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1 PURPOSE

This guideline is to ensure the correct management of severe sepsis and septic shock in patients. (See appendix 1 for Definitions)

2 SCOPE

All competent staff that care for patients in whom severe sepsis or septic shock is suspected, working within Blackpool Fylde and Wyre Hospitals NHS Foundation Trust.

3 GUIDELINES

3.1 INITIAL MANAGEMENT OF SEVERE SEPSIS/SEPTIC SHOCK

See appendix 2 Flow chart for managing patients with severe sepsis.

3.1.1 SEPSIS RESUSCITATION BUNDLE - (FIRST 6 HOURS)

Evidence-based goals that must be completed within 6 hours for patients with severe sepsis, septic shock and/or lactate > 4 mmol/L. This is instituted as soon as the diagnosis is made (usually in a ward or A&E setting).

The goal is to perform all indicated tasks 100 percent of the time within the first 6 hours of identification of severe sepsis.

Ensure adequate supplemental oxygen and large bore IV access.

3.1.2 Measure Serum Lactate measure serum lactate levels (**refer to trust biochemistry protocol in appendix 3**). Obtaining serum lactate is essential to identifying tissue hypoperfusion in patients who are not yet hypotensive but who are at risk for septic shock. Serial Lactate measurements also provide a guide to the adequacy of initial resuscitation. The prognostic value of raised blood lactate levels has been well established in septic shock patients, particularly if the high levels persist.

Take a 2ml sample of whole blood in a yellow (fluoride oxalate) or orange (lithium Heparin) bottle and send it to biochemistry on ice and marked as urgent. The normal Reference range is 0.76 to 1.25mmol/L.

Alternatively for patients in Accident and Emergency or Critical Care use the local blood gas analyser.

3.1.3 All patients with elevated lactate > 4 mmol/L will enter the early goal-directed therapy portion of the Severe Sepsis Resuscitation Bundle, regardless of blood pressure.

3.1.4 Haemodynamic therapy, in the form of rapid fluid resuscitation, should commence to reverse hypotension, hypovolemia, and organ dysfunction and to restore effective tissue perfusion and cellular metabolism in patients with sepsis and severe sepsis. In the event of hypotension and/or lactate > 4mmol/l give fluid challenges. (**See below for goals of resuscitation**).

If fluid resuscitation fails to restore adequate arterial pressure and organ perfusion, vasopressors and, potentially, inotropes should be administered (see below).

3.1.5 Microbiological Cultures

Collecting blood cultures prior to antibiotic administration offers the best hope of identifying the organism that caused severe sepsis in an individual patient.

2 or more blood cultures. At least 1 should be taken percutaneously following trust procedure on aseptic procedure (see section 7) and 1 through invasive vascular device (if present). Also cultures from other sites as appropriate e.g.) CSF, Urine, Sputum, Wounds and other bodily fluids as appropriate.

Obtaining cultures should not significantly delay the administration of appropriate antibiotics (see below).

3.1.6 Early Antibiotics within the 1st hour of recognition of severe sepsis (within 3 hours for A&E admissions). The balance of evidence unwaveringly suggests that early administration of appropriate antibiotics reduces mortality in patients with Gram-positive and Gram-negative bacteremias. The choice of antibiotics should be guided by the susceptibility of likely pathogens in the community and the hospital, as well as any specific knowledge about the patient, including drug intolerance, underlying disease and the clinical syndrome.

3.1.7 The regimen should cover all likely pathogens since there is little margin for error in critically ill patients. There is ample evidence that failure to initiate appropriate therapy promptly (i.e., therapy that is active against the causative pathogen) has adverse consequences on outcome.

3.1.8 Consider the use of combination therapy in patients with known or suspected *Pseudomonas* infections. Consider the use of combination empiric therapy in neutropenic patients. (Early discussion with microbiologist recommended)

3.1.9 Duration of therapy typically limited to 7–10 days; longer if response is slow or there are undrainable foci of infection or immunologic deficiencies. Stop antimicrobial therapy immediately if the condition is determined to be non-infectious.

3.1.10 Early discussion with microbiologist recommended and see trust antimicrobial policy-revised version.(Section7)

3.1.11 Once the causative agent and antibiotic susceptibilities have been identified, restriction of the number of antibiotics and narrowing the spectrum of antimicrobial therapy is an important and responsible strategy for minimizing the development of resistant pathogens and for containing costs.

