DTFD
Diagnosis & Therapy of Fungal Diseases
5th DIAGNOSIS AND THERAPY OF FUNGAL DISEASES
Training Course for Fungal Infections in Neonates
10/10/17 Hotel Crowne Plaza, Belgrade, Serbia; www.dtfd.org www.fems-microbiology.org

Risk Factors and Clinical Manifestations of Fungal Infections in Neonates

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Objectives

- To review the risk factors and clinical manifestations of invasive fungal infections in neonates
- Focus
  - Invasive candidiasis
  - Neonatal mucormycosis

What are the Medically Important Fungi that Most Frequently Cause by Disease in Neonates?

- *Candida* spp.
- Mucorales
- *Aspergillus* spp.
- *Fusarium* spp.
- *Trichosporon* spp.

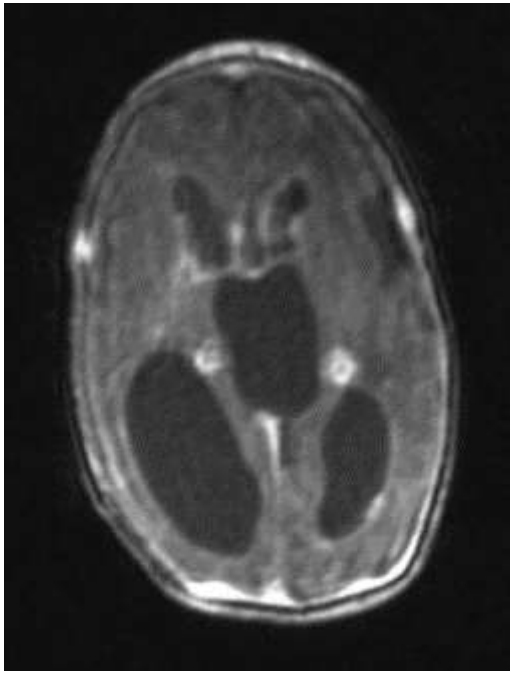
Candidiasis in Neonates

What are the Most Common Diseases Caused by *Candida* spp. in Neonates?

- Candidemia
- Disseminated candidiasis
- Hematogenous *Candida* meningoencephalitis (HCME)
- Candiduria
- Endocarditis
- Renal candidiasis
- Oropharyngeal candidiasis

Candida meningoencephalitis (HCME) in Infants and Children

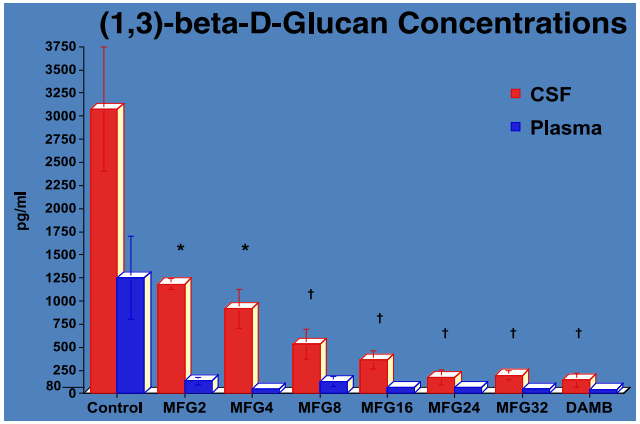
- HCME is a life-threatening infection in pediatric patients
- Associated with seizures, intraventricular hemorrhage, cortical blindness, and neurocognitive impairment, as well as the loss of developmental milestones
- Early diagnosis of HCME is difficult and recurrence following completion of antifungal therapy is common
- Also observed in Pre-B-cell ALL and in primary immunodeficiencies
- Difficult to diagnose
- High rate of relapse



Pediatrics. 112: 634-640; 2003; Early Hum Dev. 2011;87 Suppl 1:S75-6.

