



GUIDELINES FOR THE MANAGEMENT OF SEPSIS (INCLUDING NEUTROPENIC SEPSIS)

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Target audience:	Greater Manchester & Cheshire Cancer Network All clinicians		

Key points

- Sepsis'
- 'Systemic Response Syndrome'
- Neutropenia definitions.
- Assessment of septic patient
- Initial treatment, febrile at Day 4-6.
- Antibiotics, Empirical Treatments, removal of IV Lines, suitable IV antibiotic regimens.
- Early and appropriate assessment and treatment of patients with life threatening infections

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1. ASSOCIATED DOCUMENTS

[Guidelines for Hand Hygiene](#)

[Standard Precautions policy](#)

[Patient Isolation policy](#)

[Guidelines for Aseptic Technique](#)

[Sepsis Resuscitation Bundle](#)

[Guidelines for Management of Severe Sepsis and Septic Shock](#)

[NCP 29.0 - Care plan for the patient with neutropenia / neutropenic sepsis](#)

[550 Sepsis CCU](#)

2. INTRODUCTION

From 2012 onwards, Acute Oncology teams at all acute Trusts and the Christie will support the care of cancer patients who present as an emergency, especially those on current or recent treatment. For patients undergoing treatment for cancer, all infective episodes need to be rapidly assessed and treated urgently with antibiotics.

2.1 Purpose

To adhere to NICE and Peer review guidelines

2.2 Scope

This document applies to all clinical staff.

3. DUTIES

The Acute Oncology Group is now responsible for this document, under the direction of Dr P Haji-Michael.

4. MANAGEMENT OF FEBRILE CANCER PATIENTS

All Christie-registered patients on chemotherapy treatment will have been issued with an information card which will detail information about their chemotherapy regimen and the recommended empiric antimicrobial treatment. This will also provide an immediate contact number which may be the chemotherapy team (in working hours) or the Christie Acute Oncology Management Service (AOMS) incorporating the Hotline. The latter provides 24 hour advice, 7 days / week to patients and professionals.

For patients under treatment at The Christie seen in other Trusts, the AOMS should be contacted on 0161-446-3658 for advice on how to manage the patient locally or referral back to the centre.

Clinicians may also seek advice from the responsible oncology team and additional microbiology advice from the local or Christie microbiologist if needed.

Up to 60% of febrile neutropenic patients prove to have infections and 16-20% of those with a neutrophil count $<100/\text{mm}^3$ have a bacteraemia. Fever is commonly as a result of bacteraemia and usually due to Gram positive cocci (e.g. coagulase negative staphylococci, *Staphylococcus aureus*, viridans streptococci) or Gram negative bacilli (eg *Escherichia coli*, *Klebsiella* spp, *Pseudomonas aeruginosa* etc).

Fungal infections tend to occur after patients have received broad-spectrum antibiotics and have had prolonged periods of neutropenia but may present as primary infections.

Infections in neutropenic patients typically take 2-7 days to respond to antimicrobial therapy. Acute respiratory viral infections e.g. influenza or respiratory syncytial virus may be associated with severe illness in the immunocompromised host.

Fever may be absent in some infected patients who are dehydrated, severely 'shocked' (see below), taking steroids or NSAIDs.

The possibility of infection must be considered in any patient undergoing treatment for cancer who is unwell and particularly in those who are neutropenic.

Conversely fever may be a complication of non infectious causes eg transfusion, drugs such as cytarabine, and malignant disease such as lymphoma and renal carcinoma.

5. DEFINITIONS

5.1 Definitions of 'Sepsis' and 'Systemic Inflammatory Response Syndrome'

Patients are often described as being "septic" or having "septic shock". These terms are used in a variety of ways by different doctors and in 1992 'sepsis' and several new terms were formally defined:

- Systemic inflammatory response syndrome (SIRS) replaced the previous term 'sepsis syndrome'. This is the body's response to a variety of severe clinical insults. It is characterised by the presence of two or more of the following features:
 - Temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$
 - Heart rate $> 90/\text{min}$
 - Respiratory rate $> 20/\text{min}$ or $\text{PaCO}_2 < 4.3\text{kPa}$
 - White cell count $> 12 \times 10^9/\text{l}$ (in those with normal bone marrow activity)
- Sepsis is defined as SIRS in response to infection.
- Severe sepsis is sepsis associated with:
 - organ dysfunction (altered organ function such that normal physiology cannot be maintained without support)
 - hypotension (systolic blood pressure $< 90\text{mmHg}$ or a reduction of $> 40\text{mmHg}$ from the patient's normal in the absence of other causes of hypotension)
 - organ hypoperfusion (revealed by signs such as lactic acidosis, oliguria, acute alteration of mental status).
- Septic shock describes sepsis with hypotension despite adequate fluid resuscitation.
- Multiple organ dysfunction syndrome (MODS) describes a state where dysfunction is seen in several organs.

5.2 Definition of neutropenia

Increased susceptibility to infection is likely when the neutrophil count falls below $1000/\text{mm}^3$ with escalating risk at $<500/\text{mm}^3$ and at $<100/\text{mm}^3$.

The risk of infection is greater the faster the rate of decline of the neutrophil count and the longer the duration of neutropenia especially if neutropenia lasts for > 10 days.

Do not delay administration of antibiotics whilst awaiting WCC results.

6. CLINICAL ASSESSMENT OF THE SEPTIC PATIENT

Carry out a full history and examination immediately and initiate antibiotic treatment as soon as possible. ***This should be achieved within ONE HOUR from diagnosis of acute sepsis.***

The care pathway and system to monitor 'door to needle times' will be included as a future appendix to this document.

6.1 Initial assessment

Initial management of the acutely unwell septic oncology patient includes:

- Immediate assessment of the airway, breathing and circulation
- A brief history
- A limited examination of the relevant systems of the body.
- Initiation of appropriate monitoring, observations and bedside investigations
- A secondary assessment after stabilisation of the patient including a more thorough history, detailed examination by system and appropriate investigations.
- The formulation and communication of an appropriate plan including when to involve other clinical teams

The management plan should include an agreed frequency of physiological observations, with a standard trigger (Modified Early Warning Score, MEWS) for recontacting the parent clinical team or critical care outreach. Because there are often many groups involved and with many time sensitive tasks to perform, it would be appropriate for Trusts to formulate this guideline as a locally agreed Integrated Care Pathway.

There are clear unambiguous guidelines as to the initial (<6hr) and late (<24hr) management set out and agreed by all the major international critical care and infection control organisations. This is often referred to as the Surviving Sepsis Campaign. They are summarised in appendix 1 with their level and grade of evidence.

