GUIDELINE

# Candida Infections

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| **Scope (Staff):** | Nursing and Medical Staff |
| **Scope (Area):** | NICU KEMH, NICU PCH, NETS WA |

**Child Safe Organisation Statement of Commitment**

CAHS commits to being a child safe organisation by applying the National Principles for Child Safe Organisations. This is a commitment to a strong culture supported by robust policies and procedures to reduce the likelihood of harm to children and young people.

**This document should be read in conjunction with this disclaimer**

## Contents



## Aim

To identify high-risk factors for Candida infections in neonates and to provide evidence-based preventive and treatment strategies.

## Risk

Candidiasis is an important cause of infection-related morbidity and mortality in the NICU. Candida survivors have a worse neurological outcome, especially when there is infection of the central nervous system. ELBW (birth weight <1000g) are at highest risk

of invasive candidiasis (7-9%) with 20% mortality and 50% severe neurodevelopmental impairment in survivors.

## Background

Most neonates are colonized by Candida species via the maternal gastrointestinal or genitourinary tract with up to 64% getting colonized within 4 weeks of life. Skin and GIT colonized first followed by respiratory tract.

***Common:*** *C. albicans* in 60-70% cases (common in female genitourinary tract), *C. parapsilosis* in 20-30% cases (nosocomial)

***Uncommon***: *C. tropicalis, C. lusitaniae* (amphotericin resistant*), C. glabrata (*fluconazole resistant*), C. krusei* (fluconazole resistant)

## Risk Factors (National Mycosis Survey Study)

- ***Immunocompromised host***: Preterm infants, especially birth weight< 1000 grams and gestation <32 weeks; with vaginal delivery, hemodynamic compromise (DIC, shock, bacterial sepsis), low APGAR score (<5 at 5 minutes), parenteral nutrition for >5 days, Intralipid infusion for >7 days, prolonged NICU stay (>7 days), exposure to $H_2$ blockers, abdominal pathology (NEC, abdominal surgery)
- ***Compromised epithelial barriers***: skin breakdown, intubation and ventilation, central catheter (>7 days)/ PICC lines,
- ***Multiple colonisation sites***: ETT aspirates, surface swabs
- ***Increased density of candida colonisation*** ($8x10^6$ candida CFU/g of stool): prolonged broad spectrum antibiotic use (>5 days) and exposure to ≥ two antibiotics
- ***Maternal:*** chorioamnionitis, uncontrolled diabetes, HIV or other immunocompromised condition, presence of uterine or cervical foreign body

Candida species generally colonize skin, GIT, lower female genital tract, intertriginous areas (groin, armpits) and foreskin in males. *Vertical* transmission (from mother): vaginal tract or breastfeeding if Candida mastitis. *Horizontal* transmission (from health care staff/ hospital environment).

## Clinical Picture

1. ***Mucocutaneous candidiasis*****:** oropharyngeal thrush, diaper dermatitis, congenital cutaneous candidiasis, invasive fungal dermatitis
    - ***Invasive fungal dermatitis***: Presents during first two weeks of life. Risk factors include ELBW, postnatal steroids and hyperglycaemia. Presents as macular, popular, vesicular, or pustular lesions or erosions in dependent/ intertriginous areas, which may involve the whole back or abdomen.
    - ***Congenital candidiasis:*** rare, acquired in utero/ during delivery. Usually presents on the first day of life. Risk factors include rupture of membranes, the presence of uterine/ cervical foreign body or a history of vaginal candidiasis**.**

Presents as erythematous macules / papules on erythematous base, frequently involves palms and soles. Oral thrush can be present as well as papules on the umbilical cord. In preterm, may present as a widespread pustular and vesicular lesion or diffuse erythematous macular patch (crusting of skin) resembling a burn. In term infants, skin lesions resolve with desquamation by first week.

2. ***Invasive Candidiasis (IC):*** Involvement of urinary tract, CNS, eyes, heart valves, bone, and joints in addition to haematogenous dissemination. Most likely to occur at 6-7 weeks.

Signs and symptoms are similar to bacterial sepsis and include lethargy, feed intolerance, apnoea, cardiovascular instability and respiratory distress. Persistent hyperglycaemia and thrombocytopenia are strong associations with IC in ELBW neonates.

## Diagnosis

Leucocytosis is usually marked, and thrombocytopenia is almost invariable. However, thrombocytopenia occurs in many cases of bacterial sepsis, so is not pathognomonic of systemic candida infection.