3.1.12 The antimicrobial regimen should always be reassessed after 48 to 72 hours on the basis of microbiological and clinical data with the aim of using a narrow-spectrum antibiotic to prevent the development of resistance, to reduce toxicity, and to reduce costs

3.1.13 Source control

Diagnostic studies should be performed promptly to determine the source of the infection and the causative organism. Imaging studies and sampling of likely sources of infection should be performed. Some patients may be too unstable to warrant certain invasive procedures or transport outside of the clinical setting. Bedside studies such as ultrasound may be useful in these circumstances.

Every patient presenting with severe sepsis should be evaluated for the presence of a focus on infection amenable to source control measures, specifically the drainage of an abscess or local focus on infection, the debridement of infected necrotic tissue, the removal of a potentially infected device, or the definitive control of a source of ongoing microbial contamination. In general, the intervention that accomplishes the source control objective with the least physiologic upset should be employed. If intravascular access devices are potentially the source of severe sepsis or septic shock, they should be removed promptly after establishing other vascular access.

3.1.14 Fluid resuscitation – Begin fluid resuscitation immediately. In the event of hypotension and/or lactate >4mmol/L deliver an initial minimum of 20ml/kg of crystalloid (or colloid equivalent). Fluid resuscitation should be commenced as early as possible in the course of septic shock. The guideline does not restrict the amount and extent of an initial fluid challenge, but rather defines a minimum challenge.

Early urethral catheterisation is recommended to assess urine volumes. Do not delay the beginning of fluid administration for placement of central venous access.

Be prepared to deliver additional fluids. In order to reach the target central venous pressure (CVP) goal of 8-12 mmHg (12 -15mm Hg if mechanically ventilated) in subsequent steps, volumes much greater than the initial 20 ml/kg or colloid equivalent may be required.

3.1.15 Central venous catheter (CVC) – Aim to achieve early CVC access. A CVC in addition to aiding the measurement of central venous pressure will allow you to measure Central venous oxygen saturation (ScVO₂) and enable the use of vasopressors.

Rivers et al. (2001) have shown that the early provision of therapy to maintain the following haemodynamic goals significantly reduced in-hospital mortality in severe sepsis and septic shock patients compared to standard haemodynamic therapy

3.1.16 Goals of resuscitation (Early Goal Directed Therapy).

In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or Lactate \geq 4 mmol/L – aim to achieve the following resuscitation goals.

Mean arterial Pressure \geq 65 mmHg

Urine output \geq 0.5mls/kg/hr

Achieve a central venous pressure (CVP) of \geq 8 mm Hg

Achieve a central venous oxygen saturation (ScvO₂) \geq 70% or mixed venous oxygen saturation (SvO₂) \geq 65%

When an appropriate fluid challenge fails to restore adequate blood pressure and organ perfusion, therapy with vasopressor agents should be started. Vasopressor therapy may also be required transiently to sustain life and maintain perfusion in the face of life-threatening hypotension, even when a fluid challenge is in progress and hypovolemia has not yet been corrected. Contact the Intensive Care Unit (if not already done).

Adequate fluid resuscitation is a fundamental aspect of the hemodynamic management of patients with septic shock and should ideally be achieved before vasopressors and inotropes are used, but using vasopressors early as an emergency measure in patients with severe shock is frequently necessary. This usually necessitates admission to critical care.

Administer vasopressors in the event of persistent hypotension or MAP <65 mm Hg. In patients requiring vasopressors, insert an arterial catheter as soon as practical

Either norepinephrine or dopamine (through a central catheter as soon as available) is the first-choice vasopressor agent to correct hypotension in septic shock. In addition preexisting comorbidities should be considered as to most appropriate MAP target. For example, a MAP of 65 mm Hg might be too low in a patient with severe uncontrolled hypertension, and in a young previously normotensive person a lower MAP might be adequate. Supplementing end points of MAP with assessment of regional and global perfusion, such as blood lactate concentrations and urine output, is important. Consider vasopressin in refractory septic shock only.

3.1.17 During the first 6 hrs of resuscitation of severe sepsis or septic shock, if central venous oxygen saturation or mixed venous oxygen saturation of 70% is not achieved with fluid resuscitation to a central venous pressure of 8–12 mm Hg, then transfuse packed red blood cells to achieve a hematocrit of 30% and/or administer a dobutamine infusion (up to a maximum of 20mcg/kg/min) to achieve this goal. Contact the Intensive Care Unit (if not already done).