6.2 History and examination

Expected onset and anticipated duration of neutropenia may be estimated by establishing day of neutropenia in relationship to first day of the current cycle of chemotherapy.

It is useful to enquire whether:

- blood products have been administered within the previous 6-24 hours as this may account for a febrile episode.
- rigors are associated with use or flushing of a central venous line.

Check the patient record (notes and electronic annotations) for alerts such as previous infection with *Clostridium difficile* or multidrug resistant organisms.

When looking for a focus is important to enquire and look for inflammation/infection at the following sites and sample as appropriate:

- Mouth – teeth, gums, pharynx
- ENT problems esp. involving sinuses
- Eyes including fundi
- Upper gastrointestinal symptoms
- Lung – cough, shortness of breath, sputum

- Perineum especially anal area (defer PR examination until antibiotics started)
- Diarrhoea – if present, isolation precautions are advisable – discuss with a member of the infection prevention and control team (Christie ext 3731)
- Skin lesions – (NB think about fungal, *Pseudomonas aeruginosa*, generalized herpes and *Varicella zoster* infections)
- Look for genito-urinary infections or discharges. Consider the possibility of reactivation of genital herpes, fungal infection and necrotising fasciitis.
- Look at: vascular access sites especially central venous line insertion sites, bone marrow aspiration sites, nail margins, skin tunnels, surgical incision sites etc.

A full systems review should include a thorough history of overseas residence and travel, pets, hobbies, occupation, sexual history and potential environmental exposures to unusual organisms. Important overseas related organisms might include strongyloides and *Salmonella typhi* (Typhoid fever)

6.3 Investigations

- Full blood count (FBC)
- CRP (if routinely available as an urgent investigation)
- Urea and electrolytes (U+Es)
- Liver function tests (including albumin)
- Coagulation screen
- Group and save
- Blood gases (including lactate)
- ECG if hypotensive or having chest pain
- Chest radiography (if indicated)
- Abdominal ultrasound – if there is suspicion of biliary obstruction, hydronephrosis or renal failure
- Cultures of lesions - including culture for fungi – (Biopsy specimens for fungal or bacterial culture MUST NOT be sent in formalin. Histology should also be considered (send in formalin or other fixative as after discussion with Pathology)
- Stool microscopy, culture and *Clostridium difficile* toxin detection, cryptosporidium if diarrhoea - also consider whether virology would be useful - send faeces in clean plain container for electron microscopy. For gastroenteritis send samples for EM and Virology PCR.
- Urinalysis and culture - if urinary symptoms present or patient catheterised
- Blood cultures - peripheral and also through iv catheter lumens (should take blood through each lumen of line)
- Mycobacterial blood culture should be sent in special MBBact bottles if MAI is suspected.
- Respiratory secretions for rapid testing by PCR, e.g. nasal wash, NPA, BAL. Direct viral detection by PCR is the preferred method for diagnosing respiratory viral infections and can be done using NPA, BAL or if not available by nose and throat swab.
- A clotted blood sample (7-10ml, plain tube) should be sent for viral serology and a convalescent sample sent 10-14 days later if appropriate)

If *Varicella zoster* or *Herpes simplex* is being considered:

- Send a glass slide touched against an opened lesion and allowed to air dry, and transported in a slide carrier (vesicular skin lesion kit)
- swabs and blood for viral PCR
- send serum (clotted blood) for IgG and IgM.

Also in VZ - remember infection control precautions are needed to protect both staff and other patients – discuss with a member of the infection prevention and control team.

- Patients who are not getting better or are at high risk of a fungal infection should be discussed with the radiologists regarding appropriateness of additional imaging e.g. HRCT (especially useful for diagnosis of pulmonary aspergillosis), MRI, radionuclide imaging or ultrasonography.

If invasive fungal infection is being considered:

- Send EDTA blood for Aspergillus and Candida PCR
- Aspergillus galactomannan may be useful on clotted blood , CSF and BAL fluid
- Culture and PCR on sputum, BAL and other material e.g. CSF, skin biopsy.

If CMV is being considered e.g. after bone marrow transplantation:

- Send EDTA blood-for CMV PCR.
- Consider CMV PCR on BAL and GI biopsy

If Pneumocystis pneumonia is being considered:

Send bronchial washings (or if these are unobtainable then sputum or EDTA blood) for *Pneumocystis jirovecii* (PCP) PCR

- Bronchial washings should be routinely microscopically examined and cultured for bacteria, fungi, and mycobacteria.

6.4 Follow up assessment

- FBC daily
- U + Es, LFTs and coagulation at regular intervals depending on clinical features
- Serial CRPs or other acute phase reactants
- If fever persists, repeat blood cultures based on clinical assessment
- Repeat chest radiology as clinically indicated

7. INITIAL TREATMENT

7.1 Who to treat

- All febrile patients with neutrophil counts $<500/\text{mm}^3$ and those whose counts are $<1000/\text{mm}^3$ but are falling rapidly.
- Afebrile patients with neutrophil counts $<500/\text{mm}^3$ should also be treated if they have symptoms compatible with infection.

7.2 Definitions of high and low risk patients with neutropenia

7.2.1 High risk patients

- Those who are already in-patients when fever and neutropenia develop
- Outpatients who need acute hospital care for problems in addition to the fever and
- neutropenia
- Outpatients with uncontrolled cancer (e.g. acute leukaemia not in remission, those with tumours progressing during anticancer therapy)

- Patients on immunosuppressive agents e.g. cyclosporin A, steroids
- Patients with specific foci of infection e.g. intravascular catheter infection, tunnel infection,
- new pulmonary infiltrate
- Presence of any of the following features
 - abdominal pain, nausea and vomiting, diarrhoea
 - neurological or mental changes
 - allogeneic BMTs or autologous BMT
 - pregnancy
 - HIV
 - recent treatment with antibiotics (within previous 72 hours)
 - renal failure (creatinine clearance <30ml/min)
 - hepatic failure
 - respiratory insufficiency
 - haemodynamic instability
 - inability to take oral medications
- Neutropenia likely to last for more than 10 days
- Recent fludarabine treatment
- MEWS ≥ 3
- Phase I or II clinical trial patients (inform investigator)

7.2.2 Low risk patients

All those not in the above categories or MEWS ≤ 3 . If in doubt, treat as high risk patient.

7.3 Empirical treatment of high risk septic patients - suitable iv antibiotic regimens

NB. All antimicrobial doses are approximate and may need to be altered according to patient's clinical condition, weight and renal function etc.

Preferred Treatment

Piperacillin/Tazobactam 4.5g tds plus gentamicin*

In the event of specific concern about meticillin resistant or coagulase-negative *staphylococcal* sepsis, vancomycin can be given pending susceptibility testing results.

