University Hospitals Coventry and Warwickshire NHS Trust

Neutropenic sepsis in an emergency setting

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Objectives

- Understand how frequent febrile neutropenia / neutropenic sepsis is in patients receiving systemic anti-cancer treatment
- Appreciate the potential severity of the condition
- Summarise the basics of anticancer treatment
- Understand the immediate management of patients
- Learn the principles of subsequent management
- Know when and where to seek help

Case

- 54 year old man with bilobar liver metastases from colon cancer
- Received his first cycle of FOLFOXIRI 9 days ago
- Presents to ED having had a temperature of 38.6ºC at home.
- Initial observations in ED: Temp 37.5ºC, BP 108/61, HR 122, RR 20, O2 sats on air 95%

What is your initial management?

1. Continue monitoring as no fever in ED
2. Immediate antibiotics
3. Send bloods and wait for results
4. Reassure and discharge home

Definition of febrile neutropenia

- Febrile neutropenia (FN) is defined as[1]:

1. an oral temperature of >38.3°C

   or two consecutive readings of >38.0°C for 1 hour

   AND

2. an absolute neutrophil count (ANC) of 0.5 x 10^9 /l

   or less than 1.0 x 10^9/l and expected to fall below 0.5 x 10^9/l.

- Local guidelines may have a broader definition.

1. Management of febrile neutropaenia: ESMO Clinical Practice Guidelines, Klastersky, J. et al. Annals of Oncology, Volume 27, v111 - v118

When to consider a diagnosis of febrile neutropenia

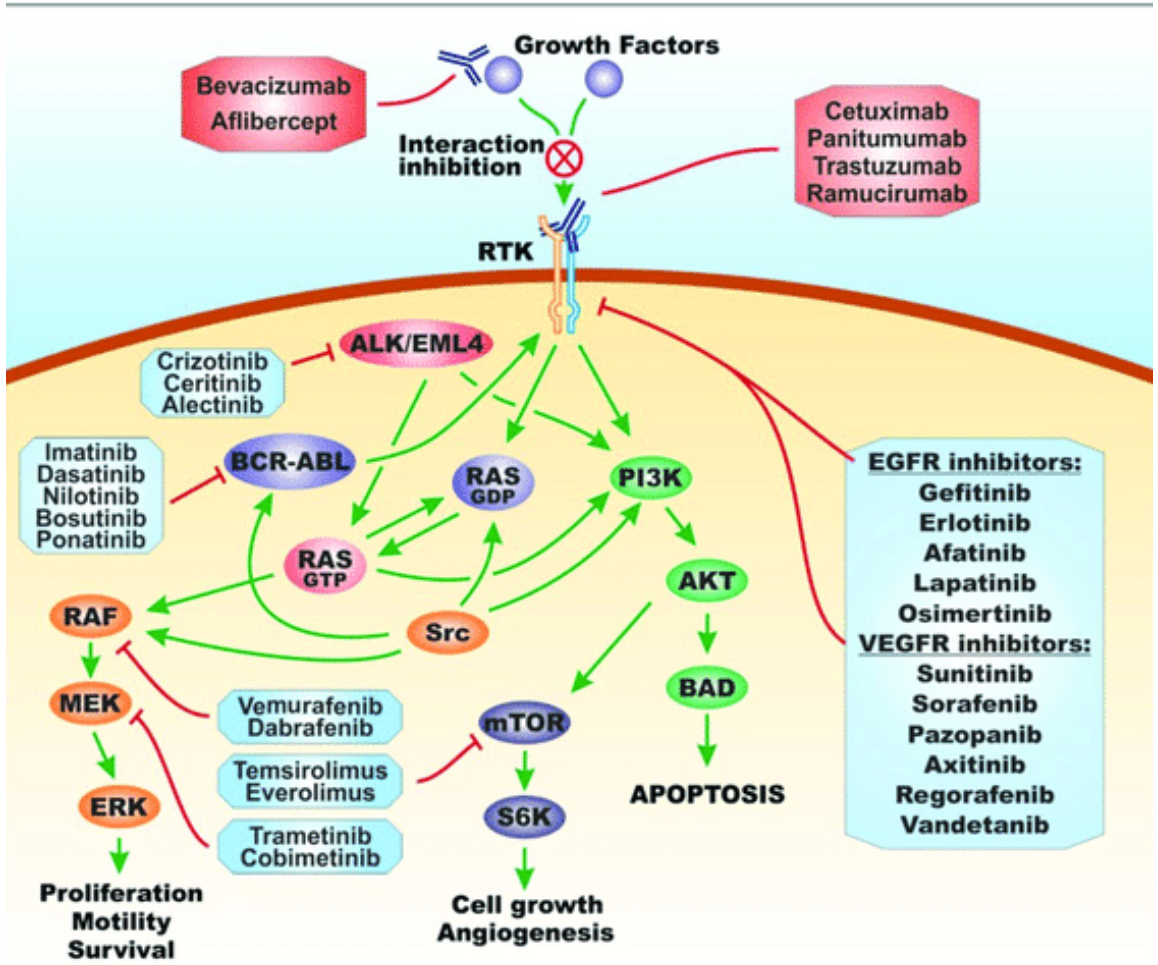
- Fever > 38°C
- Received systemic anti-cancer treatment (SACT) within the last 6 weeks
- Auto-immune diseases
- HIV/AIDS