3.2 SEPSIS MANAGEMENT BUNDLE (6-24 HOURS)

3.2.1 The following Evidence-based goals that must be completed **within 24 hours** for patients with severe sepsis, septic shock and/or lactate ≥ 4 mmol/L. These modalities are usually completed in a critical care setting.

3.2.2 Low dose steroids - consider low-dose steroids for septic shock poorly responsive to fluid therapy and vasopressors. Low dose steroids have been shown to improve vasomotor responsiveness but at the risk of increasing super-infection. Their overall effect on mortality is contentious.

If given use hydrocortisone 50 mg IV every 6 hours and consider tapering the dose rather than abrupt cessation. The Adreno-Corticotrophic Hormone (ACTH) stimulation test is no longer recommended.

3.2.3 Recombinant Activated Protein C - consider the administration of recombinant human activated protein C (rhAPC) in accordance with a NICE Guidelines.(see Appendix 4).

In Adult patients with sepsis induced organ dysfunction associated with a clinical assessment of high risk of death, (Acute Physiology and Chronic Health Evaluation (APACHE) II \geq 25 or multiple organ failure) consider rhAPC if there are no contraindications. Relative contraindications should also be considered in decision-making. Patients with severe sepsis and low risk of APACHE II \leq 20 or one organ failure do not receive rhAPC. The decision to give rhAPC should be made by a consultant Intensivist in accordance with a local ICU policy on its use.

3.2.4 Glucose Control

The NICE-SUGAR study is the largest and most compelling study to date on glucose control in ICU patients. Based on the results of this trial the Surviving Sepsis Campaign has updated its recommendations on glucose control. Therapy aimed at achieving normoglycemia is no longer recommended as it is clear that this leads to more episodes of hypoglycemia with no additional benefit. It is now recommended that Insulin therapy be commenced once blood glucose levels exceed 10mmol/L with the target blood glucose approximating 8.3mmol/L.

With this guideline, glucose should be monitored frequently after initiation of the guideline (every 30–60 minutes) and on a regular basis once the blood glucose concentration has stabilized. Initiating glycemc control without adequate provision of calories and carbohydrates will increase the risk of hypoglycemia

3.2.5 Mechanical Ventilation

Aim for a tidal volume ($6 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{lean body weight}^{-1}$) as a goal in conjunction with the goal of maintaining end-inspiratory plateau pressures of $< 30 \text{ cm H}_2\text{O}$. The largest trial of a volume- and pressure-limited strategy showed a 9 percent decrease of all-cause mortality in patients ventilated with tidal volumes of 6 mL/kg of estimated lean body weight (as opposed to 12 mL/kg) while aiming for a plateau pressure of $< 30 \text{ cm H}_2\text{O}$. Hypercapnia (allowing PaCO₂ to increase above normal, so-called permissive hypercapnia) can be tolerated in patients with ALI/ARDS if required to minimize plateau pressures and tidal volumes. This is contra indicated in the presence of raised Intra Cranial Pressure. Provide adequate supplemental oxygen to maintain a pulse oximetric saturation of ≥ 90 percent. A minimum amount of PEEP should be set to prevent lung collapse at end expiration. Setting PEEP based on severity of oxygenation deficit and guided by the FIO₂ required to maintain adequate oxygenation is one acceptable approach.

3.2.6 Mechanically ventilated patients with severe sepsis should undergo spontaneous breathing trials regularly to evaluate the ability to discontinue mechanical ventilation when they satisfy the following criteria:

- they are rousable
- they are hemodynamically stable (without vasopressor agents)
- they have no new potentially serious conditions
- they have low ventilatory pressure requirements and their FIO₂ requirements could be safely delivered with a facemask or nasal cannula.

3.3 OTHER SUPPORTIVE OPTIONS.

3.3.1 Blood product administration

Once tissue hypoperfusion has resolved and in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, acute hemorrhage, cyanotic heart disease, red blood cell transfusion occurs when hemoglobin decreases to ≤ 7.0 g/dL to **target a hemoglobin of 7.0 –9.0 g/dL.**

Do not use Fresh frozen Plasma to correct laboratory clotting abnormalities unless there is bleeding or a planned invasive procedure.