**Gentamicin 5 mg/kg (or dose as per local guidance) normally given as a single daily dose unless advised otherwise. Levels should be checked 16 - 20 hours after the first dose (and satisfactory clearance annotated) and then at least every 3 to 4 days (more frequently if there is evidence of renal impairment) according to local protocols*

Alternative Treatment

(If penicillin allergic, has poor renal function or if patient has received reno-toxic chemotherapy regimes (i.e. cisplatin, ifosfamide, high dose methotrexate and trabectedin)

Meropenem 1gm tds (or equivalent carbapenem).

In patients with renal impairment (creatinine clearance less than 50 ml/min) dose adjustment is required (see SPC).

Patients who have had platinum-based treatment in the more distant past (ie more than 7 days ago) or have had other potentially nephrotoxic treatment can still receive

Piperacillin/Tazobactam 4.5g TDS plus gentamicin – as above – but should have frequent review and monitoring of renal function.

Only consider including a glycopeptide (e.g. vancomycin) as first line treatment if:

- IV catheter related infection e.g. signs of inflammation around the catheter insertion point or along catheter track
- MRSA or penicillin resistant pneumococci are likely
- Patient has severe mucositis

Antibiotics should be given through each lumen of an involved IV catheter on a rotational basis if there is an infection of a multi-lumen catheter.

If the patient is poorly or deteriorating or if there is no improvement within 24 - 48 hours, contact the relevant oncologist, haematologist or microbiologist (for Christie patients via switchboard 0161-446-3000).

Local Trust policies for prompt administration of antibiotics to patients with suspected neutropenic sepsis (Door to needle or Door to mouth) should be followed in conjunction with these guidelines.

7.4 Treatment of low risk patient – oral antibiotic regimen

Ciprofloxacin 750mg bd OR Co-amoxiclav 625mg tds
This will normally be informed by culture results and/or clinical findings

Other oral antibiotic options:

Levofloxacin or equivalent quinolone (NB this may be less effective in *Pseudomonas* infections)

Clindamycin (if Gram positives and anaerobes are likely to be responsible e.g. cellulitis, fasciitis)

Neutropenic patients with fever should be managed in hospital but may be treated as outpatients at the discretion of the responsible clinician.

If low risk hospitalised patients are stable on antibiotic therapy, consider discharge home to continue oral antibiotics as an option if:

- patient is mentally competent,
- lives near the hospital (within an hour),
- has someone at home all the time,
- has access to transport and a telephone and
- home conditions are deemed satisfactory.

8. REASSESS AT 48 HOURS

If afebrile at 48 hours:

No cause found

- MEWS \geq 3
- Low risk – consider change to oral antibiotics if not already on them
- *High risk – discontinue aminoglycoside at 48 hrs if on dual therapy*

Cause found

- **Continue on appropriate antibiotics based on susceptibility test results**

If persistent fever at 48 hours

Reassess daily with repeat of history taking and clinical examination and repeat laboratory investigations and consider fungal infection and order radiology as clinically appropriate.

No change i.e. remains febrile “but well”

Continue antibiotics - consider stopping aminoglycoside at 48 hours if cultures negative and no focus evident.

If deteriorating

- Rotate antibiotics eg piperacillin/tazobactam to meropenem
- Consider adding in a glycopeptide eg vancomycin if there is evidence of a line infection or mucositis.

Antibiotics should be given through each lumen of an involved iv catheter on a rotational basis if there is an infection of a multi-lumen catheter

9. IF STILL FEBRILE AT DAY 4-6

Order investigations for fungal infection, including urgent HRCT Chest. Depending on availability other investigations such as Aspergillus PCR, PCP PCR, Galactomannan or Beta Glucan may be useful. Consider bronchoscopy if patient is stable enough

If radiology is suggestive of fungal infection: start appropriate antifungals

If radiology is negative: review patient and look for other sources of on-going fever

If possibility of fungal infections is suggested: start voriconazole or Ambisome (if drug interactions with azoles may be an issue). For Christie haematology patients contact the attending Consultant Haematologist for advice.

If positive BAL for fungi, or Aspergillus PCR or galactomannan assay is positive, review with clinical condition and radiology findings.

For proven/probable aspergillus: start voriconazole or Ambisome (if drug interactions with azoles are an issue)

For proven zygomycete infection eg.mucor: start posaconazole or Ambisome. Discuss with microbiology.

NB. Experienced oncologists/microbiologists may choose to prescribe doses that fall outside the manufacturer’s license (please consult BNF or respective SPC and see note on page 11).

10. DURATION OF ANTIBIOTICS

- Patients with neutrophil count greater than/equal to 500/mm³

After review may stop antibiotics if patient has been afebrile for 3 days if:

- a) cultures indicate organism eradicated
- b) all sites of infection have resolved
- c) patient free of signs and symptoms
- d) falling acute phase reactants eg CRP

- **Patients with neutrophil count less than 500/mm³**

-low risk and above factors a) to d) met,

stop antibiotics when patient has been afebrile for 5 days

-high risk (eg if patient has mucositis, ulcers, bleeding points, iv-catheter site infection present or if invasive procedures or ablative chemotherapy pending)
continue antibiotics so that patient receives at least 10 days treatment in total or until neutrophils $>500/\text{mm}^3$

Patients who have antibiotics stopped while they are still neutropenic should be monitored closely for signs of recurrent infection and fever and if these occur intravenous antibiotics should be started again

Patients who remain febrile after their neutrophil counts have returned to $500/\text{mm}^3$ should be assessed for the presence of fungal infections (consider evaluation of liver and spleen by ultrasonography for hepatosplenic candidiasis, CT, or MRI scans, serum for galactomannan, EDTA blood for candida and aspergillus PCR, and PCR for viral infections).

11. COMMON MODIFICATIONS TO INITIAL EMPIRICAL TREATMENT IN NEUTROPENIC PATIENTS

Bacteraemia

1) Pre-antibiotic cultures yield:

- Gram-positive isolate (other than meticillin-sensitive *Staphylococcus aureus*) - add a glycopeptide (eg vancomycin 1g bd (check levels and use lower dose if renal impairment) if patient has not responded satisfactorily pending full identification and sensitivities. Teicoplanin may be considered for out-patient requiring once daily administration
- Gram-negative isolate – if stable continue current regimen – if unstable consider adding an aminoglycoside especially if *Pseudomonas* is likely

2) *Organism isolated while on antibiotics*

Is an abscess present that needs draining? Is there evidence of endocarditis?

