



Standards and Guidelines Committee

REFERENCE NUMBER	To be assigned by Trust committee
Neutropenic Sepsis Guideline (NICaN)	
Summary	<p>Neutropenic Sepsis is a potentially life threatening condition. This guidance is primarily for all healthcare professionals to enable initial recognition and management of neutropenic sepsis in people with cancer. It is particularly relevant to those working in emergency departments and those providing acute oncology services. Prompt intervention during the first hour is vital as delay in diagnosis and treatment may be catastrophic for patients.</p> <p>The guidance is also aimed at those clinicians providing clinical management during the following 48 hours.</p>
Supersedes	NICaN Management of Chemotherapy Complications (Feb 2001)
Operational date	August 2010
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Version Record

Date	Version	Author	Comments
23/09/09	0.1	P Scullin	Initial NICaN draft for discussion at sub-group meeting
21/10/09	0.2	M Bell & P Scullin	NICaN draft for electronic consultation
16/12/09	0.3	M Bell & P Scullin	NICaN draft with changes following dissemination
21/05/10	0.4	M Bell & P Scullin	Final NICaN draft submitted following approval at NICaN Regional Chemotherapy Meeting
23/07/10	1		Approved by NICaN Board – for dissemination
5/8/2010	V0.6	JR Johnston	Formatting
9/8/2010	V0.7	JR Johnston	Using original pdf flowcharts
23/8/2010	V0.8	MB	Revised pdf flowcharts

Policy Record

		Date	Version
Author (s)	Approval	May 2010	1
Director Responsible	Approval	June 2010	1

Approval Process – Clinical Standards and Guidelines

Standards and Guidelines Committee	Approval		
Policy Committee	Ratify		
Executive Team	Authorise		
Appropriate Director	Sign Off		

Dissemination

Areas :	

Full Description

Neutropenic Sepsis Guideline (NICaN)

- 1. Introduction:**

Systemic infection in neutropenic patients is a potentially life threatening condition. Left unchecked it can rapidly prove fatal. Simple timely intervention can be life saving. These guidelines provide the relevant information to enable the prompt recognition and management of potential neutropenic sepsis.
- 2. Purpose:**

To ensure a safe, standardised approach to the urgent assessment and initial management of adult patients with potential neutropenic sepsis who present to any healthcare professional. Clinicians managing patients with neutropenic sepsis will move between specialities and hospitals, hence there is a need to ensure consistency of practice. It is important that those working in front line services without an extensive knowledge of Systemic Anti Cancer Therapy (SACT), have the confidence to recognise and promptly initiate treatment of neutropenic sepsis.
- 3. The Scope:**

This document is aimed at all clinical staff involved in the management of adult patients with potential neutropenic sepsis who present to any healthcare environment in Northern Ireland.
- 4. Objectives:**
 1. A reduction in morbidity and mortality for patients presenting with neutropenic sepsis
 2. To ensure a unified approach to initial neutropenic sepsis management across Northern Ireland
 3. To ensure neutropenic sepsis is recognised as a “time-dependent condition”
 4. To provide simple concise guidance on what needs to be achieved during the first hour and subsequent 48 hours
- 5. Roles and Responsibilities:**

It is the responsibility of all those involved in the management of patients with potential neutropenic sepsis to familiarise themselves with the content of these guidelines. This includes staff in A&E, Acute Receiving Units, Community staff and all those involved in receiving oncology and haematology patients.

6. The definition and background of the policy

Systemic infection in neutropenic patients is a potentially life threatening condition. Left unchecked it can rapidly prove fatal. Simple, timely intervention can be life saving.

Neutropenia can result from a number of underlying conditions: aplastic anaemia, haematological malignancies, hereditary conditions, radiation exposure, vitamin deficiencies, autoimmune conditions etc. The most predictable cause of neutropenia is cytotoxic chemotherapy resulting in myelosuppression and immunosuppression. Chemotherapy treatments are in use to manage autoimmune diseases, and cancer – systemic anti-cancer therapy (SACT).

The 2008 National Confidential Enquiry into Patient Outcome and Death (NCEPOD) study into the care of patients dying within 30 days of SACT raised significant quality and safety concerns.¹ Care was inadequate for patients readmitted with complications following SACT, especially for neutropenic sepsis. The diagnosis was often missed, and treatments were delayed. 1:5 hospitals had no policy for the emergency admission of patients with SACT toxicity.

