Norfolk and Norwich University Hospitals NHS Foundation Trust

James Paget University Hospitals NHS Foundation Trust

Joint Trust Guideline for the Management of Invasive Candida Infection in Neonates

A Clinical Guideline

For Use in:	NICU
By:	Medical and Nursing staff
For:	All neonates with invasive candida infection
Division responsible for document:	Women and Children's Services
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If Yes - does the strategy/policy deviate from the recommendations of NICE? If so why?	N/A

This guideline has been approved by the Trust's Clinical Guidelines Assessment Panel as an aid to the diagnosis and management of relevant patients and clinical circumstances. Not every patient or situation fits neatly into a standard guideline scenario and the guideline must be interpreted and applied in practice in the light of prevailing clinical circumstances, the diagnostic and treatment options available and the professional judgement, knowledge and expertise of relevant clinicians. It is advised that the rationale for any departure from relevant guidance should be documented in the patient's case notes.

The Trust's guidelines are made publicly available as part of the collective endeavour to continuously improve the quality of healthcare through sharing medical experience and knowledge. The Trust accepts no responsibility for any misunderstanding or misapplication of this document.

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Version and Document Control:

Version Number	Date of Update	Change Description	Author
3.1	04/11/2021	Reviewed with minor changes	Dr Mark Dyke

This is a Controlled Document

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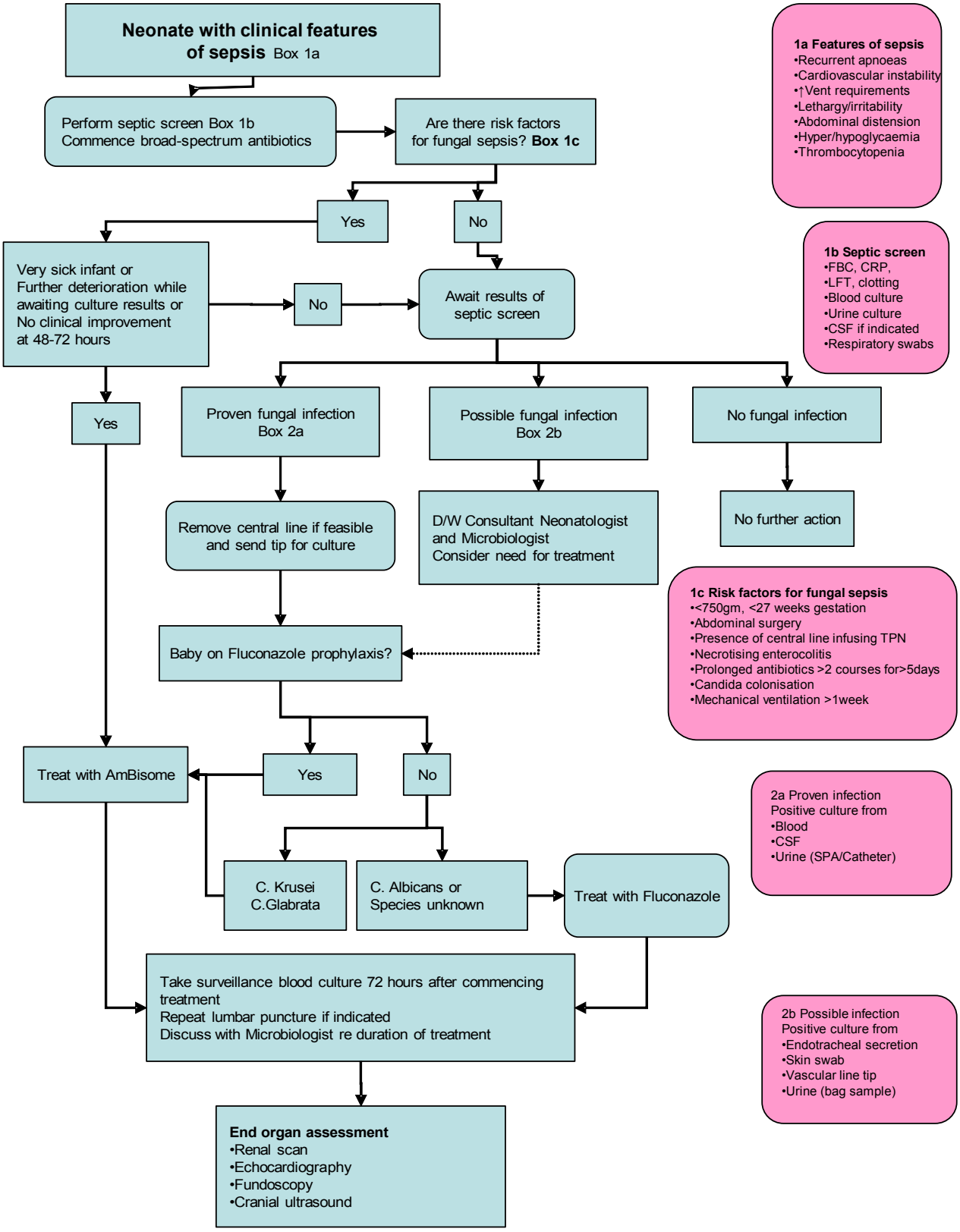
Quick reference guideline/s