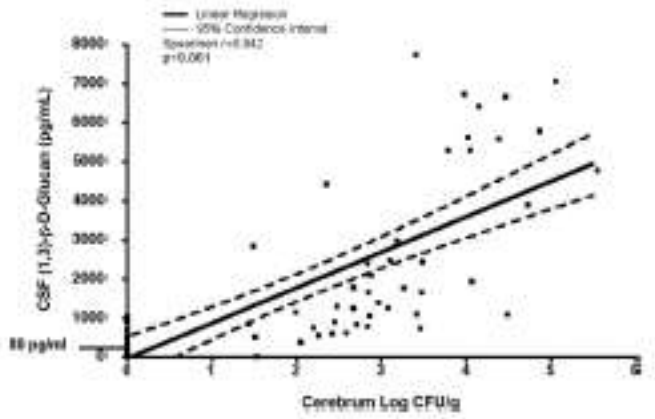
CSF BDG is a predictive biomarker for Candida tissue burden and response to antifungal therapy in experimental hematogenous Candida meningoencephalitis (HCME).

Comparison of BDG concentrations in CSF rabbits with before euthanasia.



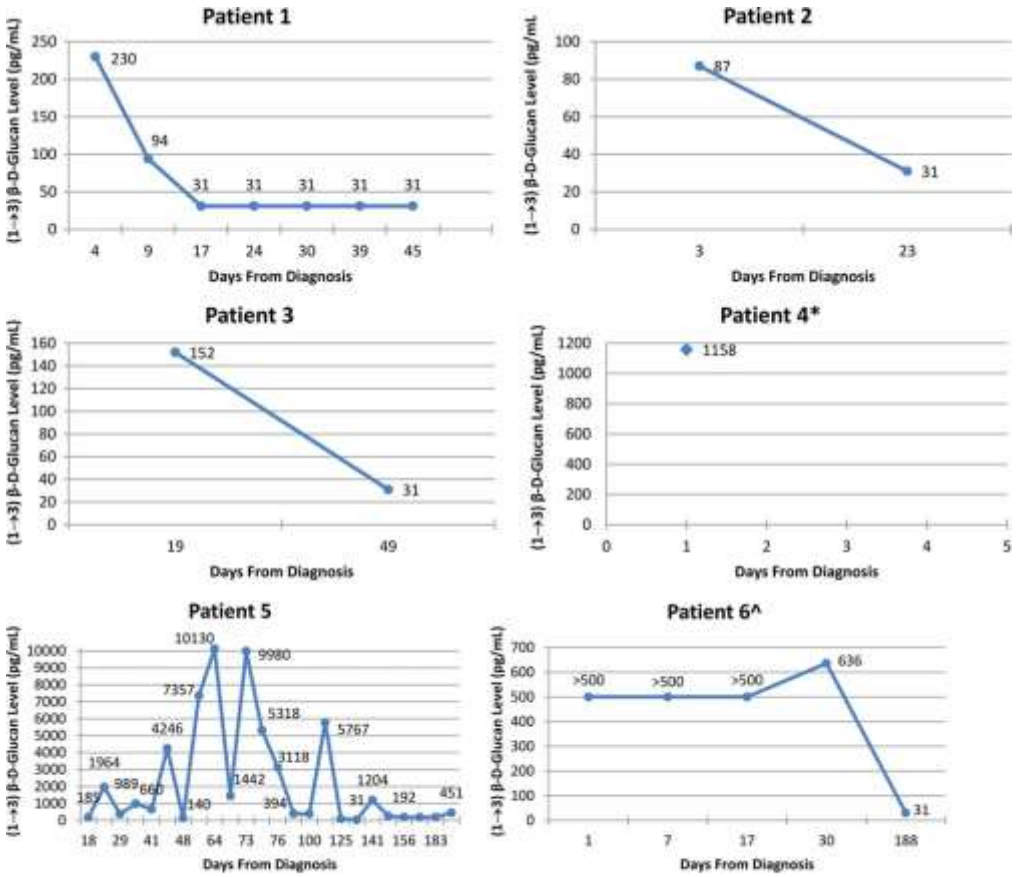
Increasing micafungin dosage significantly correlated with resolution of CSF BDG

Linear regression of BDG concentrations in CSF and fungal burden (log CFU/g) in cerebral tissue



Antimicrob Agents Chemother. 52: 4121-4129: 2008.