Administer platelets when counts $< 5000/\text{mm}^3$ regardless of bleeding. Transfuse platelets when counts are 5000 to $30,000/\text{mm}^3$ and there is significant bleeding risk. Higher platelet counts ($> 50,000/\text{mm}^3$) are required for surgery or invasive procedures.

3.3.2 Elevation of head end of bed

Unless contraindicated, mechanically ventilated patients should be maintained with the head of the bed elevated to $30 - 45^\circ$ to limit aspiration risk and to prevent the development of ventilator-associated pneumonia.

3.3.3 Further fluid strategies (after tissue hypoperfusion has resolved)

To decrease days of mechanical ventilation and ICU length of stay consider adopting a conservative fluid strategy for patients with established acute lung injury who do not have evidence of tissue hypoperfusion.

3.3.4 Sedation and Neuromuscular blockade

Use sedation protocols with a set sedation goal when critically ill mechanically ventilated patients with sepsis are sedated. Target sedation to pre determined end points.

In the absence of any contra indication, daily sedation holds are recommended with awakening and re-titration if necessary for sedation administration to septic mechanically ventilated

3.3.5 Deep vein thrombosis (DVT) prophylaxis

Patients with severe sepsis should receive deep vein thrombosis (DVT) prophylaxis with daily low-molecular weight heparin (LMWH) unless there are contraindications (i.e., thrombocytopenia, severe coagulopathy, active bleeding, recent intracerebral hemorrhage.) Septic patients who have a contraindication for heparin use should receive mechanical prophylactic devices such as graduated compression stockings or intermittent compression devices, unless contraindicated.

In very high-risk patients, such as those who have severe sepsis and history of DVT, trauma, or orthopedic surgery, a combination of pharmacologic and mechanical therapy be used unless contraindicated.

3.3.6 Stress ulcer prophylaxis

The use of stress ulcer prophylaxis using H2 blocker or proton pump inhibitor should be given to patients with severe sepsis to prevent upper gastrointestinal (GI) bleed. The benefit of prevention of upper GI bleed must be weighed against the potential effect of an increased stomach pH on development of ventilator associated pneumonia.

3.4 SEVERE SEPSIS IN PREGNANCY

Sepsis is a major cause of maternal mortality in the UK. Prompt diagnosis and treatment are crucial for successful outcome.

Additional Special features to consider in pregnancy–

- Sources of infection include chorioamnionitis, endometritis and wound infection amongst others.
- Cultures to be taken include – Blood, urine, high vaginal swab, endocervical swab and swabs from wounds.
- The fetal condition must be monitored
- The baby may need to be delivered in order to improve the chances of survival
- An empty and well contracted uterus is the aim if chorioamnionitis is the cause of sepsis.
- A high white cell count may be a normal feature of pregnancy.
- Fluid challenges have to be administered carefully in those at risk of fluid overload including patients with gestational proteinuric hypertension.

4. ATTACHMENTS

Appendix 1: Definitions

Appendix 2: Sepsis/Severe Sepsis, Screening Tool and Care Pathway

Appendix 3: Pathology lactate protocol

Appendix 4: NICE guidelines on Activated Protein C

Appendix 5: References

5. ELECTRONIC AND MANUAL RECORDING OF INFORMATION.

Database for Policies, Procedures, Protocols and Guidelines

Archive/Policy Co-ordinators office

Held By: Directorate/Department/Author

Held in format: Electronic and/or hard copy

6. LOCATIONS THIS DOCUMENT ISSUED TO.

Copy No	Location	Date Issued
1	Intranet	10/12/2009
	Wards and departments	

7. OTHER RELEVANT /ASSOCIATED DOCUMENTS.

Unique Identifier	Title
CORP/PROC/470	Taking Blood Cultures http://bfwnet/departments/policies_procedures/documents/Procedure/Corp_Proc_470.pdf
	Antimicrobial policy http://bfwnet/departments/antimicrobial/AF160708.pdf

8. AUTHOR//DIVISIONAL/DIRECTORATE MANAGER APPROVAL.

Issued By	Dr R Nichani	Checked By	Chair person
Job Title	Consultant	Job Title	Critical Care Governance Committee
Signature		Signature	
Date	December 2009	Date	December 2009

Appendix 1 Definitions

DEFINITIONS

SIRS (Systemic inflammatory Response Syndrome) is characterised by 2 or more of the following-

- Temperature $> 38.3^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$
- Heart Rate $> 90/\text{minute}$
- Respiratory Rate $> 20/\text{minute}$ **OR** $\text{PaCO}_2 < 4.3 \text{ Kpa}$ (if mechanically ventilated)
- WBC $> 12,000/\text{mm}^3$ or $< 4,000/\text{mm}^3$
- A blood sugar $> 7.7 \text{ mmols}$ in the absence of diabetes mellitus

SIRS alone may be caused by non-infectious insults such as trauma, burns and pancreatitis and not necessarily due to sepsis.

