Febrile Neutropenia (Or Suspected) Patient Management (ADULT) Procedure

Cairns and Hinterland Hospital and Health Service

Purpose

Febrile neutropenia is a common and potentially life-threatening complication of chemotherapy treatment or of a known haematological malignancy/disorder. Patients may rapidly develop sepsis and shock over the course of hours. Patients receiving anti-cancer therapy should be educated on this risk and advised to seek prompt medical advice if febrile or are feeling unwell. Patients should be advised to contact the Cancer Care Services or present to the Emergency Department if this occurs.

Scope

This procedure relates to all clinical staff in the Cairns and Hinterland Hospital and Health Service.

Supporting documents

- The Neutropenic Patient – Indications for Protective Isolation. Ref No. CHHSD-CoC-Proc-Onc-236-V1-3/11
- PA Hospital Cancer Services - Oncology Haematology Unit Handbook - Neutropenic Fever
Procedure for the Management of Patients with Febrile Neutropenia

Patients for whom the guideline is applicable:

All adult patients who are receiving chemotherapy or have a known haematological malignancy/disorder and present with:

- Temp 38 degrees Celsius or above

or

- Signs of sepsis or is unwell

and has

- Suspected or predicted neutropenia
  (do not wait for blood counts to start antibiotics)

or

- Absolute Neutrophil Count (ANC) < 0.5x10^9/L

or

- Absolute Neutrophil Count (ANC) < 1.0x10^9/L and predicted fall to below 0.5x10^9/L. 1,2

Patients who have a high risk of complications include:

- Haematological malignancy
- Recent myelosuppressive chemotherapy (within 8 weeks)
- Concurrent chemotherapy and radiotherapy
- Age >60
- Co-morbidities e.g. diabetes, poor nutritional status.
- Bone marrow involvement of cancer
- Delayed surgical healing or open wounds
- Significant mucositis
- Clinically unstable (e.g. hypotensive, oliguric)
- On corticosteroid therapy >25mg prednisolone (or equivalent) daily
- Rapidly falling neutrophil count over successive days
- Previous history of neutropenia
- Recent hospitalisation for infection
Febrile Neutropenia (or Suspected) Patient Management

**Day 1 (Admission)**

- **Triage Category 2** – Patients presenting at triage window may appear well however clinical deterioration may be rapid
- Start Febrile Neutropenia Care Pathway (see appendix 1)
- Unwell, potentially neutropenic/chemotherapy patients seen in clinic at the Liz Plummer Cancer Centre will be started on the Neutropenic Care Pathway and a direct admit to the Cancer Care Ward will be organised
- Assessment and Investigations (see below)
- **Patient history** (type of cancer, details of recent or current chemotherapy, or non-malignant disease being treated with cytotoxic therapy etc)
- **Contact on call Haematologist** (after assessment and initial work up is established). Patients reviewed in a rural facility may require transfer to Cairns Hospital as per Haematologist for further management.
- **Admission outside of Cairns Hospital** should follow the Protective Isolation Procedure for the Neutropenic Patient.

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**Ensure appropriate fluid resuscitation.**

**Empirical IV antibiotics** (see Table 1) **must** be commenced within **30 minutes** of presentation if clinically **unstable** (hypotension, hypoxia, confusion, major organ dysfunction); or within **60 minutes** if clinically **stable**.

**Do not wait for neutrophil count or blood culture results before starting antibiotic therapy**

**Blood cultures should be taken before starting antibiotics wherever possible, but should not delay antibiotic therapy.**

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**Assessments:**

Observations: Temperature, blood pressure (including postural drop), pulse rate, respiratory rate and oxygen saturation.

Physical examination: focusing on potential sites of infection (including mouth, skin, vascular access devices, chest, abdomen, peri-anal). In the absence of neutrophils, signs of infection may be subtle. NB. Avoid invasive procedures.
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**Investigations:**

- 1 set (aerobic and anaerobic bottles) from each lumen of central venous access device (CVAD) if present. N.B do not flush line before withdrawal of blood from CVAD
- 1 set peripheral blood cultures
- Full blood count
- Electrolytes / Urea / Creatinine / LFTs / CRP
- ECG
- Mid stream urine / indwelling catheter urine specimen
- Swab of CVAD exit sites
- Swab of any other suspicious or focal lesions
- Chest X-ray
- Sputum (if clinically indicated)
- Faeces (if clinically indicated)
- Consider arterial blood gases/venous blood gas
- Lumbar puncture indicated if change in neurological status