(1→3)-β-D-glucan in Cerebrospinal Fluid as a Biomarker for *Candida* and *Aspergillus* Infections of the Central Nervous System in Pediatric Patients



J Pediatr Infect Dis Soc. 5:277-86; 2016

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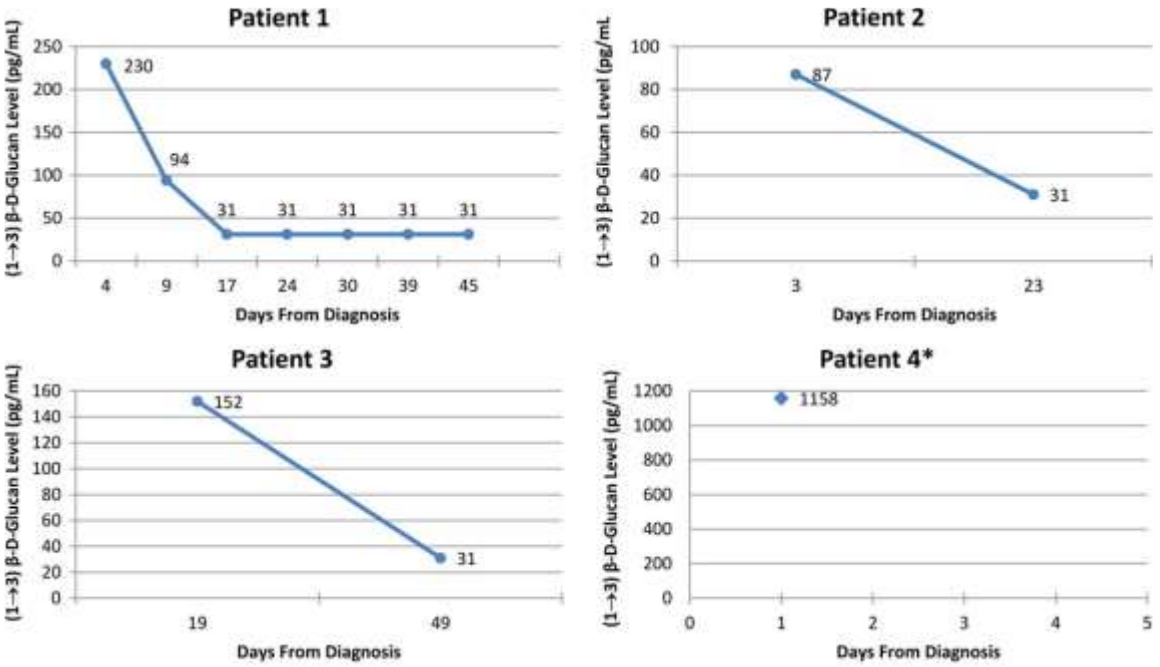

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What are the Risk Factors for Development of Invasive Candidiasis in Neonates?

- Invasive candidiasis is a leading cause of infection-related morbidity and mortality in extremely low-birth-weight (ELBW) (<1000 g) infants.
- In a study involving a prospective observational cohort of 1515 ELBW infants over three years at 19 centers of the US NICHD Neonatal Research Network, Benjamin and *et al* quantified the risk factors predicting infection in high-risk premature infants.

Pediatrics. 126:e865-873; 2010.

What are the Risk Factors for Development of Invasive Candidiasis in Neonates?

- Among the 1515 infants enrolled, 137 (9.0%) developed invasive candidiasis documented by positive culture from 1 or more of the following sources:
  - blood (n=96)
  - urine obtained by catheterization or suprapubic aspiration (n=52)
  - CSF (n=9)
  - other sterile body fluids (n=10)

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Predictive Models of for Invasive Candidiasis in Neonates

- The first model identified potentially modifiable risk factors.
- In multivariable analysis, potentially modifiable risk factors associated with candidiasis included
  - presence of an endotracheal tube
  - presence of central catheter
  - receipt of intravenous lipid emulsion
  - administration of broad-spectrum antibiotics in the week prior to culture intrapartum antibiotics

Pediatrics. 126:e865-873; 2010

Predictive Models of for Invasive Candidiasis in Neonates

- The second model predicted candidiasis at the time of blood cultures. Components of the history, physical exam, and initial laboratory evaluation that predicted candidiasis included
  - vaginal delivery,
  - week of gestational age,
  - *Candida*-like dermatitis on physical exam,
  - central venous catheter,
  - lack of enteral feeding,
  - hyperglycemia, days of antibiotic exposure in week prior to culture, and thrombocytopenia.

