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Title:	Guidelines for the management of oncology/haematology adult patients (>18) with neutropenic sepsis			
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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
05/08/10	V0.6	JR Johnston	Formatting
09/08/10	V0.7	JR Johnston	Using original pdf flowcharts
23/08/10	V0.8	MB	Revised pdf flowcharts
10/12/12	V1.1	P. Scullin & regional group	Revision in line with NICE guidelines
29/04/13	V1.2	P. Scullin	Revision after comments from NICaN SACT group consultation
July 2017	V2	As Above	To be updated in 2020 with NICaN Regional Group

1.0 INTRODUCTION / PURPOSE OF POLICY

1.1 Background

1.1.1 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.

1.1.2 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 the use of systemic anti-cancer therapy (SACT) which can result in myelosuppression and immunosuppression.

1.1.3 The 2008 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.

1.1.4 The 2009 National Chemotherapy Advisory Group 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.

1.1.5 The National Cancer Peer Review Programme Manual for Cancer Services: Chemotherapy Measures include the recommendation that guidelines should be in place for the recognition and treatment of neutropenic sepsis.[3]

1.1.6 In September 2012 NICE produced guidance on the prevention and management of neutropenic sepsis in cancer patients. A sub-group of the NICaN SACT group have updated the NICaN guidelines with reference to the NICE guidance.[4]

1.2 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 SACT, have the confidence to recognise and promptly initiate treatment of neutropenic sepsis.

2.0 DEFINITIONS/SCOPE OF THE POLICY

2.1 With this guideline, NICaN updates guidance for the recognition and management of potential neutropenic sepsis in adult patients presenting acutely to hospitals in Northern Ireland.

2.2 It is anticipated that widespread implementation of the guideline will result in a reduction in morbidity and mortality for patients presenting with neutropenic sepsis in Northern Ireland.

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

2.4 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.

2.5 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.

2.6 Guidance builds on the established work of the Surviving Sepsis Campaign, developing the concept for SACT-related neutropenia.[5] Patients clearly do not have to have neutropenia to develop sepsis. When they do however, and with other co-morbidities, they are particularly vulnerable.

2.7 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.

2.8 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.[6]

Definitions[7&8]

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

Severe Neutropenia: An absolute neutrophil count (ANC) of < 0.5 x 10^9/L

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°C or < 36 °C , Heart Rate > 90 beats/minute, Respiratory Rate > 20 breaths/minute or $PaCO_2$ < 4.3 KPa and White Cell Count > 12x10^9/L or < 4x10^9/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)

3.0 ROLES/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.

4.0 KEY POLICY PRINCIPLES

4.1 The First 60 Minutes

4.1.1 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.

4.1.2 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.

4.1.3 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 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.

4.1.4 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.

4.1.5 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.

4.1.6 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. Gentamicin should be added in cases of severe sepsis. An alternative regimen of ciprofloxacin, gentamicin and teicoplanin should be used for penicillin allergic patients with *the substitution of azteonam for ciprofloxacin* in those who have received prophylactic ciprofloxacin.

4.1.7 Initial management of any patient assessed IN ED 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 if appropriate.

4.1.8 Patients who have first dose, first line antibiotics should have their laboratory ANC result reviewed. Should neutropenia be excluded, an alternative management plan can be made.

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

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

4.1.11 Ongoing inpatient 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.

4.2 The First 48 Hours

4.2.1 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.

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

4.2.3 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.

4.2.4 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.

4.2.5 Chemotherapy Drugs: Stop chemotherapy and contact the treating team within one working day for a decision on continuing treatment.

4.2.6 Antimicrobials: If there is clinical deterioration consideration needs to be given to alternative and additional antimicrobial therapy, dose adjustments, and identification of foci of infection.

4.2.6.1 There may be early clear evidence of a specific focus of infection that would be considered responsive to alternative therapy. The initial antibiotic regimen should not be altered without clear advice from the microbiology service.

4.2.6.2 Do not switch initial empiric antibiotics in patients with unresponsive fever unless there is a clinical deterioration or a microbiological indication.