A very brief introduction to systemic anti-cancer therapies

- What is the aim of treatment?
  - Palliative
    - Aim to prolong life, reduce symptom burden
  - Adjuvant
    - Post curative surgery with aim to reduce risk of recurrence
  - Neoadjuvant
    - Pre surgery or radiotherapy with aim to shrink cancer and kill micro-metastatic disease before radical treatment

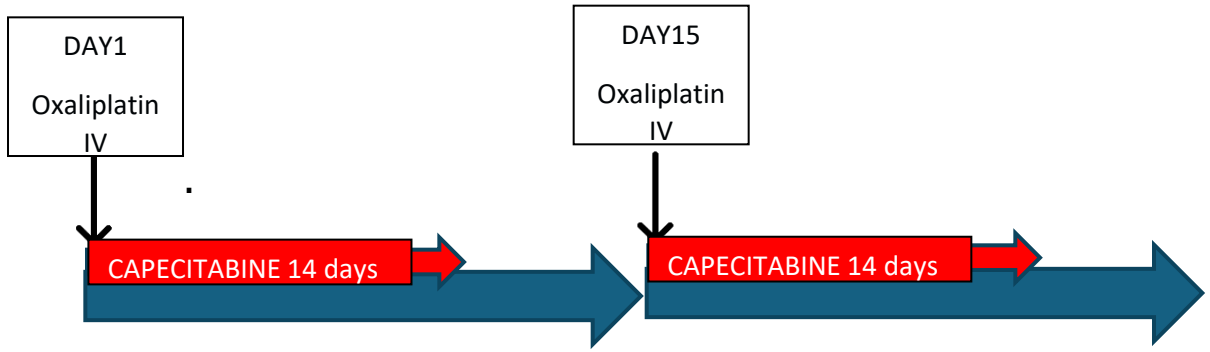
Systemic Anti-Cancer Therapies

- Hormone antagonists
- Chemotherapy
- Targeted therapy
  - ibs and mAbs
- Immunotherapy



Cycles and lines of treatment

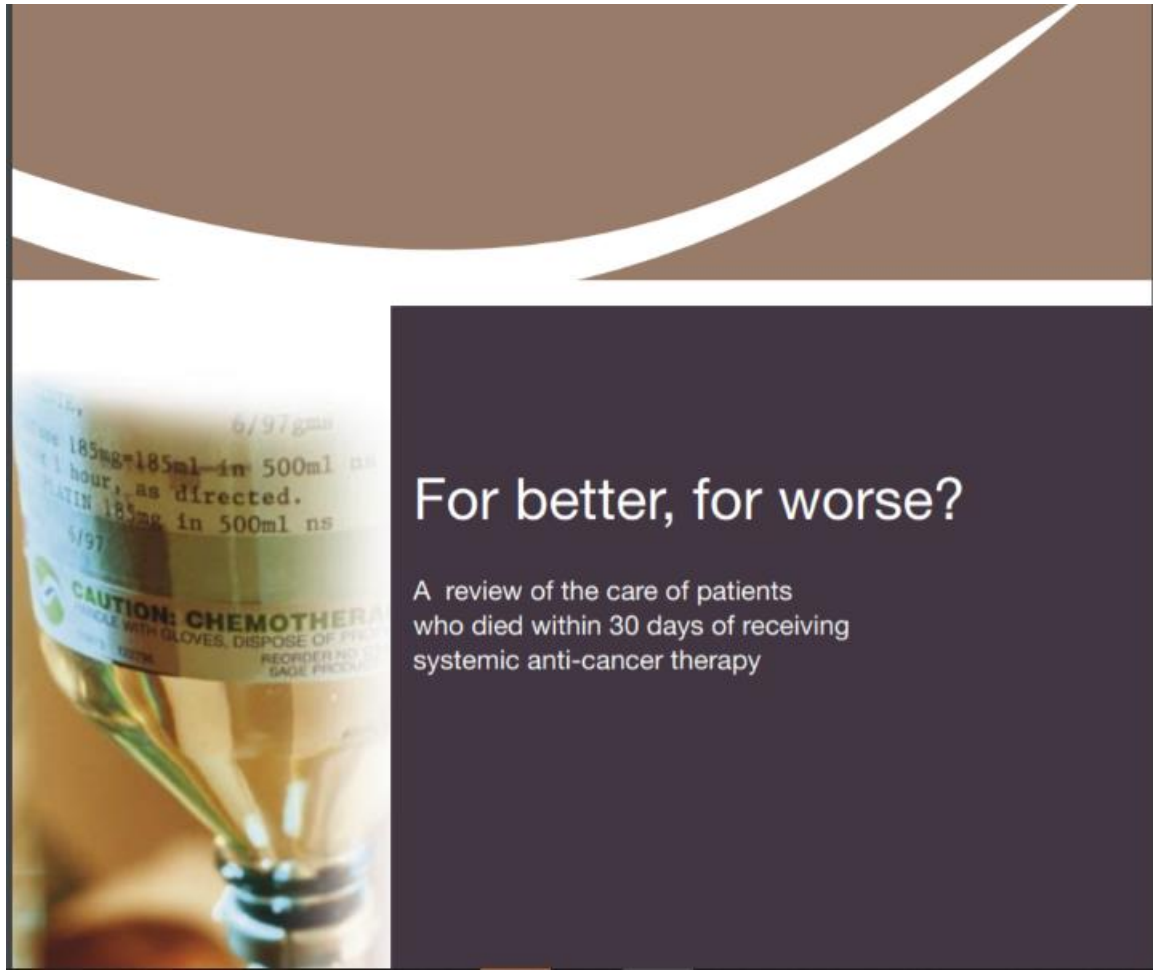
- Cycles:
  - Depending on regimen can be 2, 3, or 4 weeks