- Gram-positive isolate – consider adding a glycopeptide if not already on one; if already on a glycopeptide review antibiotic sensitivity as the organism might be a VRE or GISA (glycopeptide intermediate *Staph aureus*). If glycopeptide resistant use linezolid 600mg bd iv or orally or alternatively (if MRSA, GISA or glycopeptide resistant *Enterococci*) daptomycin. Note that daptomycin must not be used if there is evidence of pneumonia.
 - These decisions should be made after discussion with a microbiologist.
- Gram-negative isolate – change to a new combination regime based on sensitivity test results
- For *Stenotrophomonas maltophilia* consider using cotrimoxazole (1.44gm (three 480mg tablets) PO BD) or Timentin.

Head, ear, eye, nose and throat

Gingivitis – add metronidazole (500mg tds iv)

Vesicular or ulcerative lesions – consider HSV and VZ. Add aciclovir 5mg/kg tds iv for herpes simplex, 10mg/kg tds iv for VZ infection. For early lesions if not

widespread or haemorrhagic consider oral aciclovir 400 mg five times a day for HSV, 800 mg five times a day for VZ, or valaciclovir 500mg bd for HSV, 1g tds for VZ.

Sinus tenderness or nasal ulcerative lesions – suspect fungal infection eg aspergillus or zygomycetes such as mucor.

Gastrointestinal

Retrosternal symptoms – consider endoscopy – likely organisms include candida (add fluconazole 100 - 400mg daily) or HSV (add aciclovir). In severely immunocompromised patients CMV should be considered and could be diagnosed by PCR on gastric secretions or biopsy.

Acute abdominal pain – seek surgical advice – add metronidazole.

Perianal lesions – add metronidazole – consider surgery when not neutropenic. If HSV reactivation a possibility add aciclovir.

Diarrhoea – consider Clostridium difficile

This is a common cause of watery diarrhoea in hospitals and usually (but not always) follows antibiotic therapy. The elderly are at greater risk. Symptoms range from mild, self-limiting diarrhoea to life-threatening Pseudomembranous Colitis, with fever, leucocytosis and abdominal pain. Send stool for CDT test, but start treatment straight away if clinically indicated. Consider sigmoidoscopy and get urgent surgical review in severe illness if diagnostic uncertainty.

Risk factors include:

- Elderly patients > 65years (Greatest risk in > 75 years age group)
- Immunocompromised
- Exposure to antibiotics in particular 2nd / 3rd generation cephalosporins, fluoroquinolones, clindamycin
- Prolonged hospitalisation; Stay on ICU
- Administration of multiple antibiotics, multiple courses or prolonged courses
- Underlying disease
- Non-surgical GI procedures
- NG tube
- Anti-ulcer medications – e.g. proton pump inhibitors
- Previous, recent *C. difficile* diarrhoea

Minimising risk factors for *C. difficile*-associated diarrhoea (CDAD) by reducing exposure to antibiotics (number of agents and course duration) is important.

Antibiotics such as piperacillin / tazobactam, metronidazole, rifampicin, vancomycin and gentamicin are less likely to precipitate *C. difficile* diarrhoea.

Hand washing with soap and water is essential as alcohol gel is ineffective in killing many enteric organisms.

Specific treatment for *C. difficile* diarrhoea:

- For mild diarrhoea, withdrawal of precipitating antibiotics may suffice.
- For all patients STOP current antibiotic therapy if possible. If antibiotics are still required for an ongoing infection, discuss the choice with microbiology. Avoid cephalosporins, quinolones and clindamycin in patients with active *C. difficile* infection.

- Start metronidazole 400mg tds orally for 10 days (give iv 500mg tds if oral route not possible/inappropriate).
- For non responsive/relapsed disease treat with PO vancomycin 250mg qds for 10 days or until stools improve
- In severe / life threatening disease, triple therapy may be tried metronidazole iv/oral + vancomycin oral (at higher dose of 500mg qds) + rifampicin oral 450mg bd. Discuss with microbiologist. Early referral to surgeons is essential.

Indicators of severe disease include: systemic toxicity, abdominal tenderness or distention, toxic megacolon, increasing blood leucocytes (especially if $> 15 \times 10^9/l$). Some patients with *Clostridium difficile* may not have diarrhoea.

Note that reduction in volume and frequency of diarrhoea is the response gauge. Repeat testing for faecal *C. difficile* toxin (CDT) in a known positive patient is not helpful, as patients can remain CDT positive for long periods after clinical recovery. However, do send faecal samples if diarrhoea recurs, in order to test for other faecal pathogens.

For recurrent CDAD consult the local Trust Antibiotic Guidelines.

Chemotherapy-induced diarrhoea e.g Irinotecan associated diarrhoea should be treated early and aggressively.

As soon as the first liquid stool occurs patient must increase oral fluid intake and start (high-dose) loperamide 4mg first dose, then 2mg 2-hourly until 12 hours after last liquid stool - max 48 hrs due to risk of paralytic ileus. The diarrhoea occurs at a median time of 5 days. If diarrhoea persists more than 24 hours after starting oral fluid and loperamide start ciprofloxacin 500mg bd.

Admit to hospital if:

- Diarrhoea is associated with fever
- Grade 3 or 4 diarrhoea (requiring iv fluids)
- Diarrhoea persists > 48 hrs

Respiratory

A new focal lesion in a patient recovering from neutropenia may be evidence of returning normal inflammatory response.

If a new focal lesion is found in a patient remaining neutropenic:

- If possible take bronchial washings (BAL) for culture, aspergillus PCR
- Get CT scan
- Consider starting antifungal (as per policy)

A new interstitial pneumonitis - consider BAL or other respiratory tract samples for PCP PCR, aspergillus PCR and viral PCRs .If unable to collect BAL specimen the above PCRs may be done on other respiratory secretions and on EDTA blood (noting that blood may have lower sensitivity).Consider empirical (high dose) trimethoprim-sulphamethoxazole (120mg/kg daily - see BNF). Continually reassess until a diagnosis is confirmed.

For respiratory problems consider CMV, mycobacteria especially TB, *Pneumocystis jirovecii*, respiratory viruses such as RSV, influenza, swine flu parainfluenza, adenovirus and atypical bacteria such as mycoplasma or Chlamydia. Send nose and throat swabs for respiratory virus PCR. For treatment of influenza refer to Trust Influenza Policy.

In severely immuno-compromised patients chest and /or upper abdominal pain may indicate invasive aspergillosis. Discuss appropriate investigations with radiologist and send serum (clotted blood) for aspergillus galactomannan testing, and EDTA-anticoagulated blood and respiratory tract samples for aspergillus PCR.

Central nervous system infections

Consider infectious causes immediately when patients present with fever and headache or other neurological symptoms such as depressed conscious level, confusion and cranial nerve lesions. Initiate appropriate investigations and empiric antibiotic cover as soon as possible. In some instances steroids would be indicated at time of antibiotic administration.