4.2.6.3 In stable patients, consideration should be given to switching to oral therapy after 48 hours of treatment.

4.2.6.4 There are specific indications for considering 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.

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

4.2.6.6 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.

4.2.7 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.

4.2.8 Neutropenia:
There is limited evidence to support the use of GCSF in the management of patients with acute neutropenia. GSCF should **NOT** be used for afebrile neutropenic patients or for the treatment of uncomplicated febrile neutropenia[9].

However, GCSF may be *considered* for patients with febrile neutropenia who have a high risk of complications following infection. High risk features include;

- Profound neutropenia (ANC $<0.1x10^9$/l) expected to be prolonged (>10 days)
- Persistent fever despite appropriate antibiotics & antifungal treatment
- Evidence of invasive fungal infection
- Pneumonia
- Sepsis syndrome (hypotension & muti-organ dysfunction)
- Uncontrolled primary disease
- Haemodynamic compromise

In these situations, management with GCSF should only be initiated on instruction from an oncology/haematology consultant/registrar/associate specialist or staff grade. GCSF should NOT be given in cases where the patient has received pegfilgrastim.

When GCSF is appropriate, standard (i.e. non-pegylated) GCSF should be used as a daily subcutaneous injection. Discontinue after 2 consecutive days of ANC $>1x10^9$/l

4.3 Summary

4.3.1 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.

4.3.2 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.

4.3.3 The ‘First 60 Minutes’ component should be implemented in Emergency Departments, Acute Receiving Units, inpatient wards and SACT units with the goal

of achieving a maximum "door (or temperature spike for current inpatients) to needle" time for IV antibiotic administration of 60 minutes.

4.3.4 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.

4.3.5 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.

5.0 IMPLEMENTATION OF POLICY

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.

6.0 MONITORING

The management of patients with neutropenic sepsis, with particular reference to first dose of antibiotics within 60 minutes, should be audited regularly at Trust level.

7.0 EVIDENCE BASE / REFERENCES

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. The National Cancer Peer Review Programme Manual for Cancer Services: Chemotherapy Measures Version 1.1. June 2011

4. Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients. *NICE clinical guideline 151.* September 2012

5. Dellinger RP, Levy MM, Carlet JM et al. Surviving Sepsis Campaign: International guidelines for management of sever sepsis and septic shock. *Crit Care Med* 2008; [published correction appears in *Crit Care Med* 36: 1394-1396] 36: 296-327

6. YL Ong. Neutropenic sepsis – a guide to diagnosis and management. http://learning.bmj.com/learning (search term: neutropenic sepsis)

7. 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

8. CR Flowers et al. Antimicrobial prophylaxis and outpatient management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology Guideline. *JCO* 2013; 31(6); 794-810

9. Guidelines for the use of granulocyte colony stimulating factor (GSCF) in adult oncology & haematology patients *NICaN guidelines.* May 2012

8.0 CONSULTATION PROCESS

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

9.0 APPENDICES / ATTACHMENTS

Appendix 1 – NICAN Neutropenic sepsis Guideline (first 60 minutes)
Appendix 2 - NICAN Neutropenic sepsis Guideline (first 48 hours)

10.0 EQUALITY STATEMENT

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, an initial screening exercise to ascertain if this policy should be subject to a full impact assessment has been carried out.
The outcome of the Equality screening for this policy is:

Major impact ☐

Minor impact ☐

No impact. X

SIGNATORIES

(Policy – Guidance should be signed off by the author of the policy and the identified responsible director).

