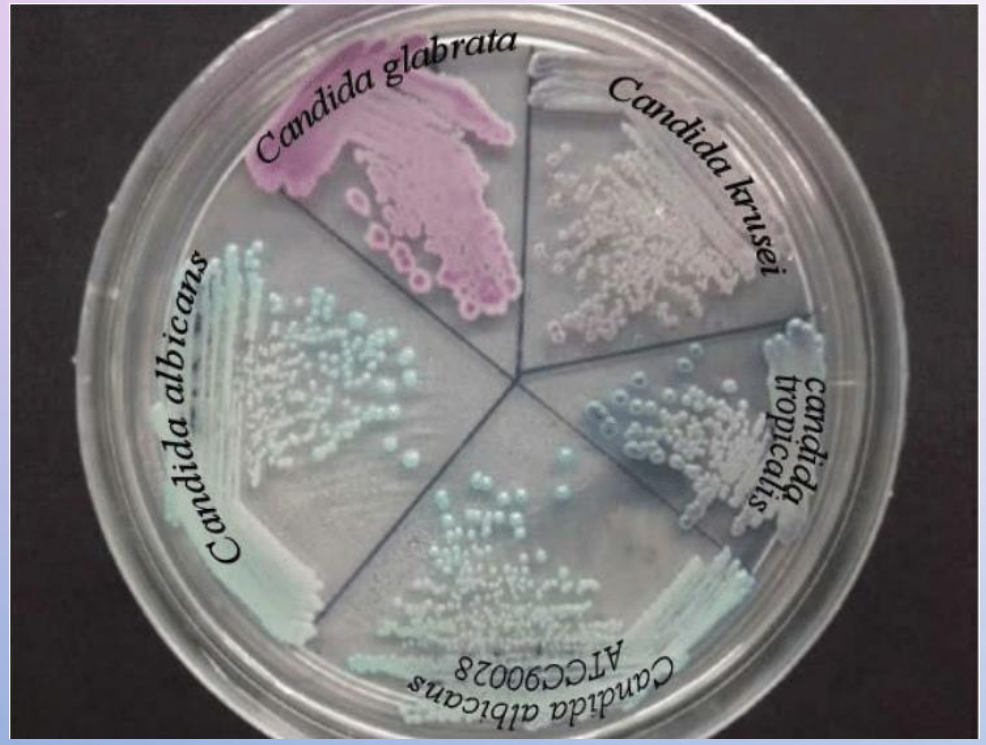
INVASIVE NEONATAL CANDIDIASIS

Introduction



- More than 150 species have been described ; of these , more 20 different species are associated with infection in humans .
- **C.albicans** is the most frequent species isolated pathogenic isolated pathogenic from human .
- Other more commonly isolated pathogenic species include **C. parapsilosis , C .tropicalis , C.glabrata , C.krusei .**

Neonatal candidiasis

- Candida is an important cause of neonatal infections and is associated with significant morbidity and mortality .
- Incidence IC in ELBW is around **10%**
- Candidemia accounts for 9% of BSI in patients with CHD cared for in NICU in the first 4 month of life .

PATHOGENESIS

- Exposure
- Adhesion
- Colonization/biofilm
- Infection (BSI /UTI /meningitis /cutaneous)
- End –organ dissemination (heart /eyes / CNS/ liver /spleen /joint)

Colonization

- Colonization is the key step in the pathway from exposure to dissemination .
- Vertical (maternal) or horizontal (nosocomial)
- Colonization occurs on the **skin and GI** tract before **respiratory tract**
- In the first weeks of life : **10%** of full –term infants compared with **27% to 62%** of VLBW
- Antibiotic treatment alone led to increased candida colonization.
- Antibiotic + dexamethasone increase colonization & dissemination

Risk factors

- Extremely preterm neonate (immature skin and GI tract)
- Prolonged ICU care (parenteral nutrition , mechanical ventilation, Central venous access)
- Medications (H2-blocking agents , PPI, corticosteroids , broad spectrum antibiotics
- GI dysmotility and disease (NEC)

OUTCOME

- **Invasive candidiasis in infant :**

- Prolonged hospitalization
- Neurodevelopmental impairment
- Death in almost 75% of affected ELBW (less than 1000G)