Sepsis is the presence or presumed presence of infection Plus Systemic Inflammatory Response Syndrome (**SIRS**)

Severe Sepsis is sepsis with one or more of the following system dysfunctions (see flowchart in appendix 2)

- Altered mental status
- Acute Respiratory, renal, cardiac or liver failure
- New onset coagulopathy or thrombocytopenia
- Global tissue hypoperfusion or Lactate $\geq 4.0 \text{ mmol/l}$

Septic shock is:

Sepsis with Mean Arterial Pressure $< 65 \text{ mmHg}$ or Systolic Blood pressure $< 90 \text{ mmHg}$ in spite of a crystalloid bolus of 20-40ml/Kg IV.

The management of severe sepsis and septic shock has 2 broad components or Bundles each of which consists of multiple evidence based interventions.

- These bundles are the Sepsis Resuscitation Bundle (aimed at the first 6 hours from diagnosis) and the Sepsis Management Bundle (which is aimed at the 6 to 24 hour period).

Sepsis/Severe Sepsis

SCREENING TOOL AND CARE PATHWAY

SEVERE SEPSIS SCREENING

1 ARE ANY TWO OF THE FOLLOWING PRESENT AND NEW TO THE PATIENT?

- ▶ Temperature >38.3 or <36 oC
- ▶ Heart rate >90 min-1
- ▶ Respiratory rate >20 min-1
- ▶ White cells <4 or >12 µl-1
- ▶ Plasma Glucose >7.7mmol in the absence of diabetes

If YES, patient has SIRS (Systemic Inflammatory Response Syndrome) now go to 2

2 IS THE HISTORY SUGGESTIVE OF A NEW INFECTION?

- ▶ Pneumonia
- ▶ Urinary Tract Infection
- ▶ Diarrhoea
- ▶ Peritonitis
- ▶ Meningitis
- ▶ Endocarditis
- ▶ Cellulitis/ Septic Arthritis/ Fasciitis/ Wound Infection
- ▶ Catheter/ Other Infection (Including Central Line Infection)

If YES, patient has SEPSIS now go to 3

3 ARE THERE ANY OF THE FOLLOWING PRESENT AND NEW TO THE PATIENT?

- ▶ Blood pressure systolic <90 or mean <65 mmHg
- ▶ New or increased O2 requirement to maintain SpO2 >90%
- ▶ Creatinine >177 µmol/l or Urine Output <0.5 ml/kg/hr for 2 hrs
- ▶ Bilirubin >34 µmol/l
- ▶ Platelets <100
- ▶ Lactate >4 mmol/l
- ▶ Coagulopathy: INR >1.5 or APTT >60 s
- ▶ Acutely altered mental status

If NO - treat for SEPSIS with:-
 ✓Oxygen ✓IV antibiotics ✓Hourly EWS ✓Fluid Therapy
 ✓Blood Cultures ✓Re-assess for Severe Sepsis hourly

If YES - patient has Severe Sepsis begin Care Pathway immediately

SEVERE SEPSIS CARE PATHWAY

STEP 1 to STEP 5 : GENERAL WARD / A&E DEPARTMENT

AT EACH STEP TAKE THE ACTIONS AS DIRECTED. TIMING IS IMPORTANT - COMPLETE STEPS 1 & 2 WITHIN ONE HOUR. IF THE FULL PATHWAY IS REQUIRED, IT SHOULD BE COMPLETED WITHIN SIX HOURS.