For patients with sepsis / severe sepsis (or other life-threatening infections), a delay in the time to administration of antimicrobials is associated with an increased risk of adverse clinical outcomes. Prescribing clinicians must take steps to ensure that antimicrobials are administered in a timely manner. This may include:

- The first “stat” dose is to be prescribed on the front sheet of the medication chart and endorsed “FEBRILE NEUTROPENIA” in addition to the charting of regular doses
- Good communication with nursing staff caring for the patient to ensure the timely administration of antimicrobials
- Variation from the suggested prescribing times on the medication chart
- Delay in less time-critical investigations until after the administration of antimicrobials

Considering the order of administration of antimicrobials such that short infusion time (e.g., “push” administration) are given before those requiring prolonged infusions.
Table 1: Initial antibiotic therapy (for patients with normal renal function)\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Recommendation (grading and level of evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INITIAL therapy only: subsequent therapy should be directed by clinical findings</strong></td>
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<tr>
<td><strong>Clinically unstable patients</strong> (i.e. sepsis) <strong>Administer within 30 minutes of presentation</strong></td>
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<tr>
<td>(The combination of a beta-lactam antibiotic with an aminoglycoside is the regimen of choice)</td>
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<tr>
<td><strong>No penicillin allergy:</strong></td>
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<tr>
<td>Piperacillin-tazobactam 4.5 g IV 6 hourly (grade A)</td>
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<tr>
<td><strong>Non-life threatening penicillin allergy (rash):</strong></td>
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<tr>
<td>Ceftazidime 2 g IV 8 hourly (grade C)</td>
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<tr>
<td><strong>Life threatening (immediate) penicillin/beta-lactam allergy:</strong></td>
<td></td>
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<tr>
<td><em>seek advice from Infectious Diseases team</em></td>
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<tr>
<td>Ciprofloxacin 400mg IV 8-hourly</td>
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<td>&amp;</td>
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<tr>
<td>Gentamicin 5-7 mg/kg ideal body weight IV once daily for maximum 3 days, then for review by Infectious Diseases team.</td>
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<td>&amp;</td>
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<tr>
<td>Vancomycin 25-30mg/kg stat, then 1.5 g IV 12 hourly (if CrCl &gt;90 mL/min, otherwise refer to eTG dosing guidelines)</td>
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</tr>
<tr>
<td><strong>Clinically stable patients</strong> <strong>Administer within 60 minutes of presentation</strong></td>
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</tr>
<tr>
<td>(Beta-lactam monotherapy is recommended unless allergy to the recommended agent/s)</td>
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<tr>
<td>Piperacillin-tazobactam 4.5 g IV 6 hourly (IV Ceftazidime or oral or IV Ciprofloxacin if penicillin/beta-lactam allergic (oral Ciprofloxacin dose: 500-750mg BD; dose reduce in renal impairment).</td>
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<tr>
<td>N.B. IV Ciprofloxacin is restricted to critically ill patients or those unable to swallow.</td>
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<tr>
<td><strong>Vancomycin</strong> 1.5 g IV 12 hourly (if CrCl &gt;90 mL/min, otherwise refer to eTG dosing guidelines) for patients known to be colonised with MRSA or who have a line infection clinically</td>
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</tr>
</tbody>
</table>
## Patient Group

### Patients with cellulitis, obviously infected vascular devices, or MRSA carriers with extensive skin breaks/desquamation

**Piperacillin-tazobactam** 4.5 g IV 6 hourly (grade A) (Ceftazidime or Ciprofloxacin if penicillin/beta-lactam allergic).

**+ Vancomycin** 1.5 g IV 12 hourly (if CrCl >90 mL/min, otherwise refer to eTG dosing guidelines)

### Patients with features of abdominal or perineal infection

**Piperacillin-tazobactam** 4.5 g IV 6 hourly (grade A)

*NB. Piperacillin/tazobactam will provide adequate anaerobic cover, other than for suspected or proven *C. difficile* infection – in this situation Metronidazole therapy is required.*

*if penicillin/beta-lactam allergic seek advice from Infectious Diseases team*

If clinical suspicion for *C. difficile* present add **Metronidazole** 500mg IV 12-hourly

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**Day 2 and 3:** Patients not responding to initial therapy and patients admitted in rural facilities should be considered for transfer to Cairns Hospital in discussion with Consultant.