Candida infections in neonate

MUCOCUTANEOUS CANDIDIASIS

- Oropharyngeal candidiasis (thrush)
- Diaper dermatitis

Invasive infections

- Congenital cutaneous candidiasis
- Candidemia
- Catheter –related infections
- Urinary tract infection
- Central nervous system infection
- Endocarditis

CONGENITAL CUTANEOUS CANDIDIASIS (CCC)

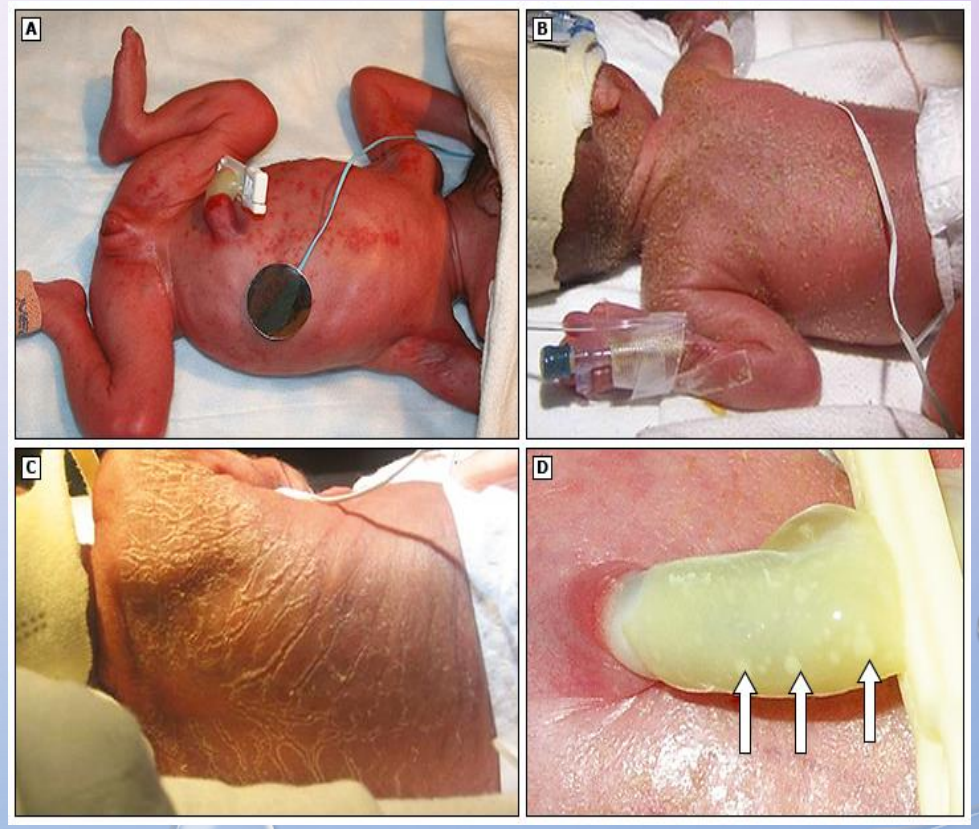
Is caused by an *ascending infection* into uterus before birth .

Risk of ascending infection is increased by:

- ✓ Ruptured membranes,
- ✓ Presence of a uterine or cervical foreign body,
- ✓ History of vaginal candidiasis

CONGENITAL CUTANOUS CANDIDIASIS

- Typically presents on the first day after birth
- Erythematous macules and/or papules on erythematous base.
- These lesions evolve into pustules, vesicles, or even bullae
- The frequent involvement of the palms and soles
- The skin involvement covers one or more areas (scalp / face / chest / abdomen /perineal /extremity)
- These lesion occasionally lead to desquamation .



CANDIDEMIA (BSI)

- Similar to bacterial sepsis
- Lethargy , hypotonia
- GI symptoms (distention , bloody stool)
- Thrombocytopenia (84%)
- Apnea , bradycardia (63%)
- Oxygen requirement
- Hypotention
- Hyperglycemia
- Elevated WBC (12%)
- Metabolic acidosis
- Absolute neutrophil count <1500
- Skin abscesses (painless pustules on an erythematous base or nodules

persistent hyperglycemia and thrombocytopenia in ELBW

CATHETER-RELATED INFECTIONS

- Infants who have indwelling catheters in place for >7 days are at risk for developing a catheter-related *candida* infection
- Infected catheters are a major cause of and risk factor for disseminated disease.