Step 1
 ✓ Give Supplementary Oxygen at 15 ltrs/min via a non rebreath mask, Titrate to O2 sats and ABGs.
 ✓ Insert Wide Bore Venous Cannula
 ✓ Check Blood Lactate ✓ Take Blood Cultures
 ✓ Give Intravenous Antibiotics
 ✓ Address source control
 ✓ Early urethral catheterisation

Step 2
 Is Systolic Blood Pressure <90mmHg, or - Lactate ≥ 4mmol/L or - Oliguric?
 ✓ Give a minimum 20mls/kg as a fluid challenge (glucose free)
 Senior Review needed.
 Other patients with severe sepsis may also benefit from a fluid challenge (senior review).

Step 5
 Is the Systolic Blood Pressure still < 90mmHg?
 Is the Lactate still >4?
YES - Move on to Step 6 - Refer to Critical Care
NO - End Care Pathway and return to hourly EWS

Step 4
 ✓ Insert Central Venous Catheter
 ✓ Read Central Venous Pressure
 ✓ Achieve CVP of 8-12 mmHg - if necessary with further fluid challenges
Move on to Step 5

Step 3
 Is the Systolic Blood Pressure still < 90mmHg?
 Is the Lactate still >4?
YES - Move on to Step 4
NO - End Care Pathway and return to hourly EWS

STEP 6 to STEP 8 : CRITICAL CARE UNIT

Step 6
 Insert Arterial Line and Administer Vasopressors to achieve a Systolic Blood Pressure of >90mmHg and a (MAP) >65 mmHg
Move on to Step 7

Step 7
 Check ScVo2 -
 If ScVo2 <70% Administer Packed Red Blood Cells to keep HCT/PCV >30
 If ScVo2 stays below 70% Consider Dobutamine.

Step 8
 All goals achieved?
YES - Care Pathway complete, return to hourly EWS
NO - Go back to Step 4 (CVP)

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Appendix 3

If you print this information, it is only valid on the day of printing. Please check the website again for the most up to date information.

Pathology Protocol

Title	Lactate
Reference Number:	Prolact.doc
Date Issued	19/1/04
Enquiries to	Dr P Bladon Ext 6627, Dr S Butler Ext 3743

Clinical indication

Lactic acid is an intermediary product of carbohydrate metabolism and is derived from muscle cells and erythrocytes. Severe oxygen deprivation of tissues results in a blockage of aerobic oxidation of pyruvate. This leads to an acidosis called "lactic acidosis" which is associated with increased lactate levels. High lactate levels are found with marked hypernea, weakness, fatigue, stupor and finally coma. The liver can normally metabolise the lactate that is produced but in decreased perfusion of the liver removal of the lactate may be impaired. Lactate in cerebrospinal fluid normally parallels blood levels. In biochemical alterations in the CNS, however, CSF lactate values change independently of blood values. Increased CSF levels are seen in cerebrovascular accidents (CVA), intracranial haemorrhage, bacterial meningitis (but not aseptic meningitis) and other CNS disorders.

Procedure

1. Take a sample of whole blood (adults at least 2ml; paediatrics at least 1ml) into a fluoride oxalate (yellow) or lithium heparin (orange) bottle on ice and bring the sample straight to biochemistry together with a completed request card.
2. Samples for CSF lactate should be taken into a fluoride oxalate (yellow top) bottle on ice.

Reference range

Serum lactate 0.76-1.25 mmol/L

CSF Lactate 0.8-2.2 mmol/L

Reference

1. Tietz Textbook of Clinical Chemistry (1999) pg 787-789

Appendix 4

Guideline 84 - NICE guidelines for the use of Xigris(Activated Protein C)

Since the NICE guidance on drotrecogin alpha (activated) was issued, the European Medicines Evaluation Agency has recommended changes to the way that drotrecogin alpha (activated) should be used. These changes can be found on the EMEA website at

<http://www.emea.eu.int/hums/hotpres/sh13844405.htm>

In summary, the EMEA consider that drotrecogin alfa (activated) should only be used in high-risk patients, mainly in situations when therapy can be started within 24 hours of the onset of organ failure. In addition, it should only be used by experienced doctors in institutions skilled in the care of patients with severe sepsis. Drotrecogin alfa (activated) should not be used in patients with single organ dysfunction, especially if they have had recent surgery (within 30 days).

NICE advises that clinicians wishing to prescribe drotrecogin alpha (activated) should take the EMEA advice into account alongside the guidance from NICE when deciding whether or not to prescribe drotrecogin alpha (activated).

Appendix 5 - Reference

1. Dellinger RP, Levy MM, Carlet JM, et. al: Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008; 36:296-327.