

# CANDIDA INFECTION IN NEONATES

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DEPARTMENT OF NEONATOLOGY – CHILDREN'S HOSPITAL 2

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# CONTENTS

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- Overview
- Antifungal therapy
- Fluconazole prophylaxis

# OVERVIEW

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- Important cause of neonatal infection
- Significant morbidity and mortality, especially in ELBW and VLBW infants
- Overall rate of Candida bloodstream infections among NICU patients was 1.5% (128 NICUs in the US from 1995 to 2004)<sup>[1]</sup>
- Similar incidence rates have been reported in studies from other regions, including China, Canada and Spain<sup>[2]</sup>

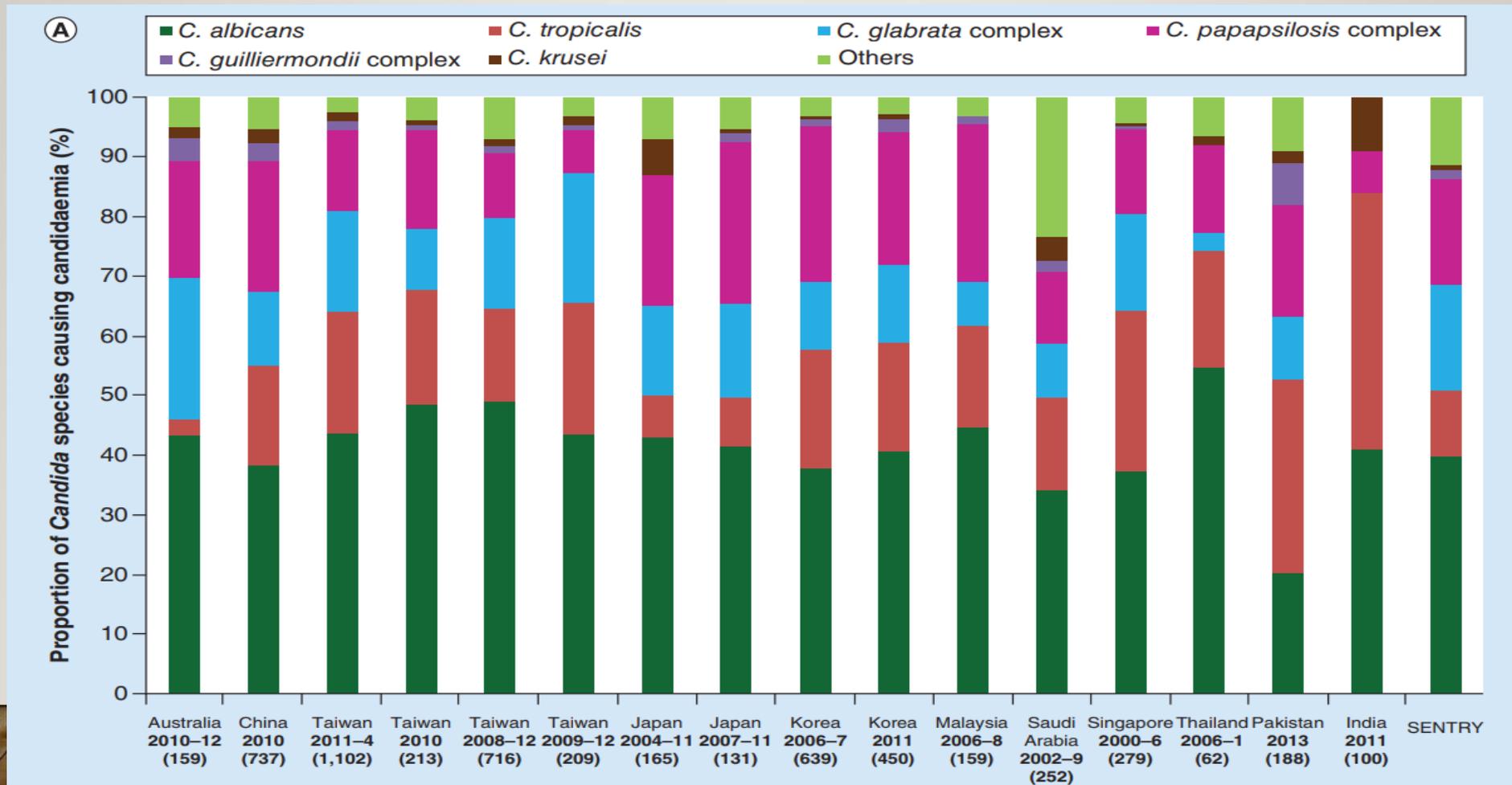
## OVERVIEW

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# Epidemiology of candidemia and antifungal susceptibility in invasive *Candida* species in the Asia-Pacific region

