



УНИВЕРЗИТЕТ У БЕОГРАДУ  
МЕДИЦИНСКИ ФАКУЛТЕТ

# UNCOMMON PRESENTATION OF CANDIDA INFECTION IN THE NEWBORN INFANTS

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# NEONATAL CANDIDA INFECTION

- Candidiasis → infection with fungi of the genus Candida
- Invasive candidiasis is defined as a positive culture from blood, urine, cerebrospinal fluid or other sterile body fluids
- Candida is a serious and third common cause of late onset sepsis in newborns with high mortality
- The incidence has increased 11 fold over the past 15 years
- Preterm infants are predisposed to Candida infections because of immaturity of their immune system and invasive interventions

# EPIDEMIOLOGY

- The incidence of *Candida* infections is greatest in extremely low birth weight (ELBW)
- The overall incidence of *Candida* blood stream infections was 1.53 per 1000 patient-days among the infants admitted to the NICU
- The annual incidences varied based upon birth weight:
  - in infants >2500 g is 0.5 per 1000 patient-days
  - in ELBW category (<1000 g) was 3.51 cases per 1000 patient-days
- in nineties and decreased to 2.68 in the later period
- ***C. albicans*** is the most commonly isolated *Candida* sp. (60%) followed by *C. parapsilosis* (approximately 1/3 of cases)
- Reported mortality rates vary from 13 to 50%

# SITE OF INFECTION

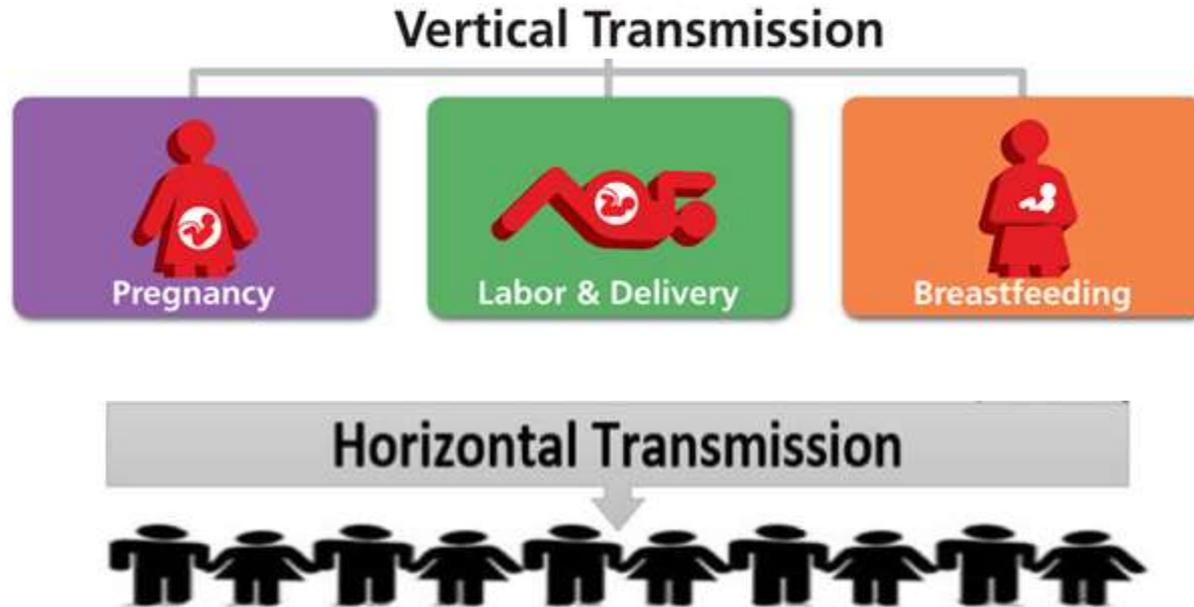
- Invasive blood stream infections are the most common neonatal presentation of *Candida* infections
- Other Candidal infections include meningitis, endocarditis, abscesses in the kidneys, spleen and liver, endophthalmitis, skin infections, urinary tract infection and osteomyelitis/septic arthritis

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Primary site of infection	%
urinary tract infection	35
gastrointestinal tract	18
skin or soft tissue	15
lung	13
central nervous system	8
cardiovascular	5
other sites	5