1. Objective/s

Joint Trust Guideline for the Management of Invasive Candida Infection in Neonates

To provide guidance on the treatment of invasive candida infection in neonates.

2. Rationale

Invasive candida infections have become the third most common late onset infection in most neonatal units. The published incidence is around 4-8% among extremely low birth weight infants [ELBW <1000g] with a crude mortality rate around 30%. Persistent infection and significant focal sequelae, such as renal fungal bezoars, endocarditis and meningitis are short term complications, and long term neurodevelopmental disability rates of >60% have been reported.

Meticulous attention to avoidable risk factors [such as prolonged presence of central venous lines and the use of broad-spectrum antibiotics eg 3rd generation cephalosporins], combined with the judicious use of anti-fungal prophylaxis has reduced invasive infection and consequent mortality and long-term sequelae in recent years. Antifungal prophylaxis is now routinely given to selected patients in the NICU (see Antifungal Prophylaxis in Neonates Trustdocs Id:1278)

3. Broad recommendations

3.1 Signs and symptoms of candida sepsis should be actively sought in newborns who are at high risk [see section 4.1 and 4.2]

3.2 Appropriate investigations and treatment should be promptly instituted where there is a high index of suspicion of candida sepsis [see section 4.3 and 5]

4. Guide to diagnosing Candida sepsis

4.1 Be aware of risk factors

Several studies have identified major risk factors for candidemia:

- extremely low birth weight [<1000g and especially <750g]
- abdominal surgery
- exposure to ≥ 2 antibiotics, particularly cephalosporins & carbapenems

Additional contributory risk factors include:

- prematurity [gestational age <32 weeks]
- parenteral nutrition for >5 days
- presence of a central venous catheter [CVC]
- known fungal dermatitis or fungal colonisation
- prolonged intubation
- apgar score <5 @ 5 minutes
- topical petrolatum care
- use of H_2-antagonists

4.2 Consider signs and symptoms

Candida infections occur primarily in VLBW infants typically between the second and sixth weeks of life. The most common clinical signs are similar to those of bacterial infection and include:

- apnoea
- increased requirements for respiratory support
- hyperglycaemia
- temperature instability
- abdominal distension
- lethargy
- hypotension
- leukopenia, leukocytosis and particularly thrombocytopaenia.

Features of sepsis that are particularly severe and/or persist after 48 hours' treatment with antibiotics (particularly if blood cultures are negative) should raise the suspicion of an invasive candida infection.

4.3 Perform appropriate investigations

In a neonate with clinical features suggestive of sepsis, a sepsis screen should be performed (see Trust Guideline for the Management of Newborn babies at increased risk of developing neonatal infection Trustdocs IdL9998)

- Full blood count, CRP, LFTs and Clotting studies
- Blood culture [peripheral **and** from CVC if high index of suspicion]
- Urine [preferably SPA or catheter specimen]
- Lumbar puncture if CNS symptoms present
- Respiratory swabs [if indicated]

5. Empirical treatment may be required:

5.1 After performing the sepsis screen, all neonates should be commenced on empirical broad spectrum antibiotics.

5.2 Empirical anti-fungal treatment with AmBisome should be commenced in neonates with risk factors for fungal sepsis who fulfil either of the following criteria:

- very unwell at presentation
- suffer further deterioration or not showing any signs of improvement within 48 hours of antibiotic treatment

If these criteria are not met, the need for treatment will be determined by the following considerations.