Consider urgent CT scan if there is evidence of raised intracranial pressure and/or focal neurology and then perform lumbar puncture if indicated. CSF should be sent for cell count, biochemistry, cytology, bacterial staining, antigens and culture, PCR for meningococci and pneumococci. Always send CSF to virology for HSV, enteroviruses and VZV PCR and consider requesting CMV, EBV, HHV-6 /7.

If subacute presentation arrange MR scan and send CSF for Toxoplasma PCR, JC polyomavirus PCR and EBV. If solitary space occupying lesion present. Toxoplasma PCR should also be done on EDTA blood.

If yeast infection is suspected do Indian ink staining on CSF and request cryptococcal antigen detection on serum and CSF, as well as yeast culture.

If Aspergillus is suspected send CSF for galactomannan and PCR.

Initial therapy for meningitis/encephalitis should be Ceftriaxone 2gm BD and consider adding aciclovir 10mg/kg tds iv.

If *Listeria* is a concern add high dose amoxycillin 2g 4hourly iv or use meropenem 2g tds. Consider vancomycin +/- rifampicin if pneumococcal penicillin resistance suspected.

Consider steroids if pneumococcal or TB infection is considered a strong possibility. Discussion with microbiologist or Infectious Diseases physician is advised.

Amend antibiotics, add antifungals or antivirals on the basis of laboratory results.

Genitourinary infections

The possibility of sexually transmitted diseases should be considered and excluded by microscopy, culture and PCR. Genital HSV infection will require aciclovir orally 800mg five times daily or aciclovir 10mg/kg tds iv.

If infection in the female genital tract is considered a possibility consider adding metronidazole or clindamycin.

Renal Obstruction

Patients presented with oligo/anuria require catheterisation and hourly urine output measurements as well as a careful 24 hour fluid balance. Urgent ultrasound is required to exclude an obstructive cause.

The Christie provides a 24/7 service for nephrostomy; however, the minority of these need to be done at night. As soon as the diagnosis of hydronephrosis is made, this needs to be discussed with the interventional team (extension 3322) or the on-call radiology registrar through switchboard and the urgency of drainage discussed.

Biliary Obstruction

Ultrasonography reliably excludes biliary dilatation; however, in patients with abnormal liver parenchyma biliary obstruction may occur without bile duct dilatation. Equally the absence of a raised bilirubin does not exclude biliary occlusion, in which case the alkaline phosphatase is usually raised to 1000 U/L.

Patients with previous biliary stents tend to have air in the bile ducts (pneumobilia) if the stents extend into the duodenum; however, it must be born in mind that in cases of biliary sepsis with gas forming organism (e.g. yeast) gas in the ducts may represent carbon dioxide.

CT or MRCP may be required for procedure planning, but this should not delay referral to the interventional team, as percutaneous transhepatic cholangiography (PTC) is only performed by a few operators and not routinely available out of hours.

12. REMOVAL OF INTRAVENOUS LINES

This should be considered if there is a subcutaneous tunnel or periport infection, septic emboli, hypotension associated with catheter use, or a non-patent catheter.

Specific infections where line removal is recommended include *Candida* spp and other fungi, and *P. aeruginosa*, and *S. aureus*. Other bacteria that may require removal due to persistent infection/colonisation of the line include *Corynebacterium jeikeium*, *Stenotrophomonas maltophilia*, *Bacillus* spp and *Acinetobacter* spp. Single isolates require confirmation with a repeat blood culture ideally from all lumens of the line and peripherally.

Persistent coagulase negative *staphylococcal* infections may also necessitate line removal.

Where line removal is not possible alcohol 70% injection may be used to try to decontaminate lines. Absolute alcohol injection may be diluted to 70% with water for Injection and used to lock an infected lumen for up to 7 days. Please contact pharmacy and/or microbiologists for advice.

THE FOLLOWING SECTION RELATES MAINLY TO PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES

13. ALLOGENEIC BONE MARROW TRANSPLANT PATIENTS

The advice of the haematologist looking after the patient should always be sought.

14. USE OF ANTIVIRAL DRUGS

Patients with lesions due to *Herpes simplex* or *Varicella zoster* should be treated with aciclovir if they are neutropenic and febrile even if it is thought the lesions are not contributing to the sepsis (HSV 5mg/kg tds iv for at least 5 days, for genital herpes reactivation use 10mg/kg tds); VZV - 10mg/kg tds iv for 10 days).

Consideration should be given to the possibility of CMV if patients have pneumonitis, gastrointestinal or CNS symptoms especially if they have had a bone marrow transplant.

These patients should have an EDTA blood sample collected together with bronchoalveolar lavage, faeces, and biopsy (as appropriate clinically) sent for CMV PCR.

Discuss the appropriate use of ganciclovir or foscarnet with a Virologist.

If CMV infection is proven, monitor response to therapy with twice weekly PCR on EDTA blood. If CMV viral load does not appear to be reducing with ganciclovir discuss resistance testing with a Consultant Virologist.

In patients with recurrent CMV, long term ganciclovir or other maintenance antiviral therapy may be indicated for example cidofovir, valganciclovir. In CMV pneumonitis, hyperimmune globulin should be used in addition to ganciclovir or foscarnet.

If a lower respiratory tract infection is suspected send nasal washings or nasopharyngeal aspirate for rapid virus antigen detection, respiratory secretions or nose and throat swab for respiratory virus PCR and blood for antibody testing. Respiratory syncytial virus and parainfluenza virus may require nebulised ribavirin. For treatment of influenza refer to Trust Influenza Policy.

15. THE ROLE OF PROPHYLACTIC ANTIMICROBIALS AND OTHER AGENTS

Prophylactic antibiotics, antivirals and antifungals are not necessary for all neutropenic patients but have a part to play in management of some conditions especially haematological malignancies and as part of some chemotherapy regimens.

Unless part of a specified protocol these will need prescribing on a case by case basis following discussion between the clinicians and microbiologist/virologist.

Passive immunization with specific immunoglobulins may be useful in selected patients eg *Varicella zoster* immune globulin (VZIG) may be used for prophylaxis after contact with VZ in the non thrombocytopenic patient. Where intramuscular injections cannot be given IV IG or antiviral prophylaxis should be considered. These cases should be discussed with a consultant virologist and haematologist.

GCSF or other colony stimulating factors should only be considered after discussion with a haematologist or consultant oncologist.

16. SUMMARY: EMPIRICAL TREATMENT OF HIGH RISK SEPTIC PATIENTS - SUITABLE IV ANTIBIOTIC REGIMENS

Preferred Treatment

Piperacillin/Tazobactam 4.5g tds plus gentamicin*

In the event of specific concern about meticillin resistant or coagulase-negative staphylococcal sepsis, vancomycin can be given pending susceptibility testing results.