- Lines:
  - Palliative treatment

Care of acutely ill cancer patients

- NCEPOD report 2008
- Only 35% of patients deemed to have good quality care
- Highlighted issues in management of neutropenic sepsis
- Development of acute oncology services



Incidence of Febrile Neutropenia

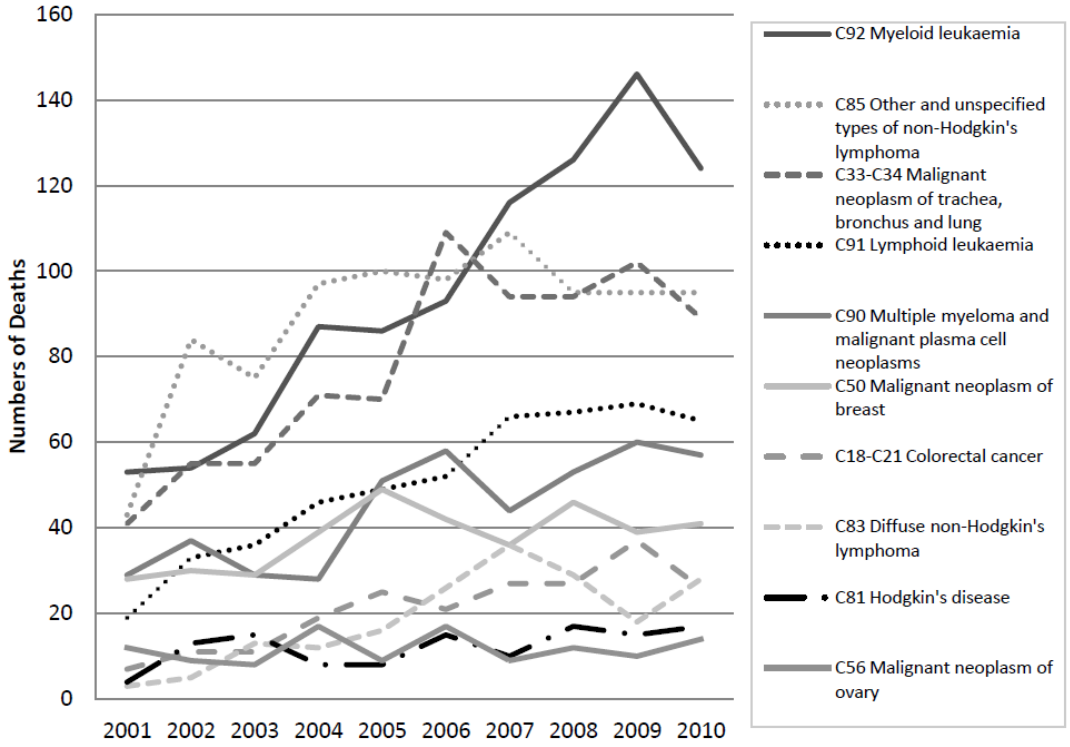
- Real world data from solid tumours and Hodgkin's / non Hodgkin's lymphoma - 5% of patients have FN on cycle 1[2].
- Data from Norwich and Norfolk – 19.4 per 1000 oncology admissions[3].
- Audits from cancer centres : 4 – 7 cases/week

- 2. Rapoport et al, Supportive Care in Cancer 2023, 31:628
- 3. Schelenz Ann Oncol 2012, 23: 1889

Risk of morbidity / mortality

- Febrile neutropenia can lead to major complications in up to 30% with overall mortality of 10%[1].
- Mortality in patients with sepsis up to 50%[2].
- In 2016 over 700 patients in England and Wales died

