. Units may find it helpful to include the definitions of SIRS criteria and the organ failure definitions used in the PROWESS trial when drawing up such guidelines. Although these are not specifically referred to by NICE they may well be the most practical way of identifying patients who have severe sepsis with at least 2 sepsis induced organ failures. If a patient is not considered suitable for aggressive intensive care for other reasons then it is unlikely that they will benefit from drotrecogin alfa (activated).



Scottish Intensive Care Society

<http://www.scottishintensivecare.org.uk>

Appendix

SIRS Criteria

The events satisfying these criteria must have been attributable to the onset of sepsis and not attributable to an underlying disease process or to the effects of concomitant therapy.

1. Core temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$. Hypothermia ($<36^{\circ}\text{C}$) must have been confirmed by a rectal or core temperature.
2. Heart rate >90 beats/min. If patients had a known medical condition or were receiving treatment that would prevent tachycardia (for example, heart block or beta blockers), they need only have met two of the three remaining criteria, excluding heart rate.
3. Respiratory rate >20 breaths/min or a $\text{PaCO}_2 <32$ mm Hg (4.3kPa), or mechanical ventilation for an acute process.
4. White blood cell count of $>12,000 \text{ mm}^{-3}$ or $<4,000 \text{ mm}^{-3}$.

Organ Failure definitions

1. **Cardiovascular:** An arterial systolic blood pressure (SBP) of <90 mm Hg or a mean arterial pressure (MAP) <70 mm Hg for at least 1 hour despite adequate fluid resuscitation, adequate intravascular volume status, or the need for vasopressors to maintain SBP >90 mm Hg or MAP >70 mm Hg. Adequate fluid resuscitation or adequate intravascular volume was defined as one or more of the following:
 - a) Pulmonary arterial wedge pressure ≥ 12 mm Hg
 - b) Central venous pressure ≥ 8 mmHg.
 - c) The administration of an intravenous fluid bolus (>500 ml of crystalloid solution, $>20\text{g}$ of albumin, or >200 ml of other colloids administered over 30 minutes or less).

Note: Vasopressors were defined as:

 - Dopamine >5 ug/kg/min
 - Nor-epinephrine, epinephrine, or phenylephrine at any dose.
 - Note: Dobutamine and Dopexamine were not considered vasopressors.
2. **Renal:** Urine output $<0.5 \text{ ml kg}^{-1} \text{ hr}^{-1}$ for 1 hour, despite adequate fluid resuscitation as described. In the presence of pre-existing impairment of renal function (defined as a serum creatinine concentration >2 times the upper limit of the normal reference range for that institution prior to the onset of sepsis), the patient must have met one of the other four organ failure criteria.
3. **Respiratory:** $\text{PaO}_2 / \text{FiO}_2 <200$ mmHg (33kPa).
4. **Haematology:** Platelet count of $<80,000 \text{ mm}^{-3}$ or a 50% decrease in the platelet count from the highest value recorded over the previous 3 days.
5. **Unexplained metabolic acidosis**, which was defined as:
 - a) $\text{pH} <7.30$ ($\text{H}^+ > 50 \text{ nmol l}^{-1}$) or base deficit $>5.0 \text{ mEq l}^{-1}$ and
 - b) A plasma lactate level >1.5 times the upper limit of normal for the reporting lab.

Infection Criteria:

Suspected or proven infection. Patients with suspected infection must have had evidence of an infection such as white blood cells in a normally sterile body fluid, perforated viscus, chest x-ray consistent with pneumonia and associated with purulent sputum production, or a clinical syndrome associated with a high probability of infection (for example, ascending cholangitis).