He Wang<sup>1,2</sup>, Ying-Chun Xu<sup>\*1</sup> & Po-Ren Hsueh<sup>\*\*3</sup>

# OVERVIEW



# OVERVIEW

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- Two categories of Candida infections in neonates:
  - Mucocutaneous candidiasis (includes oropharyngeal involvement and diaper dermatitis)
  - **Invasive infections (involves bloodstream, urinary tract, central nervous system and other focal sites)**

# ANTIFUNGAL THERAPY EVIDENCE – BASED MEDICINE

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## Invasive candida infections

Candidemia

CNS  
infection

UT  
infection

# RISK FACTORS FOR INVASIVE CANDIDIASIS<sup>[3]</sup>

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- Endotracheal intubation
- Length of NICU stay > 7 days
- Gestational age < 32 weeks
- Presence of a central venous catheter
- Exposure to  $\geq 2$  parenteral antibiotics
- Shock
- Five – minute Apgar score < 5
- Total parenteral nutrition for > 5 days
- Intralipid infusion alone for > 7 days
- Exposure to H2 blockers
- Use of broad – spectrum antibiotics

# ANTIFUNGAL THERAPY

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- Polyenes
- Triazoles
- Nucleoside analogues
- Echinocandins

# POLYENES

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- Amphotericin B deoxycholate (AmB)
- Amphotericin B liposomal complex (ABLCL)
- Amphotericin B colloidal dispersion (ABCD)
- Liposomal amphotericin B (L-AmB)

PEDIASTR INFECT DIS J. 2012 MAY; 31 (5): 439 - 443

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**Antifungal Therapy and Outcomes in Infants with Invasive  
*Candida* Infections**

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*Amphotericin B deoxycholate as reference*

	<b>Odds ratio (95% CI)</b>	<b>P</b>
<b>Mortality</b>		
Amphotericin B deoxycholate	Reference	
Amphotericin B lipid products	1.96 (1.16, 3.33)	0.01
Fluconazole	0.82 (0.46, 1.47)	0.51
Combination therapy	0.63 (0.18, 2.25)	0.48
<b>Therapeutic failure</b>		
Amphotericin B deoxycholate	Reference	
Amphotericin B lipid products	1.62 (1.00, 2.64)	0.05
Fluconazole	1.21 (0.76, 1.93)	0.42
Combination therapy	0.65 (0.26, 1.64)	0.36

*Fluconazole as reference*

	<b>Odds ratio (95% CI)</b>	<b>P</b>
<b>Mortality</b>		
Fluconazole	Reference	
Amphotericin B lipid products	2.39 (1.18, 4.83)	0.02
Amphotericin B deoxycholate	1.22 (0.68, 2.18)	0.51
Combination therapy	0.77 (0.20, 2.98)	0.70
<b>Therapeutic failure</b>		
Fluconazole	Reference	
Amphotericin B lipid products	1.34 (0.73, 2.46)	0.34
Amphotericin B deoxycholate	0.83 (0.52, 1.32)	0.42
Combination therapy	0.54 (0.20, 1.46)	0.22

# Neonatal Invasive Candidiasis: A Prospective Multicenter Study of 118 Cases

**José B. López Sastre, M.D.,<sup>1</sup> Gil D. Coto Cotallo, M.D.,<sup>1</sup>  
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# TRIAZOLES

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- Fluconazole
- Itraconazole
- Voriconazole
- Posaconazole
- Isavuconazole

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# Fluconazole Loading Dose Pharmacokinetics and Safety in Infants

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# NUCLEOSIDE ANALOGUES = FLUCYTOSINE

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- 25mg/kg 4 times daily
- Salvage therapy in patients who have not had a clinical response to initial AmB therapy
- Adverse effects are frequent

# ECHINOCANDINS

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- Caspofungin, anidulafungin and micafungin
- Not routine used in neonates

# Refractory neonatal candidemia and high-dose micafungin pharmacotherapy

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# PROPHYLACTIC ANTIFUNGAL THERAPY

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## Prophylactic Fluconazole Is Effective in Preventing Fungal Colonization and Fungal Systemic Infections in Preterm Neonates: A Single-Center, 6-Year, Retrospective Cohort Study

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# WHO SHOULD RECEIVE PROPHYLAXIS?