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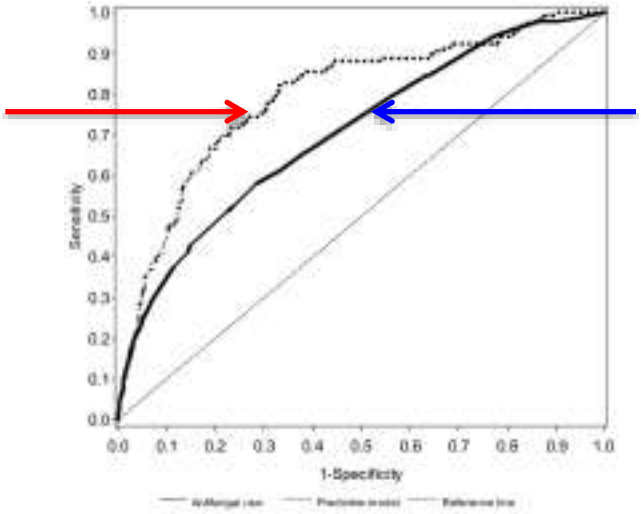
Predictive Models of for Invasive Candidiasis in Neonates

- The clinical prediction model was superior to clinical judgment.
- The clinical prediction model had an area under the receiver operating characteristic curve of 0.79, and was superior to clinician judgment (0.70) in predicting neonatal invasive candidiasis.



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What is the Risk of Mortality in Invasive Candidiasis in Neonates?

- Invasive candidiasis increases risk of death;
  - e.g., 47/137 (34%) infants with candidiasis died compared with 197/1378 (14%) without candidiasis ($p<0.0001$).
- Mortality is highest in the infants from whom *Candida* was isolated from multiple sources
  - e.g., urine and blood or urine and CSF; 16/28 (57%) of such infants died.
- Mortality is similar in patients who have *Candida* spp. isolated only from blood and those with *Candida* isolated only from urine.

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Mucormycosis in Neonates

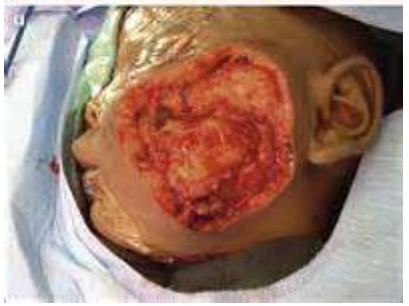
Mucormycosis in Neonates

- Among the invasive fungal infections caused by moulds in neonates, mucormycosis is the most lethal.
- In a systematic review of all published cases of 59 published cases that fulfilled stringent enrollment criteria, overall mortality of neonatal mucormycosis is 64%.
- Most of these infants (77%) were premature.
- The most common sites of mucormycosis were gastrointestinal (54%) and cutaneous (36%) tissues.
- This pattern differs from sinopulmonary and rhinocerebral patterns of older children.

Am J Perinatol. 26:565-73; 2009.

What are the Clinical Manifestations of Cutaneous Mucormycosis in Neonates?

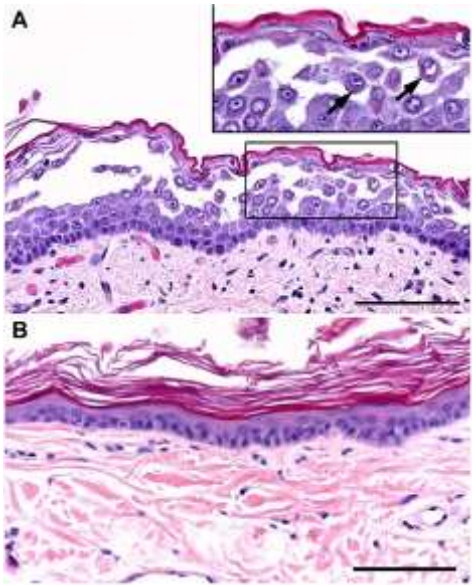
- The cutaneous lesions typically appear as small, black eschars on the back, extremities, or face that then spread rapidly to involve surrounding tissues.
- Such infections have been linked to sporangiospores contaminating sheets on which the infants are laying or to contaminated bandages or arm boards.