The 2009 National Chemotherapy Advisory Group (NCAG) report recommended actions to bring about a step change in the quality and safety of chemotherapy services, based on a care pathway model.² It was recognised that, in emergency, patients with oncology complications often access care via Emergency Departments. Key recommendations included: the establishment of an Acute Oncology Service (AOS) in all hospitals with Emergency Departments; clear and readily accessible policies for managing complications, including neutropenic sepsis, agreed across a Network; a target “door-to-needle” time of one hour for intravenous antibiotic delivery in neutropenic sepsis.

Northern Ireland Chemotherapy Service Standards include the recommendation that guidelines should be in place for the recognition and treatment of neutropenic sepsis.³

7. Policy / Guideline description:

To support clinicians in the recognition and initiation of prompt and appropriate clinical management of patients with potential neutropenic sepsis.

8. Policy statements:

- 8.1 It is essential that clinicians recognise and initiate prompt and appropriate clinical management in patients with potential neutropenic sepsis.
- 8.2 This guideline presents a care pathway for the recognition and management of potential neutropenic sepsis in adult patients presenting acutely to hospitals in Northern Ireland.

The guideline provides a basis on which the recommended audit of neutropenic sepsis management can be made.

In the early stages, those presenting with neutropenic sepsis may not have abnormal vital signs, or be perceived to have a life threatening (critical) condition. A key goal of the guideline is to get neutropenic sepsis recognised as a “time-dependent condition” alongside others such as ST-elevation myocardial infarction, acute stroke etc. The introduction of a target “door-to-needle” time should help to reinforce this.

The guideline focuses on the initial recognition and management of neutropenic septic patients. If there is delay in diagnosis or treatment, the result can be

catastrophic for the patient. Clinicians receiving patients in busy Emergency Departments and Acute Receiving Units must have simple, concise guidance on what needs to be achieved in the “golden hour”. The first part of this guideline relates to these “First 60 Minutes”. The second part of the guideline relates to the “First 48 Hours” and deals with five criteria that require further elucidation by the Acute Oncology Service in the following days.

Guidance builds on the established work of the Surviving Sepsis Campaign, developing the concept for SACT-related neutropenia.⁴ Patients clearly do not have to have neutropenia to develop sepsis. When they do however, and with other co-morbidities, they are particularly vulnerable.

It is recognised that clinicians managing patients with neutropenic sepsis will move between specialties and hospitals, each with slightly different approaches. This guideline is an effort to remove potential confusion by introducing a unified approach to initial neutropenic sepsis management for the Cancer Network in Northern Ireland.

The guideline is necessarily simple and concise. It is important that those working in front line services, without an extensive SACT knowledge base, have the confidence to recognise and promptly initiate treatment of neutropenic sepsis. Those clinicians anticipating careers in specialties such as Oncology and Haematology may wish to use it as a framework for further learning. Dr YL Ong has created an e-Learning module on neutropenic sepsis (BMJ Learning), which will provide supplementary information.⁵

Definitions⁶

Neutropenia: An absolute neutrophil count (ANC) of $< 1.0 \times 10^9/L$ regardless of the overall white cell count

Infection: Microbial phenomenon characterised by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms

Bacteraemia: The presence of viable bacteria in the blood

Systemic Inflammatory Response Syndrome (SIRS): The systemic inflammatory response to a variety of severe clinical insults (often, but not necessarily infection).

The response is manifested by two or more of the following conditions:

Temperature $> 38^\circ C$ or $< 36^\circ C$ Heart Rate > 90 beats/minute Respiratory Rate > 20 breaths/minute or $PaCO_2 < 4.3$ KPa White Cell Count $> 12 \times 10^9/L$ or $< 4 \times 10^9/L$

Sepsis: The systemic response to infection. (SIRS criteria, secondary to infection)

Severe Sepsis: Sepsis associated with organ dysfunction, hypoperfusion, or hypotension (including, but not limited to, lactic acidosis, oliguria, or altered mental state)

Septic Shock: Severe sepsis with hypotension despite adequate fluid resuscitation (requiring inotropes or vasopressors)

The First 60 Minutes

Prompt, appropriate management in the first hour after presentation is crucial to optimising outcome for the patient. Neutropenic sepsis is a time dependent condition. The goal is a “door to needle” time of 60 minutes for administration of IV antibiotics.

This part of the guideline is relevant to clinicians working in *any* hospital area that might receive unwell neutropenic patients. It is designed to be practicable in Emergency Departments/Acute Receiving Units as well as in Oncology/Haematology Departments.