Figure 1.4 Absolute numbers of cancer deaths from neutropenic sepsis by diagnosis, (paediatric and adult) England and Wales 2001-2010.
Data source: ONS



1. Management of febrile neutropaenia: ESMO Clinial Practice Guidelines, Klastersky, J. et al. Annals of Oncology, Volume 27, v111 - v118

2. Crit Care Med 40:43-49, 2012

Risk of Febrile Neutropenia

- Varies between chemotherapy regimens:
  - High risk >20% risk
  - Intermediate risk 10-20% risk
  - Low risk < 10% risk

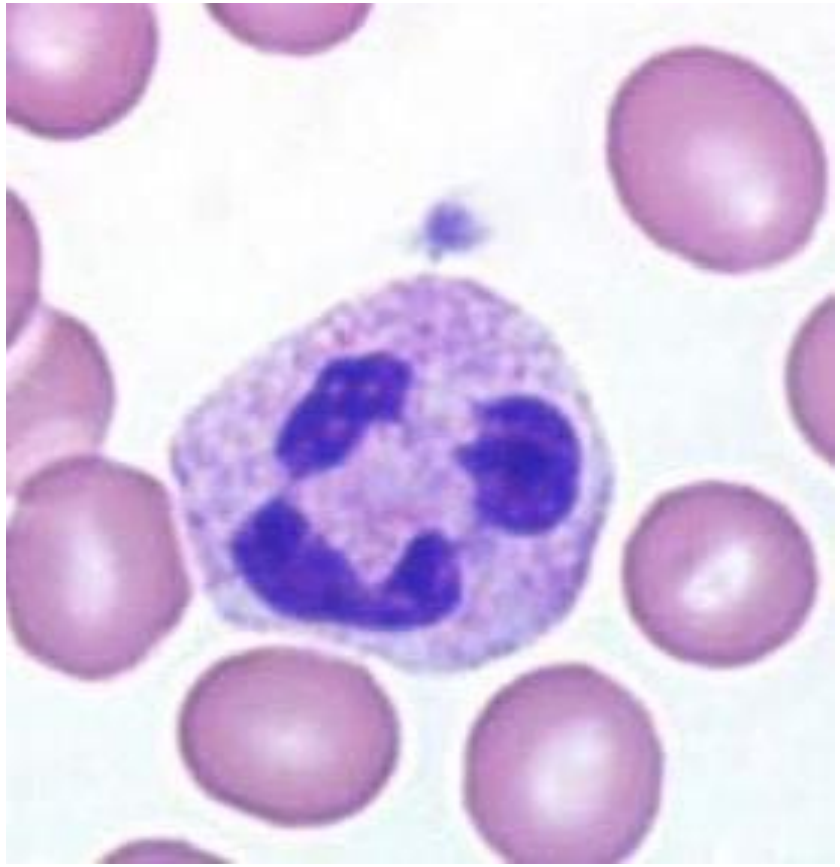
- Other SACT can cause FN
  - 5-10% of patients on cyclin dependant kinase 4/6 inhibitors get severe neutropenia
  - Anti-PD1 blockade - 0.9% risk of neutropenia and 0.45% risk of FN (Petrelli EJC 2018).

Other risk factors for Febrile Neutropenia

- Age over 65
- Poor performance status
- Metastatic disease
- Poor nutritional status
- Mucositis
- Co-morbidities especially cardiovascular
- Previous history of FN