****Gentamicin 5 mg/kg (or dose as per local guidance) normally given as a single daily dose unless advised otherwise. Levels should be checked 16 - 20 hours after the first dose (and satisfactory clearance annotated) and then at least every 3 to 4 days (more frequently if there is evidence of renal impairment) according to local protocols.***

Alternative Treatment

If penicillin allergic, poor renal function or if patient has received platinum containing chemotherapy within the last 7 days:

Meropenem 1gm tds (or equivalent carbapenem).

In patients with renal impairment (creatinine clearance less than 50 ml/min) dose adjustment is required (see SPC).

Only consider including a glycopeptide (e.g. vancomycin) as first line treatment if:

- IV catheter related infection e.g. signs of inflammation around the catheter insertion point or along catheter track
- MRSA or penicillin resistant *pneumococci* are likely
- Patient has severe mucositis

Antibiotics should be given through each lumen of an involved IV catheter on a rotational basis if there is an infection of a multi-lumen catheter.

If the patient is poorly or deteriorating or if there is no improvement within 24 - 48 hours contact the relevant oncologist, haematologist or microbiologist (for Christie Hospital patients via switchboard 0161-446-3000).

17. CONSULTATION, APPROVAL & RATIFICATION PROCESS

Consultation through Acute Oncology Group and Chemotherapy Delivery Group

18. PROCESS FOR MONITORING EFFECTIVE IMPLEMENTATION

The effectiveness of this policy will be monitored via an ongoing audit of the "One hour door to needle target", undertaken by the Acute & Critical Care Directorate. The results and subsequent action plan will be reported to the Acute & Critical Care Directorate and monitored by the same committee monthly.

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20. VERSION CONTROL SHEET

Version	Date	Author	Status	Comment
1.4	Aug 2007	Dr P.Haji-Michael, Dr K.Dodgson Dr E.Kaczmariski, Dr K.Mutton	Approved	Equality Impact Assessment - 17th August 2010
1.5	Sep 2010	June So on behalf of the DTC, the Christie	Edited	Clinical and research governance committee - October 2010
1.6	Jan 2013	Dr P Haji-Michael	Reviewed	Acute Oncology Group and NICE Guidance review request
1.7	Feb 2013	Dr P Haji-Michael	Reviewed	Reviewed with M Leahy recommendations
1.8	28 Feb 2013	Dr P Haji-Michael	Edited	By LLawrence to fit procedural template required format.
1.9	15 May 2013	Dr P Haji-Michael	Edited	To add input from radiology team on the management of renal and hepatic obstruction

21. APPENDICES

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Initial resuscitation (first 6 hours)

- Begin resuscitation immediately in patients with hypotension or elevated serum
- Lactate >4mmol/l; do not delay pending ICU admission. (1C)
- Resuscitation goals: (1C)
- Central venous pressure (CVP) 8–12 mm Hg*
- Mean arterial pressure \geq 65 mm Hg
- Urine output \geq 0.5 mL.kg⁻¹.hr⁻¹
- Central venous (superior vena cava) oxygen saturation \geq 70%, or mixed venous \geq 65%
- If venous O₂ saturation target not achieved: (2C)

consider further fluid

transfuse packed red blood cells if required to haematocrit of \geq 30% and/or
dobutamine infusion max 20 μ g.kg⁻¹.min⁻¹

* A higher target CVP of 12-15 mmHg is recommended in the presence of mechanical ventilation or pre-existing decreased ventricular compliance.

Diagnosis

- Obtain appropriate cultures before starting antibiotics provided this does not significantly delay antimicrobial administration.(1C)
- Obtain two or more blood cultures (BCs)
- One or more BCs should be percutaneous
- One BC from each vascular access device in place > 48 hours
- Culture other sites as clinically indicated
- Perform imaging studies promptly in order to confirm and sample any source of
- infection; if safe to do so.(1C)

Antibiotic therapy

- Begin intravenous antibiotics as early as possible, and always within the first hour of recognising severe sepsis (1D) and septic shock.(1B)
- Broad-spectrum: one or more agents active against likely bacterial/fungal pathogens and with good penetration into presumed source.(1B)
- Reassess antimicrobial regimen daily to optimise efficacy, prevent resistance, avoid toxicity & minimise costs.(1C)
- Consider combination therapy in Pseudomonas infections.(2D)
- Consider combination empiric therapy in neutropenic patients.(2D)
- Combination therapy no more than 3-5 days and de-escalation following susceptibilities.(2D)
- Duration of therapy typically limited to 7–10 days; longer if response slow, undrainable foci of infection, or immunologic deficiencies.(1D)
- Stop antimicrobial therapy if cause is found to be non-infectious.(1D)

Source identification and control

- A specific anatomic site of infection should be established as rapidly as possible(1C) and within the first 6 hrs of presentation.(1D)
- Formally evaluate patient for a focus of infection amenable to source control
- measures (eg: abscess drainage, tissue debridement).(1C)
- Implement source control measures as soon as possible following successful

- initial resuscitation.(1C)
- Exception: infected pancreatic necrosis, where surgical intervention best delayed. (2B)
- Choose source control measure with maximum efficacy and minimal physiologic upset.(1D)
- Remove intravascular access devices if potentially infected.(1C)

Fluid therapy

- Fluid-resuscitate using crystalloids or colloids.(1B)
- Target a CVP of ≥ 8 mmHg (≥ 12 mmHg if mechanically ventilated).(1C)
- Use a fluid challenge technique while associated with a haemodynamic improvement.(1D)
- Give fluid challenges of 1000 ml of crystalloids or 300–500 ml of colloids over 30 minutes. More rapid and larger volumes may be required in sepsis-induced tissue hypoperfusion.(1D)
- Rate of fluid administration should be reduced if cardiac filling pressures increase without concurrent haemodynamic improvement.(1D)

Vasopressors

- Maintain MAP ≥ 65 mmHg.(1C)
- Norepinephrine or dopamine centrally administered are the initial vasopressors of choice.(1C)
- Epinephrine, phenylephrine or vasopressin should not be administered as the initial vasopressor in septic shock.(2C)
- Vasopressin 0.03 units/min maybe subsequently added to norepinephrine with anticipation of an effect equivalent to norepinephrine alone.
- Use epinephrine as the first alternative agent in septic shock when blood pressure is poorly responsive to norepinephrine or dopamine.(2B)
- Do not use low-dose dopamine for renal protection.(1A)
- In patients requiring vasopressors, insert an arterial catheter as soon as practical.(1D)