6. Interpretation of investigations

6.1 Possible infection is defined as:

- a positive culture from a vascular line tip **or**
- 2 or more culture positive specimens of urine (bag specimen), respiratory and skin swabs

6.2 Proven infection is defined as a positive culture from:

- blood **or**
- CSF **or**
- urine [SPA or catheter specimen]

In the presence of possible infection, a Microbiologist should be consulted regarding commencement of antifungal agents.

In the presence of proven infection, definitive anti-fungal treatment should be commenced [see 7.1]. The continued presence of a central vascular catheter [CVC] substantially increases risk of mortality so should, if feasible, be removed and only replaced, if still required, after a minimum of 36 hours.

7. Definitive anti-fungal treatment

7.1 All neonates on Fluconazole prophylaxis who have proven infection should be commenced on AmBisome.

7.2 For neonates not on Fluconazole prophylaxis, treatment will be determined by species:

- if the species is Candida Albicans [or unknown] then Fluconazole should be commenced
- if the species is known to be Candida Krusei or Candida Glabrata, AmBisome should be commenced

7.3 Dosage

FLUCONAZOLE	AMBISOME
Neonate < 2 weeks • 6-12mg/kg every 72 hours **Neonate > 2 weeks** • 6-12mg/kg every 48 hours	• Test dose 100mcg/kg, then 1mg/kg once daily • Increased to 3mg/kg once daily (empirical) **or** • 5mg/kg once daily (for proven infection)

8. Further management

8.1 Assessing response to treatment

After 72 hours of treatment:

- a repeat blood culture should be performed [along with CRP and Fbc as well as LFTs, renal function and clotting where appropriate]
- in cases of CNS disease, a repeat lumbar puncture should be performed

8.2 Duration of treatment should be discussed with a Consultant Microbiologist, especially in the case of candida meningitis or any focal infection.

8.3 Investigations for end organ damage

Candida species are capable of invading all vital organs after candidaemia. A critical review of the literature using meta-analytic techniques for neonatal candidaemia and end organ damage has not been able to provide strong evidence-based conclusions for end organ evaluation. The data reviewed was largely retrospective case series and there was evidence of heterogeneity.

The reported median prevalence for end organ damage are:

- Endophthalmitis 3%
- Meningitis 15%
- Brain abscess or ventriculitis 4%
- Endocarditis 5%
- Positive renal ultrasound 5%

It is recommended that all neonates with proven candida sepsis should have

- Echocardiogram
- Renal ultrasound scan
- Cranial ultrasound scan
- Fundoscopy

Clinical audit standards

1. Neonates with invasive candidal infection should receive antifungal treatment determined by clinical status +/- candida species
2. Vascular lines should be removed in all newborns with invasive candida infection (or if not removed reason for decision documented)
3. Neonates with invasive candidal infection should have fundoscopy, echocardiogram, renal ultrasound scan and cranial ultrasound scan.

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Glossary

1. CNS central nervous system
2. CRP C-reactive protein
3. CSF cerebrospinal fluid
4. ELBW extremely low birth weight
5. SPA supra pubic aspirate
6. VLBW very low birth weight

Summary of development and consultation process undertaken before registration and dissemination

This guideline was originally drafted by Drs Bose and Dyke on behalf of the Neonatal Department and Paediatric Directorate in 2007. It was circulated for comments to Neonatal Consultants, junior doctors and ANNPs. It was discussed at the departmental guidelines meeting and amendments made to incorporate further suggestions and comments. Consultants in medical microbiology were actively involved in authoring the guideline and the neonatal unit pharmacist reviewed it. Suggestions for improvements were incorporated in subsequent drafts and the published version represented a final draft upon which agreement by all parties had been reached. The 2015, 2018 and 2021 revisions followed further reviews of recently published papers which required only minor revision of the guideline. Consultants in Neonatology and Microbiology approved revised drafts.

Distribution list/ dissemination method

a. Hospital intranet
b. Neonatal Unit.

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