Although it is common practice to add vancomycin to the initial regimen after 48 hours if fever persists, no significant benefit has been demonstrated in controlled trials. **Vancomycin** is indicated if a **Gram-positive organism resistant to other drugs** is isolated from blood culture or if the patient has **progression of a clinical infection**. If indicated, add to regime

**Vancomycin** 1.5g IV, 12- hourly (if CrCl >90 mL/min, otherwise refer to eTG dosing guidelines; refer to eTG for monitoring and subsequent dose-adjustment guidelines)
**Day 4 and 5:** Patients not responding to antibacterial therapy

In patients, particularly high risk patients (see Table 2 for risk stratification), who have persistent fevers of unknown origin for **96 hours** despite broad-spectrum antibiotics, a **chest x-ray** and **CT of the chest and sinuses** should be done as a matter of priority to investigate for fungal infection. **Antifungal therapy** is then initiated as indicated according to Figures 1 and 2 on the following pages and in consultation with the Infectious Diseases team.

Also, on consultation with the Infectious Diseases team, consider changing Piperacillin/Tazobactam (or Ceftazidime) to **Meropenem +/- addition of Vancomycin** if not on Vancomycin therapy already.

### Table 2: Estimating the risk of fungal complications in cancer patients

<table>
<thead>
<tr>
<th>Infection Risk</th>
<th>Disease/Therapy examples</th>
<th>Fungal Infection Risk</th>
</tr>
</thead>
</table>
| **Low**        | • Standard chemotherapy regimens for most solid tumours  
                 • Anticipated neutropenia <7 days | Low |
| **Intermediate** | • Autologous haematopoietic stem cell transplant (HSCT)  
                       • Lymphoma  
                       • Multiple myeloma  
                       • Chronic lymphocytic leukaemia  
                       • Purine analogue therapy: fludarabine, clofarabine, nelarabine, cladribine  
                       • Anticipated neutropenia 7-10 days | Usually **high**, but some experts suggest modifications depending on patient status  
                       Purine analogues: intermediate risk when used as sole therapy, high risk when used in an intensive chemotherapy regimen |
| **High**       | • Anticipated neutropenia >10 days  
                     • Allogenic HSCT  
                     • Acute leukaemia – induction, consolidation  
                     • Alemtuzumab therapy  
                     • Graft versus host disease treated with high dose steroids | Usually **high**, but significant variability exists related to duration of neutropenia, immunosuppressive agents, and status of underlying malignancy |
Figure 1: Antifungal management guidelines for low/intermediate risk patients\textsuperscript{1,2}

Persistent fevers of unknown origin for 96 hours despite broad-spectrum antibiotics in a LOW / INTERMEDIATE RISK (refer to Table 2) neutropenic patient

URGENT CXR, CT chest and sinuses

On prophylactic fluconazole?

No

Evidence of Invasive Aspergillosis?

No

Monitor patient and continue investigations as clinically indicated. Consider Oral or IV Fluconazole

Yes

Oral or IV Voriconazole, depending on patient’s clinical state

Evidence of Invasive Aspergillosis?

No

Monitor patient and continue investigations as clinically indicated. Consider IV Caspofungin

Yes

Oral or IV Voriconazole, depending on patient’s clinical state
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Figure 2: Antifungal management guidelines for high risk patients

Persistent fevers of unknown origin for 96 hours despite broad-spectrum antibiotics in a HIGH RISK (refer to Table 2) neutropenic patient.

URGENT CXR, CT chest and sinuses

On prophylactic posaconazole?

No

Evidence of Invasive Aspergillosis (IA)?

No

IV Caspofungin

Yes

Oral or IV Voriconazole depending on patient’s clinical state

Yes

Consider alternative source of infection
Consult with Infectious Disease Unit

Continue posaconazole prophylactic therapy.
Send away posaconazole level.
**Febrile Neutropenia (or Suspected) Patient Management**

Table 3: Recommended doses of antifungal agents\(^1,3\)

<table>
<thead>
<tr>
<th>Antifungal Agent</th>
<th>Dose and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fluconazole</strong></td>
<td>IV 400 mg once daily (an 800 mg loading dose can be given). Higher doses have been used.</td>
</tr>
<tr>
<td><strong>Voriconazole</strong></td>
<td>IV 6mg/kg Q12H for 2 doses, then 4mg/kg Q12H (to nearest 50mg).</td>
</tr>
<tr>
<td><strong>Caspofungin</strong></td>
<td>IV 70 mg on the first day, then 50 mg once daily (70 mg once daily if &gt;80 kg).</td>
</tr>
</tbody>
</table>

Table 4: Additional precautions/contraindications to antifungal agents\(^3,4\)

- **Renal impairment:** Ambisome, Voriconazole and Fluconazole.
- **Hepatic impairment:** Voriconazole and Caspofungin.
- **Drug interactions:** All agents, but particularly azole antifungals.