As candida may grow slowly in cultures (blood, urine, CSF), false-negative results of blood cultures and lumbar punctures can potentially lead to misdiagnosis or delayed diagnosis. A high index of suspicion is necessary, especially in high-risk patients. Fungal PCR, T2 Candida platform, Candida mannan and anti-mannan antibody assessments are some newer biomarkers.

Once the diagnosis is confirmed, an abdominal (renal, liver, spleen) and cranial ultrasound is indicated. A cardiac echo may be indicated to assess for cardiac thrombi or vegetations. An ophthalmologic review is warranted. Osteomyelitis is rare and presents as swelling or decreased range of motion (may need synovial fluid or bone aspirate).

## Prophylaxis of Candida Infections

- Minimise and rationalise antibiotic use, especially broad-spectrum antibiotics
- Consider early extubation
- ***Nystatin:*** Current practice for infants requiring any form of respiratory support (Ventilation/ CPAP/ HHF) is to administer oral Nystatin 1ml TDS until off such respiratory support (*Austin 2015, Cochrane review 2015, Erikson 2016*). Nystatin vs placebo: significantly reduced IC (RR: 0.2; 95% CI: 0.14-0.28), no difference in mortality (RR: 0.87; 95% CI: 0.72-1.05); nystatin vs fluconazole: interrupted due to poor enrolment; showed higher mortality in nystatin group (7.5% vs 0%; p=0.03; n=80 VLBW infants) (Violaris 2010).
- ***Miconazole:*** No role as possible increased risk of developing resistance to azoles.
- ***Fluconazole:*** Cochrane review (Cleminson et al 2015) included 10 trials (n=1371 VLBW infants): IC incidence (6.2% vs 15.7%, RR 0.43; 95% CI: 0.31-0.59). Similar results in ELBW infants (RR: 0.30, 95% CI: 0.14-0.63). Limited

data on long term outcomes of fluconazole prophylaxis suggest no adverse effects (*Kaufman et al 2011, Greenberg et al 2012)*

- ***Ongoing Surveillance***: Further studies needed
- ***Empiric antifungal therapy:*** Further studies needed
- ***Lactoferrin:*** data limited in ELBW infants. bovine Lf vs placebo: significant reduction in IC (0.7% vs 7.7%) (Manzoni 2012)
- ***Probiotics:*** insufficient data. Decreased Candida colonisation (RR: 0.43; 95% CI: 0.27-0.67), no difference in IC (RR: 0.88; 95% CI: 0.44-1.78) (Hu 2017)

## Treatment of mucocutaneous candidiasis

- Oral candidiasis: Topical antifungals (nystatin and azole preparations). If inadequate response, consider oral fluconazole once daily for seven days). Prevent reinfection by including sterilisation or decolonisation of items such as bottle nipples and pacifiers.
- Diaper dermatitis: topical nystatin or azole creams

## Treatment of Invasive Candidiasis (IC)

- Consider removal of central lines. The drug of choice for systemic candidiasis is Amphotericin (Fungizone). The drug is extremely well tolerated in neonates, with few renal adverse effects. The drug must be infused over 6 hours. In some instances where venous access is difficult, and parenteral nutrition cannot be ceased for the 6 hour infusion, consideration can be given to using Amphotericin Liposomal (Ambisome). This formulation has no other specific benefits, except slightly reduced nephrotoxicity and can be infused over 30-60 minutes. Not routinely recommended as high rates of treatment failure, morbidity, and mortality with IC. Consider only when urinary and CNS involvement have been excluded and to salvage therapy in discussion with clinical microbiologist. Fluconazole - Consider loading dose (rapid attainment of therapeutic levels). May cause transient elevation of creatinine or hepatic enzymes (AST and ALT> 3-fold). Avoid with *C. glabrata* or *C. krusei* infection.
- Flucytosine (nucleoside analogue): not recommended currently in neonates. May need to be added, especially in cases of meningitis (excellent penetration into CSF and urine) after consultation with clinical microbiologist. Used as adjunct with initial treatment failure and never as monotherapy (high rates of resistance).
- Length of treatment will vary (***refer to Figure 1***); systemic treatment may be continued with oral Fluconazole, but there is a paucity of data evaluating its efficacy. Oral Fluconazole may be appropriate for isolated uncomplicated UTI after discussion with microbiology.
- **Echinocandins**: efficacy against Candida biofilm, extended spectrum Candida species and favourable safety. Caspofungin (limited data as low enrolment in

study by Scott 2020), only recommended as salvage therapy. Micafungin (no data in neonates). Anidulafungin (studied in infants, no neonatal data)

- Goals of treatment: During first week of life: At least two negative blood cultures (24 hrs apart), negative urine and CSF culture. Continue antifungals for at least 2 weeks after evidence of clearance of infection. Refer to Appendix 2.