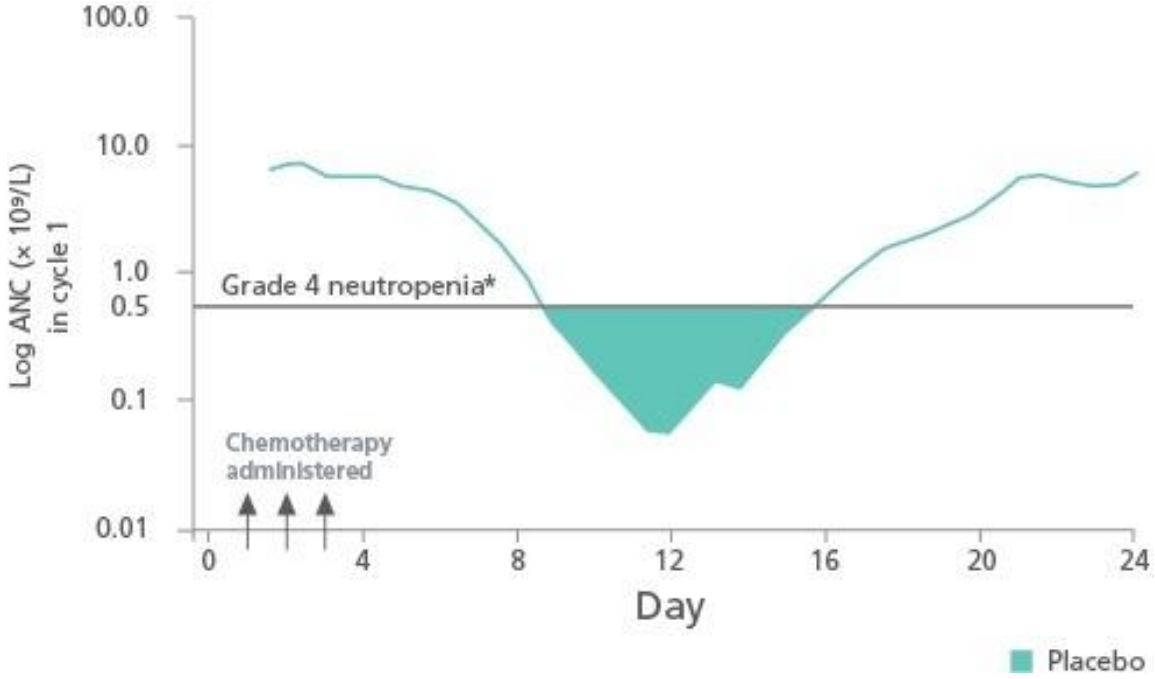
The neutrophil

- Frontline defence of the innate immune system.
- Quick response to inflammatory stimuli.
- Half life 6-8 hours.
- Directly kill organisms by
  - Phagocytosis
  - Degranulation
  - Production of neutrophil extracellular traps (NETS)
- Release cytokines and chemokines
  - Promotes inflammation
  - Attracts other immune effector cells



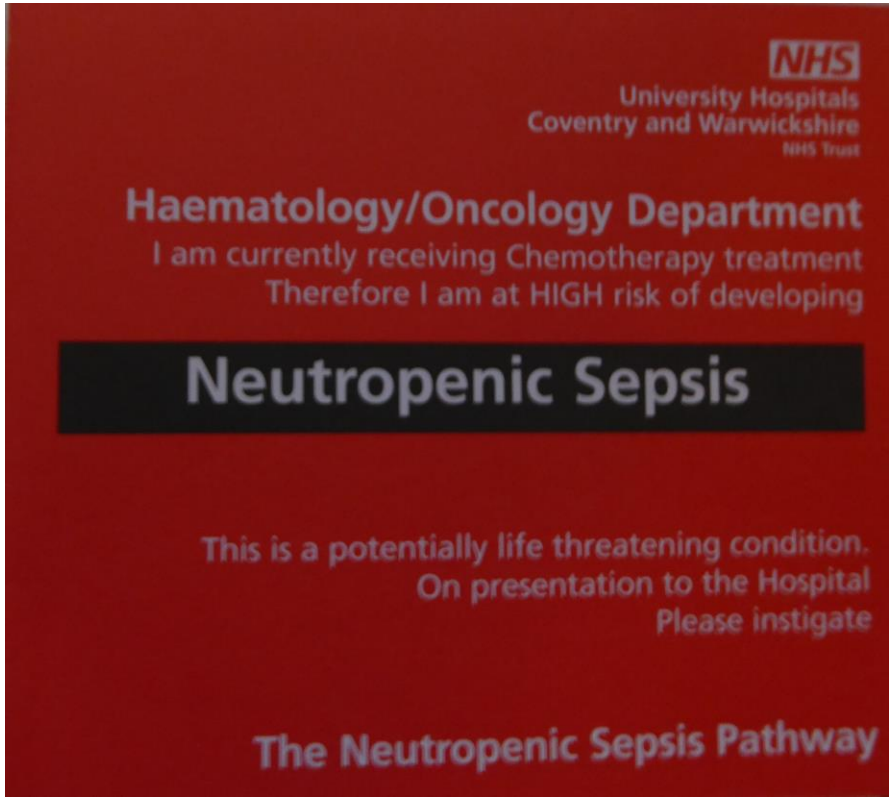
Neutropenia

- Most standard chemotherapy regimens are associated with 6-8 days of neutropenia.
- Caused by effects of chemotherapy on differentiating cells in the bone marrow.
- Neutrophil nadir varies with drugs and regimens.
- Risk of infection affected by depth and duration of neutropenia



Management of SACT related cytopenia risk

- Safety net information for patients - signs to look out for / check temperature regularly
- FBC before each dose of chemotherapy
- Delay until blood counts recovered
- Use of prophylactic G-CSF in high risk regimens



NICE Guidance

- **1.3 When to refer patients in the community for suspected neutropenic sepsis**
- 1.3.1.1 Suspect neutropenic sepsis in patients having anticancer treatment who become unwell.
- 1.3.1.2 Refer patients with suspected neutropenic sepsis immediately for assessment in secondary or tertiary care.

NICE guidelines: management

1.4 Managing suspected neutropenic sepsis in secondary and tertiary care

1.4.1 Emergency treatment and assessment

1.4.1.1 Treat suspected neutropenic sepsis as an acute medical emergency and offer empiric antibiotic therapy immediately.