Table 5: Administration requirements of antifungal agents\(^4\)

- **Posaconazole:**
  - Tablet: Take with or without food. Food does not influence absorption
  - Oral suspension: Take with fatty food as this influences absorption
- **Voriconazole:**
  - Take on an empty stomach 1 hour before or 2 hours after food to maximise absorption.
- **Ambisome:**
  - Ensure filter is used when adding reconstituted vials to glucose infusion bag; pre-check that the intended infusion volume will produce final concentration of 0.2-2mg/L *before* adding the contents of vials to the infusion bag.
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**Ongoing Management**

- Patients undergoing treatment with chemotherapy and who present with febrile neutropenia may benefit from the addition of Granulocyte Stimulating Colony Factor (G-CSF), which can reduce the time to neutrophil recovery and decrease the length of stay in hospital.

Patients who received pegfilgrastim (Neulasta®) prophylactic therapy as part of their chemotherapy treatment, do not require further G-CSF. For patients who have not received any G-CSF the addition of filgrastim 5micrograms/kg (Tevagrastim®) should be discussed with the covering consultant.

- Medication history recorded and cessation of any oral anti-cancer therapy including targeted agents e.g. sunitinib, lenalidomide and capecitabine.

- Patient should be admitted to a single room on the ward and cared for as per The Neutropenic Patient – Indications for Protective Isolation. Ref No. CHHSD-CoC-Proc-Onc-236-V1- 3/11 http://qheps.health.qld.gov.au/cairns/docs/pro_neutropenic.pdf

- Patients at high risk should be transferred as soon as is practical to Cairns Hospital for further management.

**Definition of Terms**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition / Explanation / Details</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>A single temperature equivalent to ≥ 38 or above 38 degrees Celsius</td>
<td>Immediate Management of Neutropenic Fever. Cancer Institute NSW. eviQ Cancer Treatments Online, version 2 (last modified 21 Jan 2014)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Definitions of Sepsis can be found:</td>
<td>Uptodate online</td>
</tr>
<tr>
<td>Severe Sepsis</td>
<td>“Sepsis and the systemic inflammatory response syndrome: Definitions, epidemiology, and prognosis”</td>
<td></td>
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<tr>
<td>Septic Shock</td>
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</tr>
</tbody>
</table>
References and Suggested Reading


Febrile Neutropenia (or Suspected) Patient Management

Consultation

Consultant Haematologist (x 2)  Director of Oncology Clinical Services
Consultant Oncologist (x 2)  Medical Director, Emergency Department
Consultant Infectious Diseases (x2)  Director of Pharmacy
Cancer Care Pharmacist  Nurse Unit Manager, Day Oncology Unit
Infectious Diseases Pharmacist  Trinity Medication Management Committee
Oncology Clinical Educator (x3)
Nurse Educator, Emergency Department

Procedure Revision and Approval History

<table>
<thead>
<tr>
<th>Version No.</th>
<th>Created/Modified by</th>
<th>Amendments authorised by</th>
<th>Approved by</th>
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<tbody>
<tr>
<td>1.0</td>
<td>Jason Black, Advanced Pharmacist Cancer Care</td>
<td></td>
<td>Executive Director of Medical Services</td>
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<tr>
<td>2.0</td>
<td>Belinda Aspinall, Senior Pharmacist Cancer Care, Jason Black, Advanced Pharmacist Cancer Care</td>
<td>Medicines Management Committee – Trinity Hub</td>
<td>Executive Director of Medical Services</td>
</tr>
<tr>
<td>3.0</td>
<td>Jason Black, Advanced Pharmacist Cancer Care</td>
<td>Medicines Management Committee</td>
<td>Executive Director of Medical Services</td>
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</tbody>
</table>