**Table 4 Fluconazole prophylaxis algorithm for preterm infants**

High risk groups	<1000 g birth weight or $\leq 27$ weeks gestation	1000–1500 g birth weight
Criteria	<5 days of life Endotracheal tube or CVC	Antibiotic therapy for >3 days With CVCs
Dosing	3 mg/kg intravenous fluconazole twice a week	
Length of prophylaxis	Twice a week (start DOL 1 ) up to 42 days  Prophylaxis will be stopped prior to 6 weeks if:  1. No need for intravenous (peripheral or central) access 2. Initiation of treatment of documented invasive fungal infection	During antibiotic treatment  While CVC is in place 3 mg/kg intravenous twice a week 1. During antibiotic treatment 2. While CVC is in place
Monitoring	Weekly liver function testing <sup>a</sup> Susceptibility testing of all clinical isolates <sup>b</sup>	
Level of evidence	Based on randomized placebo-controlled trials	Retrospective study Needs further study

# PROPHYLACTIC FLUCONAZOLE

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*The NEW ENGLAND JOURNAL of MEDICINE*

ORIGINAL ARTICLE

## A Multicenter, Randomized Trial of Prophylactic Fluconazole in Preterm Neonates

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# PROPHYLACTIC FLUCONAZOLE

## Comparison of antifungal prophylaxis agents: fluconazole vs. nystatin

	Fluconazole	Nystatin
Effect on colonisation	Decreases skin, gastrointestinal, respiratory, CVC and multisite colonisation	Decreases skin, gastrointestinal, and multisite colonisation
Effect on species colonisation	Highly effective against <i>C. albicans</i> Very good efficacy against <i>C. parapsilosis</i>	Highly effective against <i>C. parapsilosis</i> Very good efficacy against <i>C. albicans</i>
Route of administration	Given intravenously Can be given to all high risk infants including those with NEC, intestinal perforation, or ileus	Given enterally. Often not given in infants not on enteral feeds such as those with NEC, intestinal perforation, or ileus
Level of evidence	Multiple RCTs demonstrating efficacy even in extremely preterm infants (A-I). Efficacy and safety data in [REDACTED].	[REDACTED] <1500 g intubated infants (A-I). Limited efficacy data infants of low gestational age. Efficacy and safety data in 6 studies.
Efficacy	[REDACTED] <i>Candida</i> -related mortality decreased by 90%	[REDACTED]

# PROPHYLACTIC FLUCONAZOLE

Comparison of antifungal prophylaxis agents: fluconazole vs. nystatin

	Fluconazole	Nystatin
Resistance	No significant resistance to fluconazole (D II)	No data on resistance
Dosing	Twice-a-week dosing	3 to 4 times per day
Safety	Mostly well-tolerated with minimal side effects	Mostly well-tolerated with minimal side effects
Approximate cost of 4-week course (in the USA)	\$111	\$311

# PROPHYLACTIC FLUCONAZOLE

**Preterm infants**  
Birth weight < 1000 grams  
OR  
≤ 27 weeks gestation

## Dosing

3 mg/kg IV fluconazole  
Twice a week  
(First dose DOL 1, then Tuesdays, Friday at 10AM or other designated time)  
Give over 30-60 minutes (if central line present, give via central line)

## Length of Prophylaxis

Discontinue when no further need for IV access (Central or Peripheral)

## Treatment of invasive fungal infections (with non-azole antifungal)

For Documented or Suspected invasive fungal infections:  
Amphotericin B deoxycholate (Start at 1 mg/kg daily) **OR**  
Amphotericin B lipid formulations (If need to give via PIV)  
Start at 5 mg/kg daily

## Prevent Emergence of Resistance

1. Limit length of prophylaxis to time period IV access needed
2. Use Amphotericin for treatment of infections
3. If possible: obtain fluconazole susceptibilities (MIC) on all clinical and colonization fungal isolates in the NICU

# FLUCONAZOLE PROPHYLACTIC

Lee et al. *BMC Pediatrics* (2016) 16:67  
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BMC Pediatrics

RESEARCH ARTICLE

Open Access



## Efficacy and safety of fluconazole prophylaxis in extremely low birth weight infants: multicenter pre-post cohort study

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# SUMMARY

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- AmB deoxycholate 1mg/kg daily (Grade 1B)
- Fluconazole 12mg/kg intravenous or oral daily (in patients who have not been on fluconazole prophylaxis) (Grade 1B)
- CVC removal (Grade 1B)
- Duration of therapy for candidemia without obvious metastatic complications is for 2 weeks after documented clearance of Candida species (Grade 1B)