  Nonspecific symptoms of sepsis

  (temperature instability, feeding intolerance, apnea, hyperglycemia)
- An infected thrombus or fungal ball can form on the catheter tip, can be a source of septic emboli.

Urinary tract infection

- In ELBW : *Mortality rates in candida UTI alone (26%) similar to candida BSI (28%)* .
- **Similar to sepsis / Elevated Cr** in the absence of other pathology .

Risk factors for *Candida* UTI

congenital anomalies of the kidney and urinary tract, obstruction, urinary stasis, an indwelling bladder catheter

The spectrum of *Candida* UTI

isolated candiduria , fungal debris within the renal collecting system , renal abscess .

CENTRAL NERVOUS SYSTEM INFECTION

- CNS infections can occur in association with candidemia .
- usually manifest as meningitis. (15% of cases of candidemia)
- Less commonly, brain abscesses, ventriculitis, vasculitis, and fungal masses within the subarachnoid space

CLINICAL MANIFESTATION VARIES :
subacute, indolent illness, which is only identified because of a high index of suspicion , to severe illness with cardiorespiratory instability and multiorgan failure . Clinical signs may be the same as in acute bacterial meningitis(temperature instability, irritability, poor feeding or vomiting, respiratory distress, and apnea) .

CENTRAL NERVOUS SYSTEM INFECTION

➢ *Complications of CNS infection :*

obstructive hydrocephalus,

cerebral atrophy, and

poor neurodevelopmental outcome

periventricular leukomalacia

- **CSF parameters may be normal . definitive diagnosis is based on isolating *candida* from the CSF culture**
- Infants diagnosed with *candida* CNS infection should be evaluated for other manifestations of systemic infection

ENDOCARDITIS

- **5.5 % to 15%** of cases of fungal sepsis .
- is a common complication of candidemia
- All infants diagnosed with candidemia should undergo echocardiography
- fungemia that lasted five or more days were more likely to have cardiac lesions .
- Central vascular catheters place infants at increased for endocarditis .

OCULAR INVOLVEMENT

- In the neonate, ocular involvement results from the hematogenous spread of *candida* to the eye.
- Indirect ophthalmoscopic examination /candidal chorioretinitis in all infants
- Candidemia without ocular involvement may be associated with an increased risk of developing severe retinopathy of prematurity (ROP)


DIAGNOSIS

BLOOD CULTURE

The diagnosis of candidemia is made by isolating a *Candida* species from the blood culture

Special fungal culture media are not needed to grow candida species

Sensitivity : 50%

multiple or repeat blood cultures should be performed

median time to positivity of 2–3 days, ranging from 1 to ≥7 days)

Focus on Obtaining sufficient blood culture volume ≥1ml

the catheter and a peripheral vessel

URINARY TRACT & CNS

- ***CANDIDA* URINARY TRACT INFECTION**
- A positive urine culture (>1000 colony forming units per ml [CFU/ml] in a specimen collected by suprapubic aspiration
- >10,000 CFU/ml in a catheterized specimen)

- **CNS INFECTION**
- Isolating a *candida* species from the cerebral spinal fluid (CSF) culture.
- CSF findings (cell count, chemistries) are variable
- **Normal CSF findings do not exclude CNS** involvement because the inflammatory response may be limited or delayed

CONGENITAL CUTANOUS CANDIDIASIS (CCC)

- culture from skin lesion & potassium hydroxide preparation ≥ 2 sites
- Skin biopsies are not needed
- Pathologic examination with fungal staining of the umbilical cord and placenta
- Blood , CSF (unless rash over back) , urine cultures (risk for dissemination)

HISTOLOGY /PCR / ANTIGEN

- **Histopathologic examination** (in differentiating tissue invasion from surface colonization)
- **PCR** : The sensitivity ranged from 77 to 95 percent and specificity ranged from 70 to 95 percent (up to date)
- **Serum βeta-D-glucan assay** :

  a major cell wall component of most fungi .