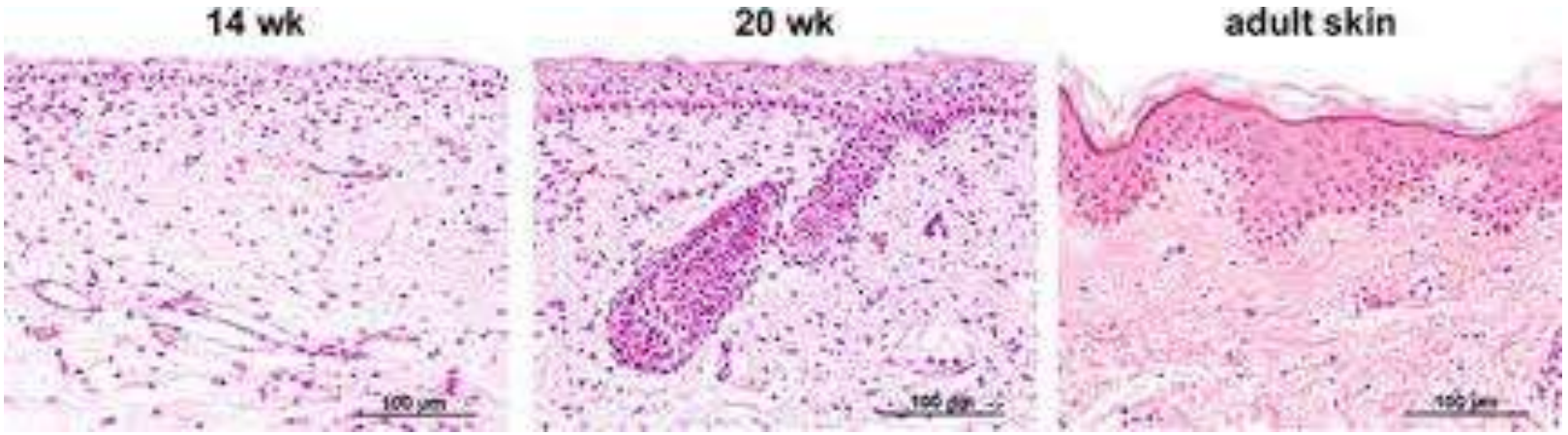


Pediatr Dermatol. 34:e116; 2017; Arch Otolaryngol Head Neck Surg. 2008;134:206-9.

What are the Clinical Manifestations of Cutaneous Mucormycosis in Neonates?

- The tenuous skin and immaturity of the innate immune system of neonates provides conditions in which local hyphal invasion may occur.