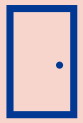
1.4.1.2 Include in the initial clinical assessment of patients with suspected neutropenic sepsis:

- history and examination
- full blood count, kidney and liver function tests (including albumin), C-reactive protein, lactate and blood culture.

Immediate Management

START TREATMENT AT POINT OF SUSPICION

Immediately: Take bloods and administer 1st IV antibiotics (DON'T wait for FBC result)



Door to needle time for first antibiotics should be less than one hour.

Question

How good do you think we are at delivering correct antibiotics within 1 hour?

- 90%
- 75%
- 50%
- 25%
- Less than 25%

Clinical assessment:

History

- Date of last SACT
- Duration of fever
- Localising symptoms
- Presence of a PICC line / PORT
- Check for previous antibiotic resistance

Examination

- Observations
- Clinical examination ? Focus of infection

Suspicion of Neutropenic Sepsis Screening Tool

NHS University Hospitals Coventry and Warwickshire NHS Trust

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To be applied to all non-pregnant adults over 16 with a suspicion of neutropenic sepsis or who are clearly unwell with any abnormal observations

Staff member completing form: suspicion of sepsis time

Date (DD/MM/YY):

Name (print):

Designation:

Signature:

FOR SCANNING PURPOSES
AFFIX PATIENT LABEL

Important: Is an Individual Plan of Care for the Dying Person in place? (✓) Yes ☐ No ☐
If YES; de-escalate the sepsis screening tool and refer to the patients Individual Plan of Care for the Dying Person for the management plan.

Observation time (:) NEWS2 score ( )

1) Is the patient likely to be neutropenic?

	(✓)
Received chemotherapy in the last 6 weeks?	☐
Known neutropenia for other reason?	☐

If yes → If no → Discontinue the sepsis screening tool and document in the medical notes; review if deteriorates

2) Are any of the below present?

	(✓)
Suspicion of infection? (Consider infective cause)	☐
Patient presenting with a fever >38°C (measured at home or in A&E)? OR <36°C	☐
History of rigors, feeling hot or cold?	☐

If yes → If no → Discontinue the sepsis screening tool and document in the medical notes; review if deteriorates

Red Flag Sepsis start Sepsis 6® pathway Now (see overleaf)
This is time critical, immediate action is required.

If you suspect Sepsis, you have 1 hour to give prescribed IV antibiotics.

Complete the Sepsis 6® then liaise with teams below:		
Acute Oncology Nurses	(Available: 24/7)	Bleep 1641
Oncology Registrar	(Available: 9am – 5pm, 7 days a week)	Bleep 1660

Suspicion of Neutropenic Sepsis Six® pathway

NHS University Hospitals Coventry and Warwickshire NHS Trust

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To be applied to all adults and young people over 16 years of age with suspected or confirmed Red Flag Sepsis.

Make a treatment escalation plan and decide on CPR status
Inform clinician (Use SBAR) patient has Red Flag Sepsis

clinician informed (✓) ☐ — Name and signature of clinician

Action (complete ALL within 1 hour)	Time complete	Initials	Reason not done/variance
1. Administer oxygen Aim to keep saturations > 94% (88-92% in NEWS2 scale 2)			
2. Take peripheral blood cultures. Also take full bloods (FBC, U+Es, LFTs, CRP, lactate and clotting) Blood cultures to be taken from indwelling catheter if present - only done if staff are appropriately trained to do so			
3. Give broad spectrum IV antibiotics **Tazocin** 4.5g QDS + **Gentamicin** 5mg/Kg **ONE DOSE ONLY** ** If history of infections with **Extended Spectrum Beta-Lactamase (ESBL) producers** in the past, use **Meropenem** 1g TDS IV infusion instead of Tazocin. *If Penicillin allergic give:* 1. Non-severe reactions including delayed, non-urticarial rash: **Meropenem** 1g TDS + **Gentamicin** 5mg/Kg **ONE DOSE ONLY** ** 2. Severe reaction including Anaphylactic / accelerated reaction (e.g. within 24 hours): **Gentamicin** 5mg/kg **ONE DOSE ONLY** ** + **Ciprofloxacin** 400mg BD + **Teicoplanin** 600mg OD 12 hourly for first 3 doses and then 600mg 24 hourly thereafter. **Note:** The dose is 800mg for patients with an estimated lean body mass of >80kg. In renal impairment please see Trust Teicoplanin policy. ** See CG1932 for maximum dose of Gentamicin and further information surrounding monitoring and renal function			
4. Give IV fluids (use with caution in renal and heart failure) If hypotensive / lactate ≥2mmol/l, 500 ml stat. May be repeated if clinically indicated - do not exceed 30ml/kg/ideal body weight. If applicable call the Acute Team now if ≥2.5L administered with no improvement - Acute Team contact details below			
5. Check serial venous lactates Avoid arterial blood gas due to thrombocytopenia. If lactate >4mmol/l, call the acute team, recheck after each 10ml/kg fluid challenge. If not reducing contact ITU reg (bleep 1634)			
6. Measure urine output Review blood results before considering catheterisation (high risk of thrombocytopenia and/or neutropenia) commence hourly fluid balance monitoring			Is catheter required? Yes No