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# PATHOGENESIS: Transmission



- Both vertical and horizontal transmissions contribute to neonatal colonization
- Several outbreaks of *Candida* infection have been reported due to horizontal transmission from health care staff
- Exposure to surfaces that are contaminated by *Candida* is also a potential source of horizontal transmission

# PATHOGENESIS:

## Colonization & Penetration of host defense

- *Candida* generally colonizes the skin, GI and genital tract
- Colonization usually precedes invasive fungal infection
- In NICU, colonization occurs in 30-60% of patients
- Factors that promote gastrointestinal overgrowth, such as the use of broad-spectrum antibiotics are associated with an increased risk of *Candida* infection
- The penetration of the organism through the epithelial barriers from the sites of colonization results in locally invasive or disseminated infection
- The balance between benign colonization and invasive infection is primarily dependent on host factors

# RISK FACTORS FOR INVASIVE CANDIDIASIS

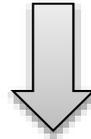
- Immunocompromised host :
  - low levels of circulating maternal IgG in preterm infants
  - reduced opsonization and complement functions
  - neutropenia
  - immature epithelial barriers (thin and delicate, readily break down), provide minimal protection
- Compromise of epithelial barriers:
  - invasive procedures (central venous and arterial catheters, intubation or surgery)
  - clinical conditions (NEC, BE)
- Increased density of candidal colonization (candidal overgrowth)
- Multiplicity of colonization sites in infants

# RISK FACTORS FOR INVASIVE CANDIDIASIS IN INFANTS

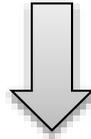
Saiman L et al. Pediatr Infect Dis J 2000	Benjamin DK Jr et al. Pediatrics 2010	Lee HJ et al. Pediatr Infect Dis J 2013*
Endotracheal intubation	central catheter	day of life >7
Length of NICU stay > 7days	broad-spectrum antibiotics (third-generation cephalosporins)	vaginal birth
Gestational age < 32 weeks	intravenous lipid emulsion	broad-spectrum antibiotics
Central venous catheter	endotracheal tube	central venous line
≥ 2 parenteral antibiotics	antenatal antibiotics	platelet count < 50 000
Shock		
Five-minute Apgar score < 5		
Total parenteral nutrition > 5 days		
Intralipid infusion alone > 7days		
H2 blockers		

\* in infants >1500 g birth weight

**Transmission**



**Colonization**

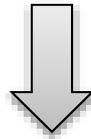


**Infection**

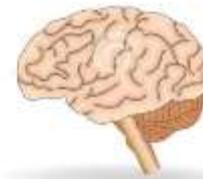
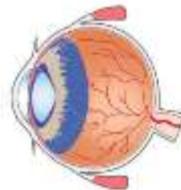
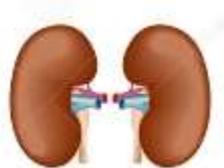
Immature immune defenses  
Tissue injury  
Co-infection

Adherence properties

Persistent fungemia  
Delayed vascular catheter removal  
Delayed diagnosis  
Inadequate antifungal dosing



**End-organ dissemination**



# CLINICAL MANIFESTATIONS



## Mucocutaneous candidiasis

- oropharyngeal candidiasis (thrush)
- diaper dermatitis



## Systemic candidiasis (Neonatal candidemia)

- catheter-related
  - localized infections
- } progress to disseminated infections and multiorgan involvement



## Catheter-related infections without multiorgan involvement



## Invasive focal infection

- meningitis, urinary tract infections, peritonitis, endophthalmitis, osteomyelitis, and septic arthritis.

# Case presentation

- A male infant was a first child in family
- Pregnancy was uneventful, delivery at term, 39 weeks, CS
- BW was 4300g, Apgars were 7 and 8 in 1<sup>st</sup> and 5<sup>th</sup> minute, respectively
- Because of signs of respiratory distress parenteral antibiotics were started at 1<sup>st</sup> day of life (DOL)
- Initial lab analyses revealed elevated c-reactive protein (CRP) of 55mg/l and Enterococcus sp was isolated from gastric aspirate
- In the 8<sup>th</sup> DOL elevation of CRP occurred again and third generation cephalosporin was commenced
- In the 13<sup>th</sup> DOL antibiotics were changed to meropenem, CRP concentration was slightly elevated (30 mg/l) and all cultures were sterile
- Infant was transferred to tertiary level hospital in the 22<sup>nd</sup> DOL because of necessity for further investigation