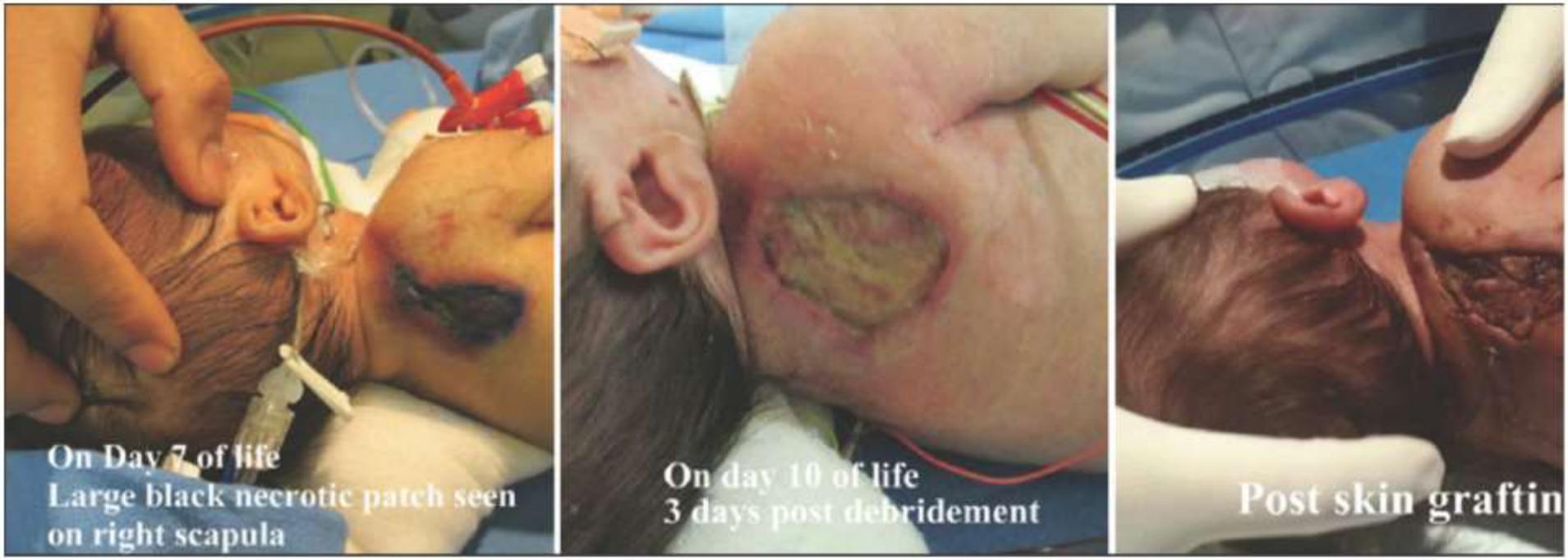
What are the Clinical Manifestations of Cutaneous Mucormycosis in Neonates?

- As the differential diagnosis is broad, a definitive diagnosis may be delayed, many patients (37%) received no antifungal therapy.
- A higher fraction of neonates treated with amphotericin B and surgery survived than those who received no therapy (70% versus 5%).
- A combination of amphotericin B and surgery is common management strategy in survivors.

Am J Perinatol. 26:565-73; 2009.

What are the Clinical Manifestations of Cutaneous Mucormycosis in Neonates?

Lesions on the back may extend to involve the paraspinal muscles, intercostal muscles, and thorax resulting in extensive loss of soft tissue.



J Clin Neonatol. 5:262-4; 2016

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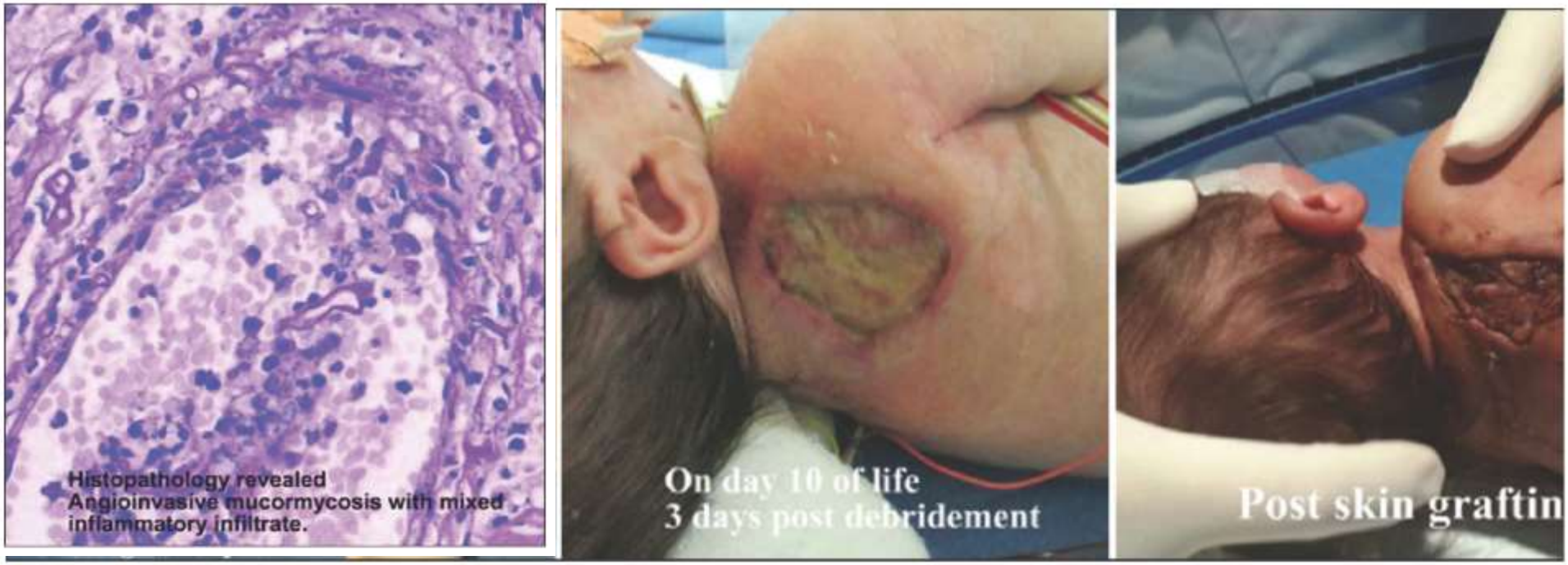