  sensitivity (ranging 49% to 76%) – significant number of false positive

Mannan antigen :

a major component of the cell wall in candida spp:

it can be found in serum during infection

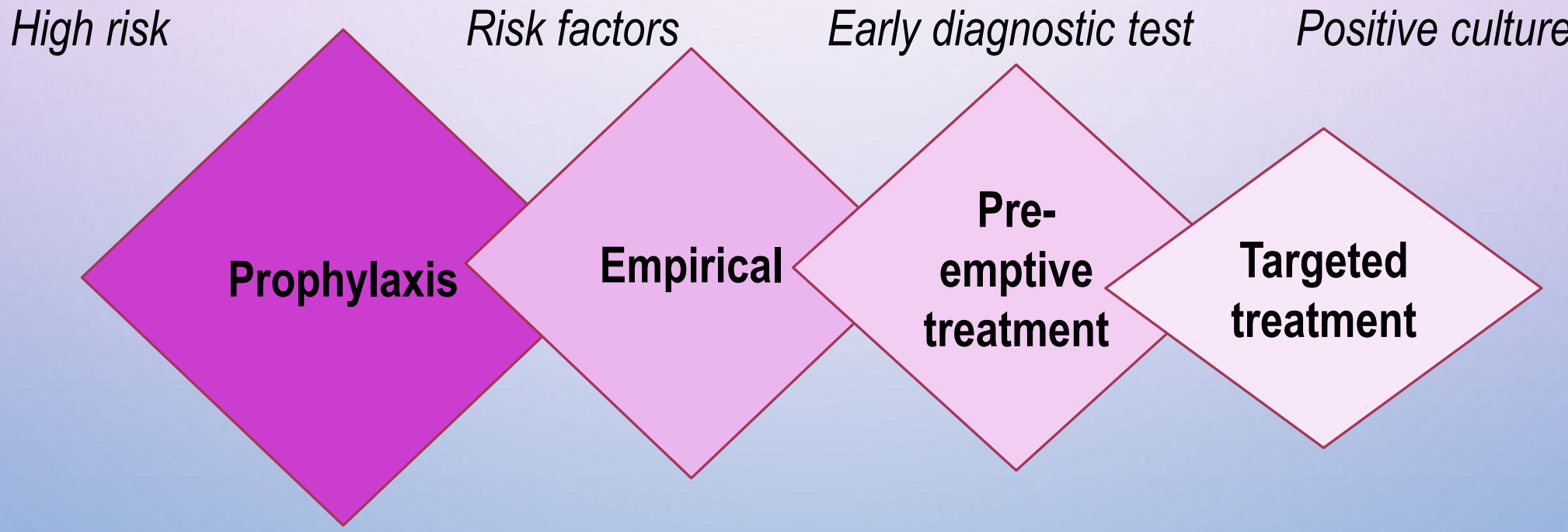
EVALUATION FOR EXTENT OF DISSEMINATION

Candida infection involving the bloodstream, urinary tract, CNS, eyes, heart valves, bone, or joints should undergo evaluation for systemic disseminated infection,

- Cultures of the blood, urine, and CSF (LP)
- Dilated eye examination to evaluate for endophthalmitis
- Echocardiography to assess for cardiac thrombi or vegetations
- Ultrasonography of the liver, spleen, kidneys, and bladder
- Head ultrasound

TREATMENT

APPROACHES TO INVASIVE CANDIDA INFECTION



ANTI FUNGAL DRUGS

- **AMPHOTERICIN B DEOXYCHOLATE**

  The preferred drug for treatment of most systemic neonatal candida infections

  lower test dosage are not needed

LIPOSOMAL AMPHOTERICIN B

The lipid formulations should **not** be used in patients with candida urinary tract infections

Decrease infusion related reaction and nephrotoxicity

CANDIDEMIA

- Amphotericin B (1 mg/kg per dose IV once daily).
- Monotherapy with fluconazole (12 mg/kg given iv once daily) / alternative for susceptible isolates if CNS infection has been excluded
- **Uncomplicated candidemia** (without a focal infection) for a minimum of 14 days after the first sterile blood culture and resolution of signs attributable to candidemia
- **Complicated candidemia associated with focal infection** – candidemia associated with focal infections (endocarditis, renal fungal masses) is often persistent and/or difficult to eradicate. Prolonged therapy is generally warranted in these infants (**usually 4 to 6 weeks).**

CANDIDEMIA

- Document clearance ≥ 3 cultures .
- Persistent candidemia ≥ 5 days :

repeat EOD screen

combination therapy with second anti fungal

TREATMENT (UTI)