# Case presentation

- Clinical examination on admission was normal except signs of diaper dermatitis and mild hypotonia
- Lab analysis showed mild anaemia with thrombocytosis (631 000) and slightly elevated CRP (28 to 41 mg/l)
- Antimicrobial therapy included meropenem, vankomicin and fluconazole
- On the 4<sup>th</sup> day of hospitalization (26<sup>th</sup> DOL) swelling of left knee and reduced movements of the leg were noticed
- X-ray of the knee was performed and after consultation of pediatric orthopedic specialist infant was transferred to Surgery department because of clinical and radiological evidence of septic arthritis

# Case presentation



# Case presentation

- Arthrotomy with drainage of left knee was performed at the same day of transfer
- *Candida albicans* was isolated from drained fluid
- After the sensitivity of *Candida* was determined the therapy with amphotericin B colloidal dispersion (ABCD) was started and continued for 3 weeks parenterally.
- Per oral therapy with intraconazole was continued for next 3 weeks

# CANDIDA ARTHRITIS (CA)

- Rarely occurs as an isolated event and typically is a result of disseminated infection
- The signs and symptoms of CA are similar to those that occur in SA caused by bacteria
- Diagnosis of CA is based on:
  - clinical findings: swelling and decreased range of motion
  - radiological finding: widening of joint spaces
  - isolation of Candida in cultures of synovial fluid and blood
- In majority of studies *Candida albicans* is the most common fungal pathogen



# CANDIDA ARTHRITIS (CA)

- CA occurs as mono or oligoarthritis
- Knee joint is mostly involved
- CRP is more sensitive than ESR as indicator of CA and as a marker of patient's response to therapy
- **Amphotericin B** is the recommended as the preferred initial therapy in neonates with CA (during 3-12 weeks)
- **Fluconazole** is alternate therapy (alone or in combination with Amphotericin B)
- Surgical treatment includes aspiration or arthrotomy and open drainage



# Group of patients

- During short period in 2009, four infants with Candida arthritis (CA) were hospitalized in three tertiary level neonatal institutions in Belgrade
- All infants were born in same Maternity hospital
- Diagnosis of CA were made on the basis of clinical and radiological signs of arthritis and isolation of Candida from synovial fluid and blood culture

# Characteristics of four infants with SA

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Characteristic	Number
Gender M:F	2:2
Gestation	
Preterm	3 (36.4 ± 0.23 wks)
Term	1 (39 wks 6 d)
Mode of delivery	
Vaginal : CS	1:3
Body weight (grams)	2945±907g
5 <sup>th</sup> minute Apgar (Med)	9.5
Early exposure to broad-spectrum antibiotics	4
Length of NICU stay > 7days	4
Central lines, intubation, TPN	0

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# Clinics & Labs

Patient	Early symptoms (DOL)	Antibiotics (day of start)	Symptoms of SA	Joint	WBC	Plt	CRP	Patogen	Sample	Therapy	Sequeles
<b>1</b>	3	3	49	Knee	↓	↓	↑	Candida albicans	BC/SF	Fluconazol ABCD	None
<b>2</b>	1	1	26	Knee	↓	⊥	↑	Candida albicans	SF	Fluconazol ABCD	None
<b>3</b>	2	1	53	Knee	↓	↓	↑	Candida albicans	BC	Fluconazol ABCD	None
<b>4</b>	1	1	31	Elbow /knee	↑	⊥	↑	Candida albicans	SF	ABCD	None

BC - blood culture; SF - synovial fluid; ABCD – amphotericin B colloidal dispersion

# CONCLUSION

- Arthritis is an uncommon presentation of Candida infection in newborns
- All infants with disseminated Candida infection must be evaluated for signs of joint involvement
- Diagnosis of CA is based on clinical and radiological findings and confirmed by isolation of Candida in cultures of synovial fluid and blood
- The high index of suspicion is necessary for timely diagnosis
- Amphotericin B is the recommended as the preferred initial therapy in neonates with CA
- Prevention efforts have focused on the preterm infants in NICUs who are at the highest risk for invasive Candidal infections