The key to successful implementation is early recognition of a patient's potential to have neutropenic sepsis. If this is missed at Triage assessment, treatment delays will be incurred and the patient could be put at increased risk. All patients within 6 weeks of SACT presenting as an emergency must be assumed to have neutropenic sepsis until proven otherwise. Patients must be educated to inform at Triage, Help-lines should give advance warning, and Triage Nurses should have a high index of suspicion. This sensitive measure should identify all potential SACT-related neutropenic sepsis patients, and allow the time dependent pathway to be initiated. The principle needs to be applied to even apparently well ambulatory patients presenting with perceived minor complaints.

Laboratory confirmation of neutropenia cannot usually be guaranteed within the necessary timescale. A full blood count/differential white cell count (along with other baseline bloods and blood cultures if the patient is pyrexial) should be requested at the earliest opportunity. Unless there is availability of calibrated Point of Care Testing that can promptly deliver an absolute neutrophil count (ANC), treatment should not be delayed for an ANC if there are any signs of sepsis.

Acute sepsis assessment should be based on the *clinical* criteria included in the given definitions. Thus patients with any clinical SIRS criterion (Temp > 38 or < 36, Pulse > 90, or RR > 20) should be assumed to have **early sepsis**. Those with additional new signs of organ dysfunction (altered mental state, hypoxia, or shock) should be managed as **severe sepsis**. In both of these groups first line neutropenic sepsis antibiotics must be administered with fluid resuscitation at the earliest opportunity.

First line antibiotics should be immediately accessible in any area where patients are received. Regimens should be similar across the network, and will be under regular review. The preferred regimen is piperacillin/tazobactam with gentamicin. Teicoplanin should be added in cases of severe sepsis. An alternative regimen of ciprofloxacin, gentamicin and teicoplanin should be used for penicillin allergic patients. In hospitals where quinolones are discouraged, a local alternative should be made clear, and accessible.

Initial management of any patient assessed as having severe sepsis must be in a Resuscitation area with full monitoring facilities. Patient haemodynamics and oxygen delivery should be optimised, with early HDU/ICU admission.

Patients who have first dose, first line antibiotics for clinical signs of early sepsis should have their laboratory ANC result reviewed. If this confirms neutropenia, the patient should be admitted to a neutropenic sepsis bed with continuation of therapy. Should neutropenia be excluded, an alternative sepsis management plan can be made.

Care should be taken with neutropenic patients who do not meet sepsis definition criteria, but have low-grade pyrexia. These patients may require admission for monitoring as they may deteriorate.

Patients should only be discharged when physiologically stable, with their co-morbidity treated. Advice on neutropenic sepsis should be reinforced.

Ongoing management of the neutropenic sepsis patient should be in a Cancer Unit or Centre. If the patient has self-presented to a hospital without such a facility, transfer should be arranged. Help-lines should ensure that patients requiring urgent assessment are directed to the appropriate Unit/Centre hospital. Ambulances transporting these patients should bypass hospitals without the appropriate facility.

The First 48 Hours

This section of the guideline is directed at ongoing management of patients admitted to appropriate hospital neutropenic sepsis beds. It assumes initiation of appropriate management in the first hour after patient presentation.

Patients should be closely observed, with clear and frequent documented communication between clinicians managing the patient at ward level, Pharmacists and the Microbiology service.

In the first days, there are five main areas that should be constantly reviewed in order to manage the patient optimally: Monitoring, Chemotherapy Drugs, Antimicrobials, Fluid & Electrolyte Balance and Neutropenia.

Monitoring: All patients should have vital signs recorded on an Early Warning Score (EWS) chart with urgent reassessment by a senior clinician should patient deterioration be indicated. Frequent observations should be recorded until the patient is assessed as stable. In the 24-48 hour period after admission if monitoring of temperature indicates only a partial response to therapy, mucositis (stomatitis and enteritis) should be considered.

Chemotherapy Drugs: All patients with neutropenic sepsis receiving SACT must have this immediately discontinued with drugs quarantined. SACT must not be recommenced during treatment for sepsis.

Antimicrobials: Consideration needs to be given to alternative and additional antimicrobial therapy, dose adjustments, and identification of foci of infection.

There may be early clear evidence of a specific focus of infection that would be considered responsive to alternative therapy. The First Line antibiotic regimen should not be altered without clear advice from the Microbiology service. On Day 2, in stable patients, consideration should be given to stopping Gentamicin to avoid nephrotoxicity. However, after 48 hours of unresponsive fever, or deterioration in a patient's condition, therapy should change to Second Line antibiotics – currently Meropenem with Amikacin (with Teicoplanin if indicated).