Asymptomatic candiduria : neutropenic patients , VLBW (<1500 gr) , undergo urologic evaluation

1) The urinary catheter, if present, should be removed
2) In all neonates :B/C – LP –eye examination

   Brain Imaging – Abdominal

   Sonography

- Amphotericin B (1 mg/kg per dose IV once daily) for 10 to 14 days
- Fluconazole (12 mg/kg given orally or IV once daily) is an acceptable alternative for susceptible isolate
- Echioncandins have poor urinary concentration (Red book)

CATHETER-ASSOCIATED CANDIDEMIA

For catheter-associated candidemia without evidence of dissemination:

- Amphotericin B (1 mg/kg per dose given intravenously [IV] once daily)
- removal of the CVC.
- The duration of therapy is typically 14 days from the first negative culture.
- Fluconazole (12 mg/kg given IV once daily) is an acceptable alternative for susceptible isolates.

CNS INFECTION

- Amphotericin B monotherapy (1 mg/kg per dose IV once daily).
- Therapy is for at least **three weeks** and should be continued until clinical signs, CSF abnormalities, and radiographic abnormalities (if present) have resolved.
- CNS devices (shunts and ventriculostomy drains), if present, should be removed . flucytosine is not routinely recommended because of concerns regarding toxicity
- An alternative regimen is liposomal Amphotericin 5 mg/kg daily (IDSA)

CCC

- Systemic antifungal therapy for neonates with CCC (14 –day course of IV antifungal)
- for premature infants and infants with complicated infection (clinical signs of sepsis or respiratory distress), amphotericin B is appropriate therapy .
- Term infants who are tolerating feeds can be treated with oral fluconazole.
- The risk of dissemination is greatest in extremely low birth weight

PROPHYLAXY

- Is recommended for ELBW cared for in NICU with high rate of invasive candidiasis **≥ 10%** .(IDSA – RED BOOK)
- Prophylaxis prevents IC by decreasing candida colonization & IC

Iv fluconazole during the first 48 to 72 hours after birth at a dose of 3 to 6 mg /kg then twice a week for up to 6 weeks or until intravenous access no longer is required .

(for infants who tolerate enteral feeds , fluconazole **oral** absorption is good ,even in preterm

Strategies to reduce neonatal morbidity &mortality

- ❑ Use antifungal prophylaxis
- ❑ Start treatment of documented infections with appropriate antifungal
  - Consider starting empiric antifungal therapy if invasive candidiasis is suspected
  - promptly treat congenital cutaneous candidiasis
- ❑ Decreased broad –spectrum antibiotic use
- ❑ Decreased h2 blocker and PPI

  (use only for proven gastritis , restrict use to 3 days or until symptoms resolved
- ❑ Monitor rates of invasive candidiasis and feedback to staff

DX

- THE OVERALL SENSITIVITY OF BLOOD CULTURES FOR DIAGNOSING INVASIVE CANDIDIASIS IS ROUGHLY 50% [IDSA)
- THEY MAY BE NEGATIVE IN CASES OF EXTREMELY LOW-LEVEL CANDIDEMIA, INTERMITTENT CANDIDEMIA, DEEP-SEATED CANDIDIASIS THAT PERSISTS AFTER STERILIZATION OF THE BLOODSTREAM, OR DEEP-SEATED CANDIDIASIS RESULTING FROM DIRECT INOCULATION OF CANDIDA IN THE ABSENCE OF CANDIDEMIA. BLOOD CULTURES ARE LIMITED BY SLOW TURNAROUND TIMES (MEDIAN TIME TO POSITIVITY OF 2–3 DAYS, RANGING FROM 1 TO ≥7 DAYS)

- ECHINOCANDINS, WHICH INCLUDE CASPOFUNGIN, ANIDULAFUNGIN, AND MICAFUNGIN, ARE NOT ROUTINELY USED IN NEONATES. THEY MAY BE CONSIDERED IN INFANTS FOR WHOM THE USE OF FLUCONAZOLE AND AMPHOTERICIN IS PRECLUDED BECAUSE OF DRUG TOXICITY OR CANDIDAL RESISTANCE (UP TO DATE)
- GUIDELINES DO NOT RECOMMEND AS INITIAL THERAPY FOR NEONATAL CANDIDIASIS

  (BECAUSE OF CONCERNS ABOUT PENETRATION IN THE CSF)