If after delivering the Sepsis Six®, patient still has:
- Systolic B.P <90 mmHg
- Reduced level of consciousness despite resuscitation
- Respiratory rate over 25 breaths per minute
- Lactate not reducing or over 4mmol/l

Or if patient is clearly critically ill immediately contact one of the Acute Team

Acute Team
- Critical Care Outreach bleep 2909
- Hospital at Night (after 20.00hrs) via Hahbleep
- ITU reg bleep 1684
- For Rugby SHO bleep 4127

Check CRRS for infection alerts

Patient not clinically septic
See alternative treatment plan documented in medical notes

DESIGNATION	
PRINT	
SIGNATURE	
BLEEP	
DATE / TIME	/ / :

Investigations

Bloods:

- Full blood count, kidney and liver function tests (including albumin), C-reactive protein, lactate.
- Blood cultures – peripheral and central.

Bedside

- Urine culture, viral PCR, stool culture, throat swab, sputum.

Imaging

- Directed by symptoms eg CXR

Management

Antibiotics

- Does the patient have a penicillin allergy?
- Start broad spectrum antibiotics as per local guidance, typically Tazocin
- IV gentamicin as directed local microbiological guidance
- Investigations to identify possible source of infection

Sepsis management

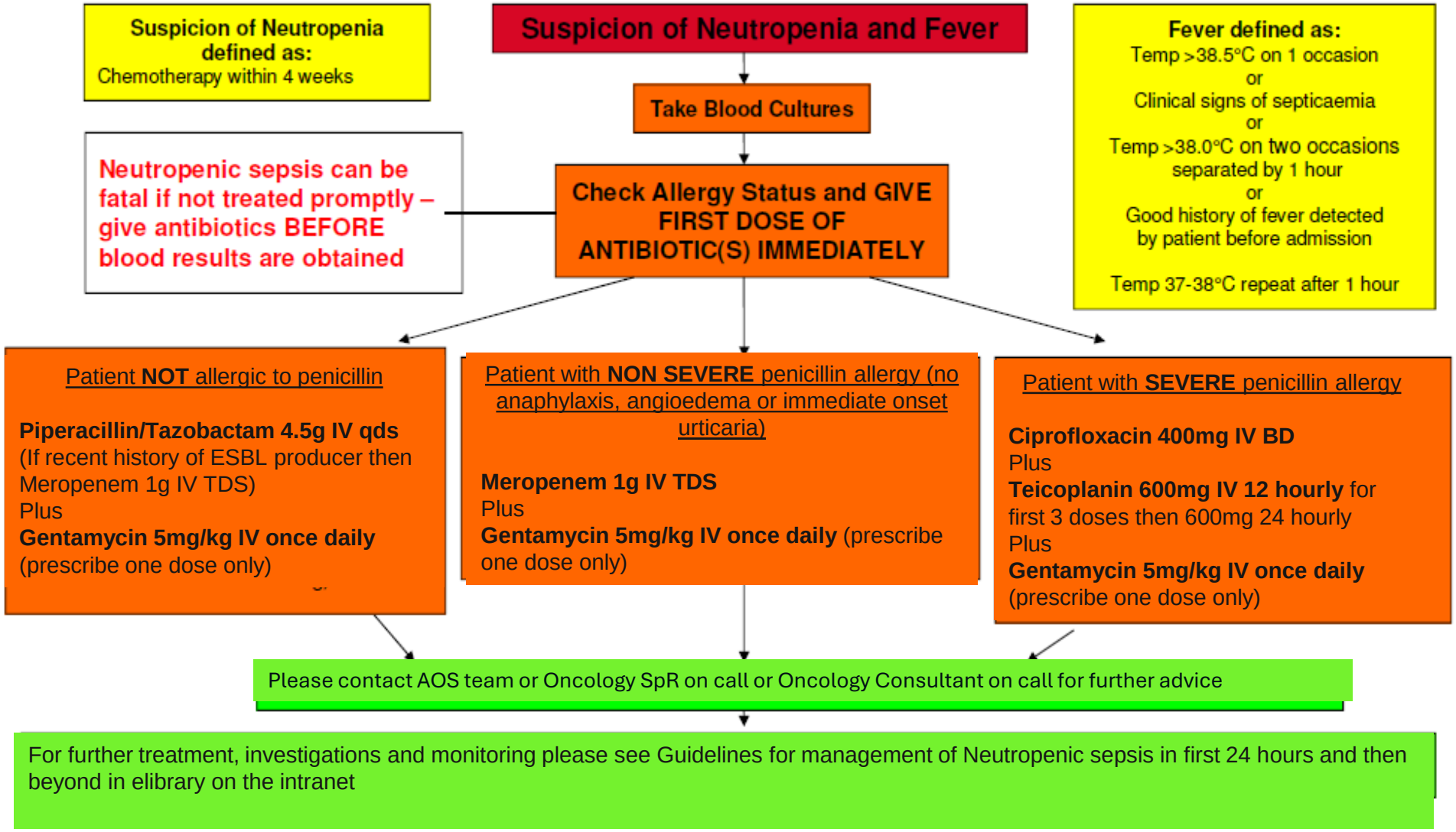
- IV fluids, oxygen
- Fluid balance
- Plan for monitoring