There are specific indications for the addition of Teicoplanin to the regimen – clinically evident serious soft tissue infection, indwelling catheter infection, or if the patient is positive for MRSA. Viral and fungal infections must be considered and managed appropriately.

Some antimicrobial doses must be adjusted in the elderly and where there is renal impairment, notable Gentamicin, Teicoplanin and Amikacin. Pre-dose levels should be monitored, with appropriate dose adjustment based on Pharmacy and Microbiology advice.

Early cultures must be made of samples from any site that could lead to microbial identification or source of infection – lines, blood, sputum, urine and throat/skin swabs. These cultures should be repeated before antimicrobial regimens are

altered, or if the patient deteriorates. There needs to be frequent communication with the Microbiology service.

Fluid & Electrolyte Balance: Dehydrated patients require aggressive fluid replacement. This may require invasive haemodynamic monitoring. The best indication of successful volume replacement is urine output. Hourly urine output measurement should be measured during the resuscitation phase. Electrolytes should be replaced judiciously, and monitored regularly.

Neutropenia: Early correction is only indicated for patients meeting severe sepsis criteria, or where there is suspected invasive fungal infection. Correction should also take place if fever is persistent 48 hours after antimicrobial therapy has commenced. Correction is relatively contraindicated if there has been PEG-filgrastim use in the preceding three weeks. Correction is with recombinant human Granulocyte colony stimulating factor (G-CSF). An example of this is Filgrastim 30 million units (300mcg). Several bio-generic versions are available, so, when prescribing, it is recommended that the brand name be used.

Summary

Neutropenic sepsis is a potentially life threatening condition. It needs to be recognised as a Time Dependent Condition, with early therapeutic intervention required to reduce morbidity and mortality.

This NICaN guideline is designed as an uncomplicated, concise ready-reference, to be used throughout the province to promote early identification of neutropenic septic patients, with subsequent safe and effective care.

The 'First 60 Minutes' component should be implemented in Emergency Departments and Acute Receiving Units with the goal of achieving a maximum "door to needle" time for IV antibiotic administration of 60 minutes.

The 'First 48 Hours' component should be used by clinicians managing patients in hospital neutropenic sepsis beds. It elucidates the main areas that need to be reviewed to ensure optimal patient management in the first days after neutropenic sepsis has been identified.

The NICaN Neutropenic Sepsis Guideline provides a basis for multidisciplinary clinical audit of management of neutropenic sepsis patients across the cancer network in Northern Ireland.

9. Implementation / Resource requirements:

For circulation to all staff in contact with oncology haematology patients with potential neutropenic sepsis across Northern Ireland.
Raise awareness locally with regards to the implementation of the guidelines.

10. Source(s) / Evidence Base:

NCEPOD¹, NCAG², The ACCP/SCCM Consensus Conference Committee⁶, e-Learning module on neutropenic sepsis (BMJ Learning)⁵

11. References, including relevant external guidelines:

1. *For better, for worse? A review of the care of patients who died within 30 days of receiving systemic anti-cancer therapy.* National Confidential Enquiry into Patient Outcome and Death. November 2008
2. *Chemotherapy Services in England: Ensuring quality and safety.* A report from the National Chemotherapy Advisory Group. August 2009

3. *Northern Ireland Chemotherapy Service Standards*. NICaN Regional Chemotherapy Group. July 2006
4. Dellinger RP, Levy MM, Carlet JM et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2008; [published correction appears in *Crit Care Med* 36: 1394-1396] 36: 296-327
5. YL Ong. Neutropenic sepsis – a guide to diagnosis and management. <http://learning.bmj.com/learning> (search term: neutropenic sepsis)
6. RC Bone, RA Balk, FB Cerra, RP Dellinger, AM Fein, WA Knaus, RM Schein. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992;101; 1644-1655

12. Consultation Process:

Through the auspices of Northern Ireland Cancer Network Chemotherapy Group which has widespread membership

13. Equality and Human Rights screening carried out:

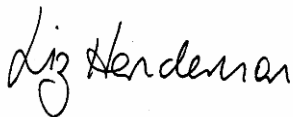
In line with duties under the equality legislation (Section 75 of the Northern Ireland Act 1998), Targeting Social Need Initiative, Disability discrimination and the Human Rights Act 1998, NICaN has carried out an initial screening exercise to ascertain if this policy should be subject to a full impact assessment.

Screening completed
No action required.

Full impact assessment to be carried out.

14. Procedures:

Appendix 1 = flowcharts



NICaN Director

Liz Henderson

Date: June 2010

Author

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Date: May 2010