Audit Strategy

<table>
<thead>
<tr>
<th>Level of risk</th>
<th>High</th>
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<tbody>
<tr>
<td>Audit strategy</td>
<td>Audit of triage category and Febrile Neutropenia Care Pathway</td>
</tr>
<tr>
<td>Audit tool attached</td>
<td>NA (audit of ieMR clinical documents and data)</td>
</tr>
<tr>
<td>Audit date</td>
<td>Quarterly</td>
</tr>
<tr>
<td>Audit responsibility</td>
<td>NUM and Clinical Director Emergency Department</td>
</tr>
<tr>
<td>Key elements / indicators / outcomes</td>
<td>Patients triaged appropriately and compliance with Febrile Neutropenia Care Pathway</td>
</tr>
</tbody>
</table>
Febrile Neutropenia (or Suspected) Patient Management

Cairns and Hinterland Health Service District

(Affix patient identification label here)

URN:
Family Name:
Given Names:
Address:
Date of Birth:
Sex: [ ] M [ ] F

TRIAGE: CATEGORY 2

For patients who:
- Are receiving chemotherapy or have suspected/confirmed neutropenia (Neutrophil count < 1.0)
- Have a temperature ≥ 38°C (including reported pre-hospital) or > 37.5°C if on steroid therapy

CONTACT TREATING ONCOLOGIST/ HAEMATOLOGIST

ASSESSMENT

<table>
<thead>
<tr>
<th>Attended</th>
<th>Time</th>
<th>Staff Initial</th>
<th>Date</th>
</tr>
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<tbody>
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</table>

- Establish non-invasive monitoring immediately – BP, HR, RR, SpO₂
- Physical examination, focusing on potential sites of infection
- Obtain IV access either peripherally or use CVAD (Central Venous Access Device). If unable gain IV access seek medical assistance
- Collect blood including BLOOD CULTURES (minimum 2 sets) via peripheral AND CVAD access.
- FBC/ ELFTs/ CRP/ CMP/ Xmatch/ Coags

DO NOT DELAY ANTIBIOTICS WHilst Awaiting BLOOD RESULTS
See standing order below: Must give within 30 mins of presentation if septic or 60 minutes if clinically stable
- Urinalysis (+ sputum culture/ faeces if indicated)
- Chest X-Ray
- ECG if hypotensive or indicated (e.g. chest pain)
- Swab any venous access devices if redness/pus around exit site
- Swab any wounds/focal lesions (if present)
- Repeat physical assessment frequently and assess response to treatment by constant clinical observation and uninterrupted monitoring

Record medications in Medication Chart.

- Allergies and Contraindications checked & documented

MEDICATIONS Instructions for standing orders:
- The person administering a medication according to this protocol must record on the medication chart in the ‘once only’ section. THIS FORM DOES NOT SERVE AS A MEDICATION CHART
- The responsible Medical Officer must check this record and confirm by signing within 2 hours.
- If patient is allergic to any of the antibiotics below, consult medical staff. Do not administer. (NB. Alternative antibiotic options are listed in Table 1 on page 5 of this protocol).

STAT Antibiotics – can be NURSE INITIATED

<table>
<thead>
<tr>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin 4g/ Tazobactam 0.5g</td>
<td>4.5g</td>
<td>IV</td>
<td>Q6H</td>
</tr>
<tr>
<td>Gentamicin 5mg/kg</td>
<td>1.5 gram</td>
<td>IV</td>
<td>Daily</td>
</tr>
<tr>
<td>Vancomycin 1.5 gram</td>
<td>1.5 gram</td>
<td>IV</td>
<td>BD</td>
</tr>
</tbody>
</table>

If in septic shock add

<table>
<thead>
<tr>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin 5mg/kg</td>
<td>1.5 gram</td>
<td>IV</td>
<td>Daily</td>
</tr>
<tr>
<td>Vancomycin 1.5 gram</td>
<td>1.5 gram</td>
<td>IV</td>
<td>BD</td>
</tr>
</tbody>
</table>

Regular appropriate antibiotics MUST be charted before a patient is admitted to the ward

Staff to complete if initials appear on this form

<table>
<thead>
<tr>
<th>Name</th>
<th>Signature</th>
<th>Designation</th>
<th>Initials</th>
<th>Date</th>
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Clinical Indicators:
1. Patient triaged as minimum Category 2
2. Patient appropriately isolated
3. Evidence of continuous monitoring
4. Antibiotics commenced within 1 hour of triage