Involve other teams

- Refer to local acute oncology services
- Consider referral to outreach / ITU

Christie NHS Trust: Clinical guidelines for the management of sepsis (incl neutropenic sepsis)
Management of febrile neutropaenia: ESMO Clinical Practice Guidelines, Klastersky, J. et al. Annals of Oncology, Volume 27, v111 - v118

Summary of Guidelines for the Immediate Management of Suspected or Confirmed Febrile Neutropenia in Oncology Patients



Additional antimicrobials

Line infection

- Consider adding Teicoplanin via lumen of line

Abdominal sepsis

- Add metronidazole

Mouth ulceration

- Fungal infections – fluconazole
- Herpes simplex – acyclovir

Risk assessment

- MASSC score
- Score 21 or above – low risk of complications – 5% mortality rate
- Score less than 15 – high risk of mortality (up to 40%).

Characteristic	Score
Burden of illness: No / mild symptoms Moderate symptoms Severe symptoms	 5 3 0
No hypotension (systolic BP > 90mmHg)	5
No COPD	4
Solid tumour / lymphoma with no previous fungal infection	4
No dehydration	3
Outpatient at time of fever	3
Age less than 60	3

Management from day 2 onwards

Afebrile and ANC > 0.5 at 48 hours:	Low risk and no cause of infection consider switching to oral antibiotics. High risk and no cause for infection continue IV antibiotics
Febrile at 48 hours:	Clinically stable continue IV antibiotics Clinically unstable – discuss with microbiology, consider switch to meropenem
Continues to be febrile beyond day 4:	Consider unusual infections Consider CT thorax and upper abdomen Consider starting empirical anti-fungal

Management of febrile neutropaenia: ESMO Clinical Practice Guidelines, Klastersky, J. et al. Annals of Oncology, Volume 27, v111 - v118
Early discontinuation of antibiotics for febrile neutropenia versus continuation until neutropenia resolution in people with cancer (Review) Cochrane review 2019

Duration of antibiotic therapy

Neutrophils > 0.5 x 10^9/l may stop if afebrile for 3 days and:

- All sites of infection resolved
- Falling CRP
- Patient has no signs / symptoms
- Negative blood cultures

Neutrophils < 0.5x10^9/l:

- Low risk and factors above are met, stop if afebrile for 5 days
- High risk continue for 10 days or until ANC >0.5

Use of Granulocyte-Colony Stimulating Factor (G-CSF)

Should not used in routine management of neutropenic sepsis.

- Does not shorten duration of fever or antibiotic course

Indicated if severe neutropenia (<0.1 x 10^9/L)

And any of the following:

- Age over 65
- Expected prolonged neutropenia (>10 days)
- Hypotension
- Pneumonia
- Multi-organ dysfunction
- Hospitalised at time of development of fever
- Invasive fungal infection

Microbiology

- Only 20% patients have positive blood cultures.
- Increased risk of mortality with proven bacteriaemia
- Gram positive cocci are now more common than Gram negative bacilli.
- Fungal infections can occur after prolonged periods of neutropenia

Other cytopenias

- Anaemia
  - Use packed red cells as needed

- Thrombocytopenia
  - Threshold for platelet transfusion is 20 x 10 /l in patients with febrile neutropenia

Ambulatory care of patients with low risk febrile neutropenia

- Initial full assessment and delivery of IV antibiotics within 1 hour.
- Criteria for selection
  - Low risk of complications: MASCC score > 21
  - No known antibiotic resistance
  - Psychosocial: live within 1 hour, family member present 24/7, compliance
- Choice of antibiotics
  - Fluoroquinolone and co-amoxiclav
- Follow up
  - Daily review for 3 days
  - If no improvement, admit to hospital

- Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update. JCO 2018 36: 1143
- Ambulatory management of low-risk febrile neutropenia in adult oncological patients. Systematic review. Supportive Care in Cancer 2023 31: 665

Summary

- Febrile neutropenia / neutropenic sepsis are common in patients receiving systemic anti-cancer treatment
- Mortality rate 10%
- Make yourself aware of your local neutropenic sepsis guidelines
- Immediate management – IV antibiotics within 1 hour, don’t wait for FBC results
- Manage sepsis aggressively – may need outreach / ITU referral
- Involve your local acute oncology team
- Review patients on at least a daily basis and alter antibiotics as needed