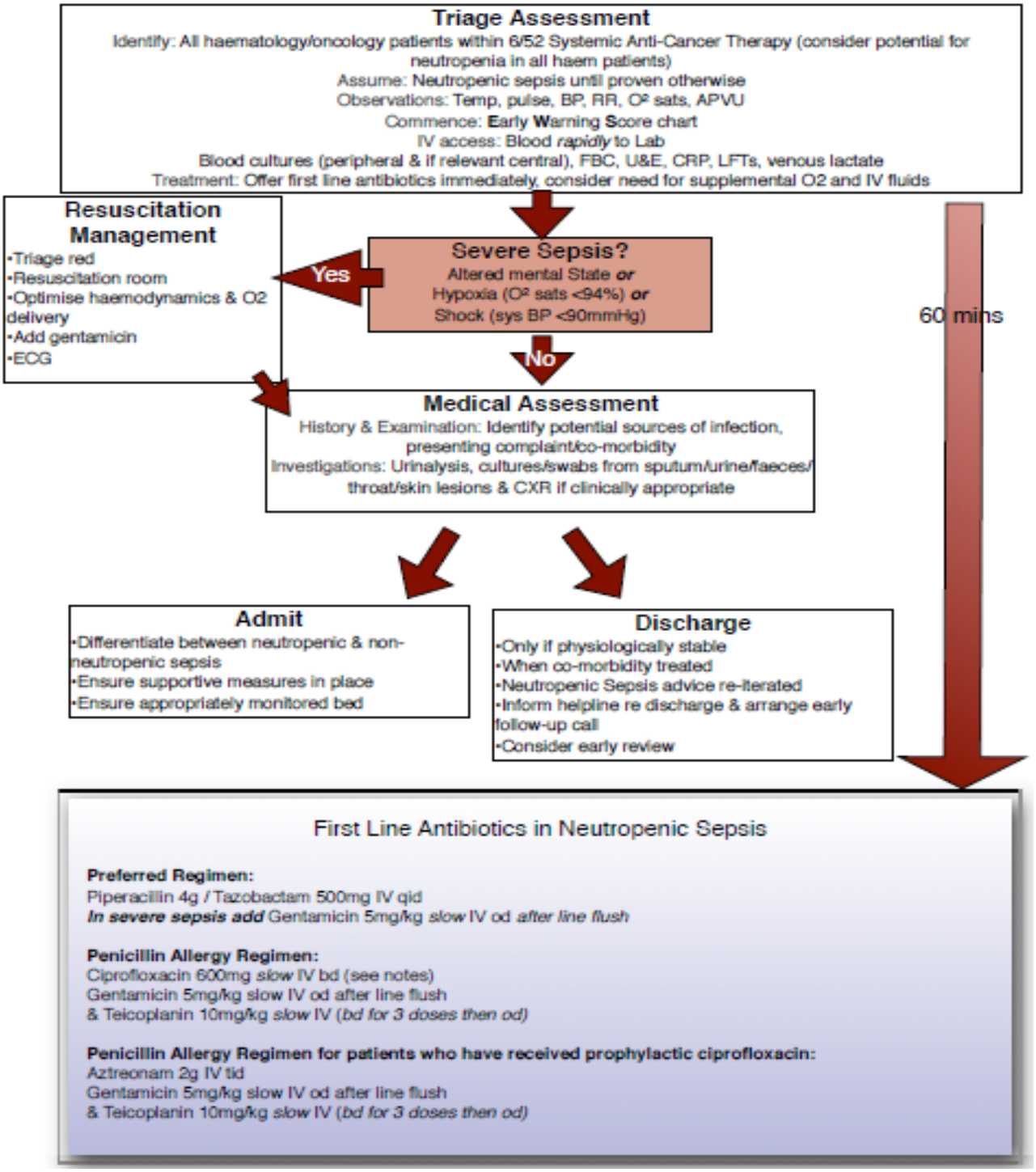
_____ **Date: _____Dec 2013_____**

Author

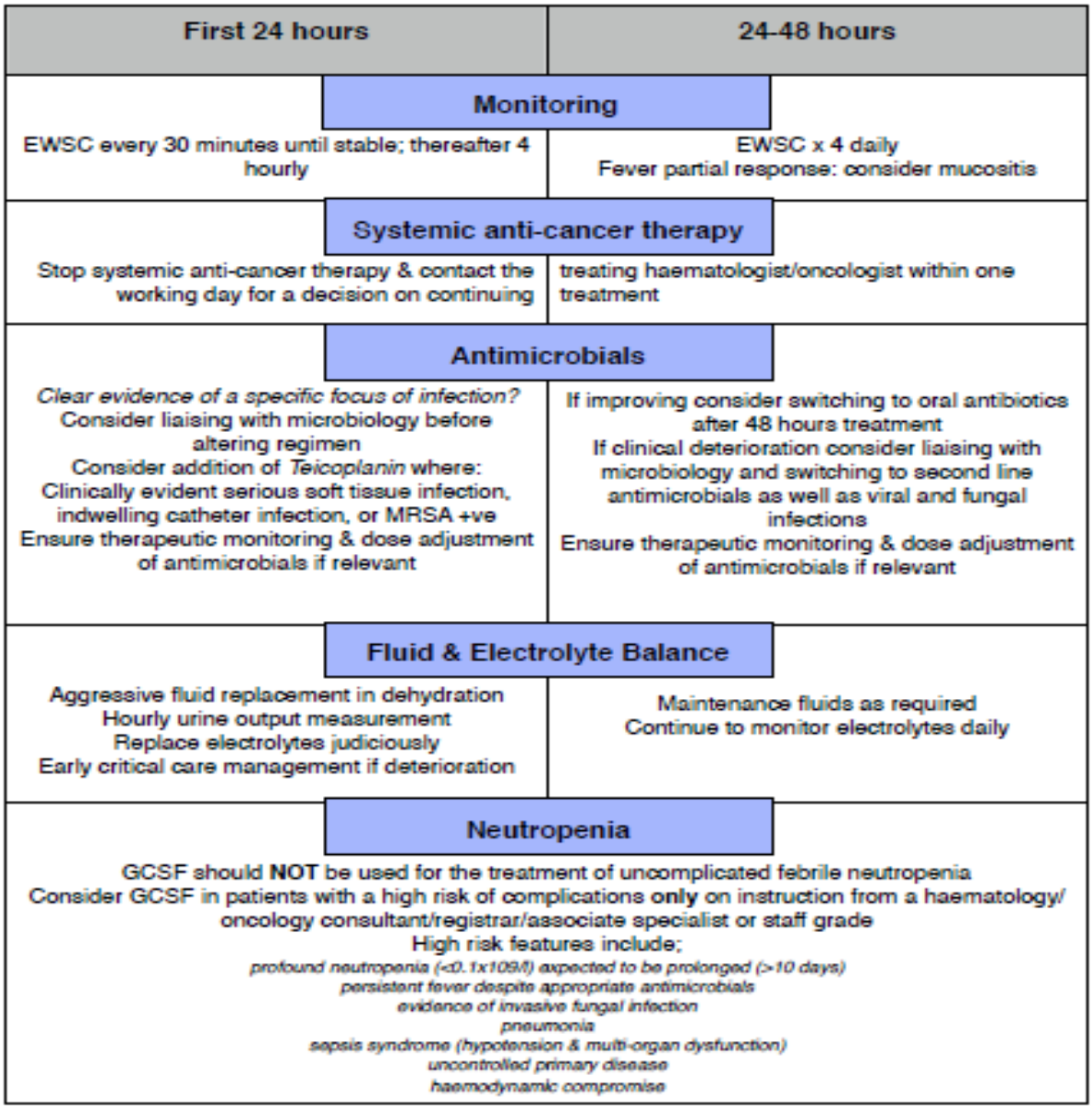
_____ **Date: _____Dec 2013_____**

Director

Appendix 1 - NICAN Neutropenic sepsis Guideline (first 60 minutes)



Appendix 2 - NICAN Neutropenic sepsis Guideline (first 48 hours)



Second Line Antibiotics in Neutropenic Sepsis
Consider discussion with microbiology
If not allergic to penicillin
Meropenem 1g slow IV tds
& Amikacin 15mg/kg slow IV od
+/- Teicoplanin 10mg/kg slow IV (bd for 3 doses then od) - indications above