## Related CAHS internal policies, procedures, and guidelines

Neonatology Medication Protocols

## References and related external legislation, policies, and guidelines


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- *Kim J, Nakwa FL, Araujo Motta F, et al. A randomized, double-blind trial investigating the efficacy of caspofungin versus amphotericin B deoxycholate in the treatment of invasive candidiasis in neonates and infants younger than 3months of age. J Antimicrob Chemother 2020; 75: 215–20*
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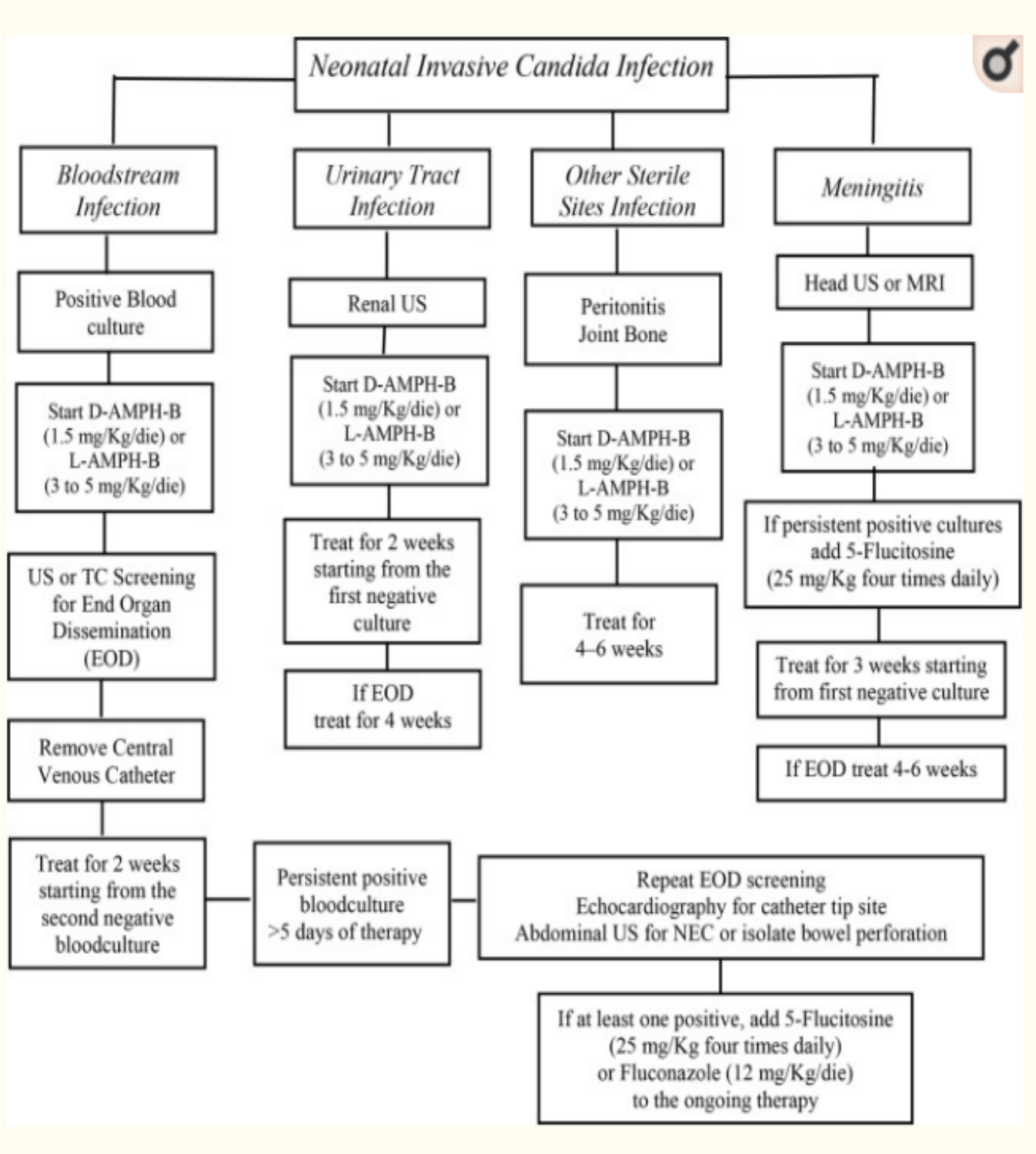
# Appendix 1: Flow Chart for Proven Invasive Candidiasis