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Gastrointestinal Mucormycosis

- Gastrointestinal mucormycosis is an uncommon but highly fatal disease
- Constitutes approximately one-half of all mucormycosis infections among neonates.
- Possible risk factors include
  - Premature birth
  - malnutrition,
  - hyperglycemia,
  - Metabolic acidosis,
  - corticosteroid use,
  - recent surgery,
  - instrumentation with orogastric or nasogastric tubes,
  - exposure to contaminated products
- Combination of impaired mucosal integrity and an immature innate immune system.

Current Fungal Infect Reports, 9: 269–274

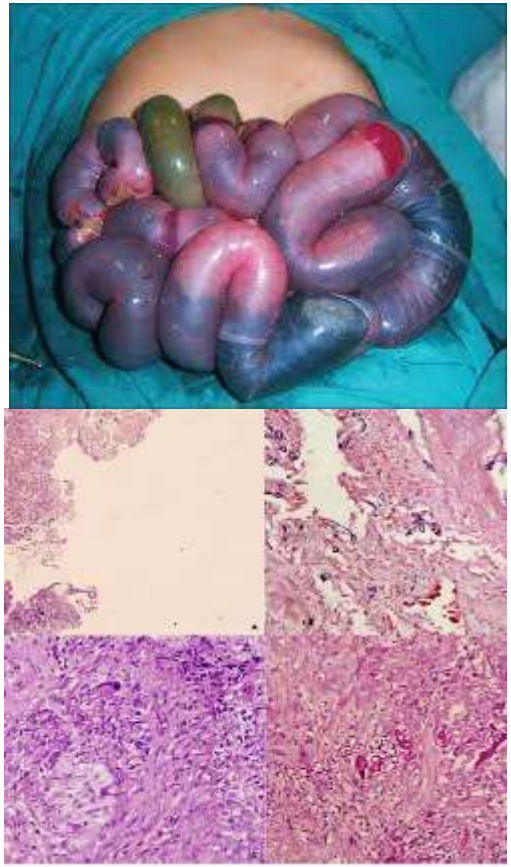
Gastrointestinal Mucormycosis

Clinical manifestations simulate necrotizing enterocolitis:

- abdominal pain and distention
- vomiting
- hematochezia
- fever
- peritonitis
- sepsis

Diagnosis is based on evidence of organisms in tissue

Mortality approaches 80 % but may be reduced with early surgical and medical intervention.



Current Fungal Infect Reports, 9: 269–274

Journal of Infection and Public Health 6:58—61; 2013

Summary

- Reviewed the risk factors and clinical manifestations of invasive fungal infections in neonates
- Focused
  - Invasive candidiasis
  - Neonatal mucormycosis