Inotropic therapy

- Use dobutamine in patients with myocardial dysfunction as indicated by elevated cardiac filling pressures and low cardiac output.(1C)
- Do not increase cardiac index to predetermined supranormal levels.(1B)

Steroids

- Consider intravenous hydrocortisone for adult septic shock when hypotension remains poorly responsive to adequate fluid resuscitation and vasopressors.(2C)
- ACTH stimulation test is not recommended to identify the subset of adults with septic shock who should receive hydrocortisone.(2B)
- Hydrocortisone is preferred to dexamethasone.(2B)
- Fludrocortisone (50 μ g orally once a day) may be included if an alternative to hydrocortisone is being used which lacks significant mineralocorticoid activity.
- Fludrocortisone is optional if hydrocortisone is used.(2C)
- Steroid therapy may be weaned once vasopressors are no longer required.(2D)
- Hydrocortisone dose should be < 300 mg/day.(1A)

- Do not use corticosteroids to treat sepsis in the absence of shock unless the patient's endocrine or corticosteroid history warrants it.(1D)

Recombinant human activated protein C (rhAPC)

- Consider rhAPC in adult patients with sepsis-induced organ dysfunction with clinical assessment of high risk of death (typically APACHE II \geq 25 or multiple organ failure) if there are no contraindications.(2B,2C for post-operative patients)
- Adult patients with severe sepsis and low risk of death (eg: APACHE II $<$ 20 or one organ failure) should not receive rhAPC.(1A)

Blood product administration

- Give red blood cells when haemoglobin decreases to $<$ 7.0 g/dl ($<$ 70 g/L) to target a haemoglobin of 7.0 – 9.0 g/dl in adults.(1B)
- A higher haemoglobin level may be required in special circumstances (eg: myocardial ischaemia, severe hypoxaemia, acute haemorrhage, cyanotic heart disease or lactic acidosis)
- Do not use erythropoietin to treat sepsis-related anaemia. Erythropoietin may be used for other accepted reasons.(1B)
- Do not use fresh frozen plasma to correct laboratory clotting abnormalities unless there is bleeding or planned invasive procedures.(2D)
- Do not use antithrombin therapy.(1B)
- Administer platelets when: (2D)
 - counts are $<$ 5000/mm³ (5 X 10⁹/L) regardless of bleeding.
 - counts are 5000 to 30,000/mm³ (5–30 X 10⁹/L) and there is significant bleeding risk.
 - Higher platelet counts (\geq 50,000/mm³ [50 X 10⁹/L]) are required for surgery or invasive procedures

Glucose control

- Use IV insulin to control hyperglycaemia in patients with severe sepsis following stabilisation in the ICU.(1B)
- Aim to keep blood glucose $<$ 150 mg/dl (8.3mmol/L) using a validated protocol for insulin dose adjustment.(2C)
- Provide a glucose calorie source and monitor blood glucose values every 1-2 hrs (4 hrs when stable) in patients receiving intravenous insulin.(1C)
- Interpret with caution low glucose levels obtained with point of care testing, as these techniques may overestimate arterial blood or plasma glucose values.(1B)

Renal replacement

- Intermittent haemodialysis and continuous veno-venous haemofiltration (CVVH) are considered equivalent.(2B)
- CVVH offers easier management in haemodynamically unstable patients.(2D)

Bicarbonate therapy

- Do not use bicarbonate therapy for the purpose of improving haemodynamics or reducing vasopressor requirements when treating hypoperfusion-induced lactic acidaemia with pH \geq 7.15.(1B)

Deep vein thrombosis (DVT) prophylaxis

- Use either low-dose unfractionated heparin (UFH) or low-molecular weight heparin (LMWH), unless contraindicated.(1A)
- Use a mechanical prophylactic device, such as compression stockings or an intermittent compression device, when heparin is contraindicated.(1A)
- Use a combination of pharmacologic and mechanical therapy for patients who are at very high risk for DVT.(2C)
- In patients at very high risk LMWH should be used rather than UFH.(2C)