Adapted from Kaufman et al, J Ped 2009, Bersani et al Front Pediatr 2019



# Appendix 2: Invasive Candidiasis Prevention and Treatment Timeline

*(Kilpatrick et al 2022)*

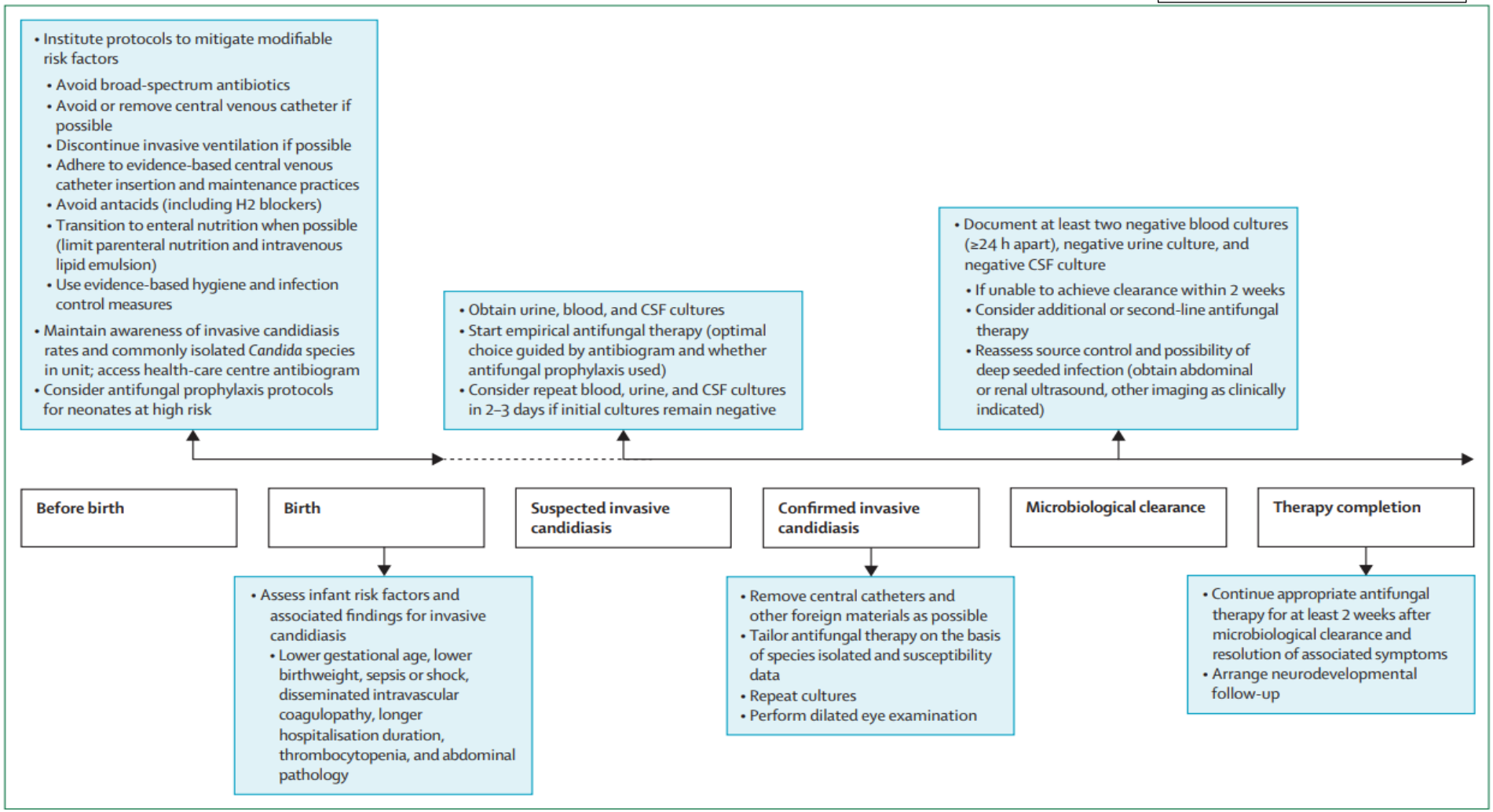



***Figure:*** **Invasive candidiasis prevention and treatment timeline**
The dashed line represents time elapsed until suspected invasive candidiasis. CSF=cerebral spinal fluid.