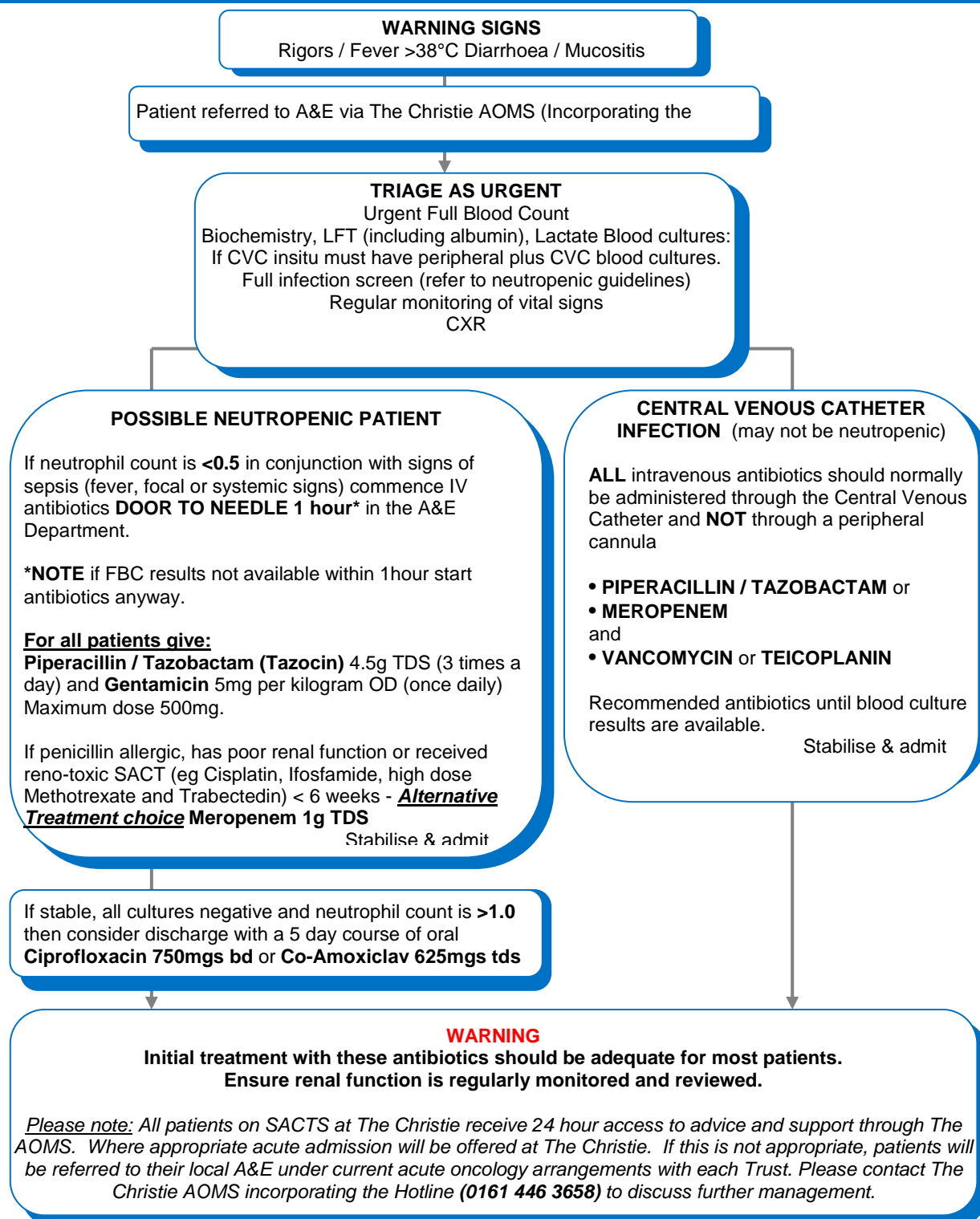
Stress ulcer prophylaxis

- Provide stress ulcer prophylaxis using H2 blocker(1A) or proton pump inhibitor(1B). Benefits of prevention of upper GI bleed must be weighed against
- the potential for development of ventilator-acquired pneumonia.

Consideration for limitation of support

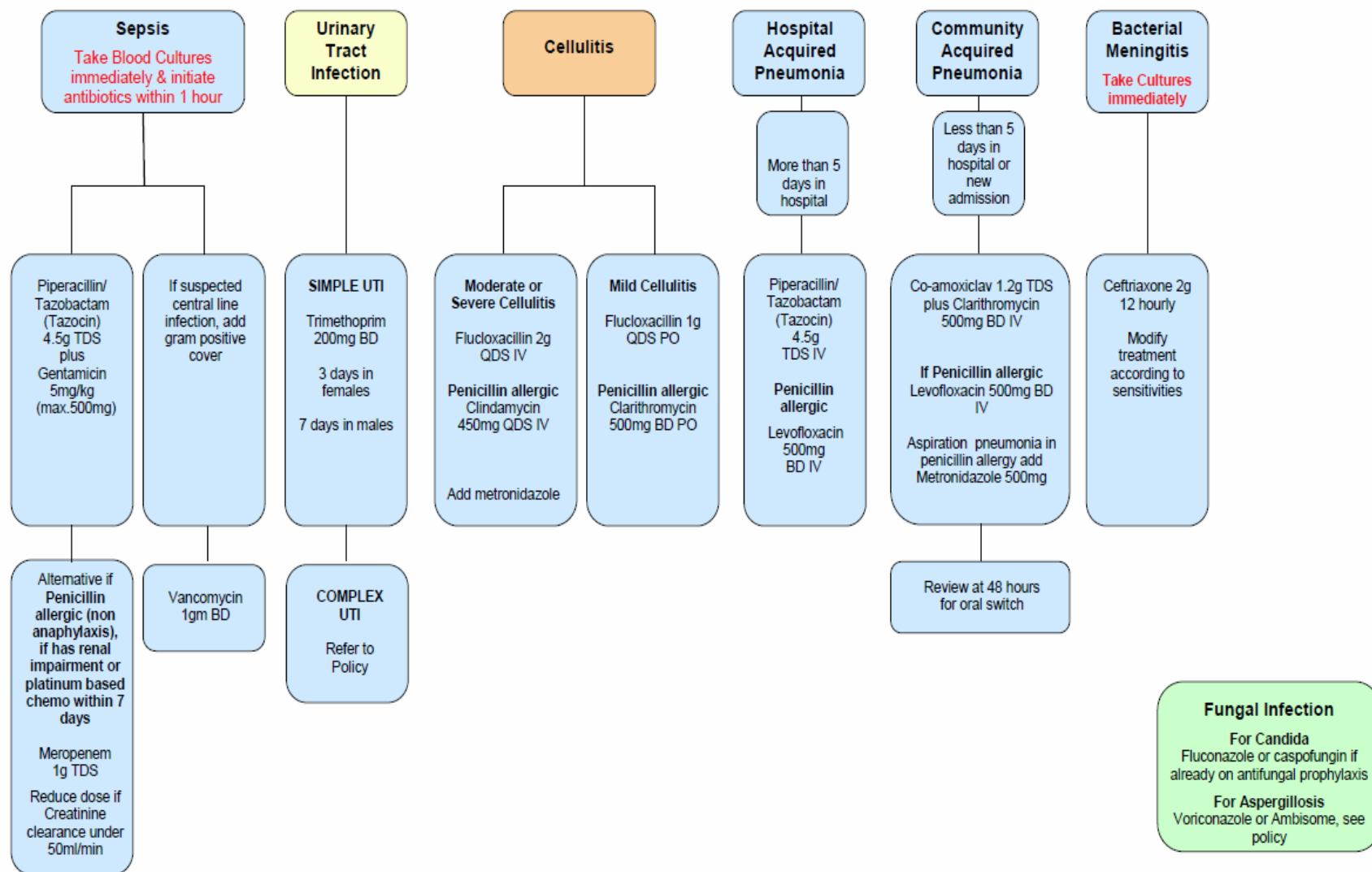
- Discuss advance care planning with patients and families. Describe likely outcomes and set realistic expectations.(1D)

Management of patients with signs of sepsis following Chemotherapy treatment or with a possibly infected Central Venous Catheter (CVC)



Reviewed May 2013: A Moreman, P Hall, P Hajimichael

Antimicrobial Guidelines for common infections



Guidelines for the Management of Sepsis (including Neutropenic Sepsis)

Document Ref: Sepsis

Version 1.8

Biliary sepsis table

Procedure	Drug and dose	Penicillin allergy		Previous / current MRSA colonised	Intra-op / post op doses
		Low risk	High risk		
Biliary surgery (open)	Co-amoxiclav 1.2g IV	Cefuroxime 1.5g IV + metronidazole 500mg IV stat	Clindamycin 600mg IV + gentamicin 120mg IV stat	Add Teicoplanin 400mg IV stat	Continue for 48hours if peritoneal soiling
ERCP – No evidence of infection / jaundice	No routine antibiotic prophylaxis required				
ERCP in patients with jaundice *	For patients with ongoing cholangitis treat as recommended				
ERCP in patients with neutropenia / advanced malignancy	Gentamicin 120mg IV stat For patients where gentamicin is contra-indicated: Ciprofloxacin 750mg orally 60-90mins pre-procedure			Gentamicin 120mg IV stat	Ciprofloxacin 500mg bd for 48 hr
					NA