

What's New in Neonatal Candidiasis

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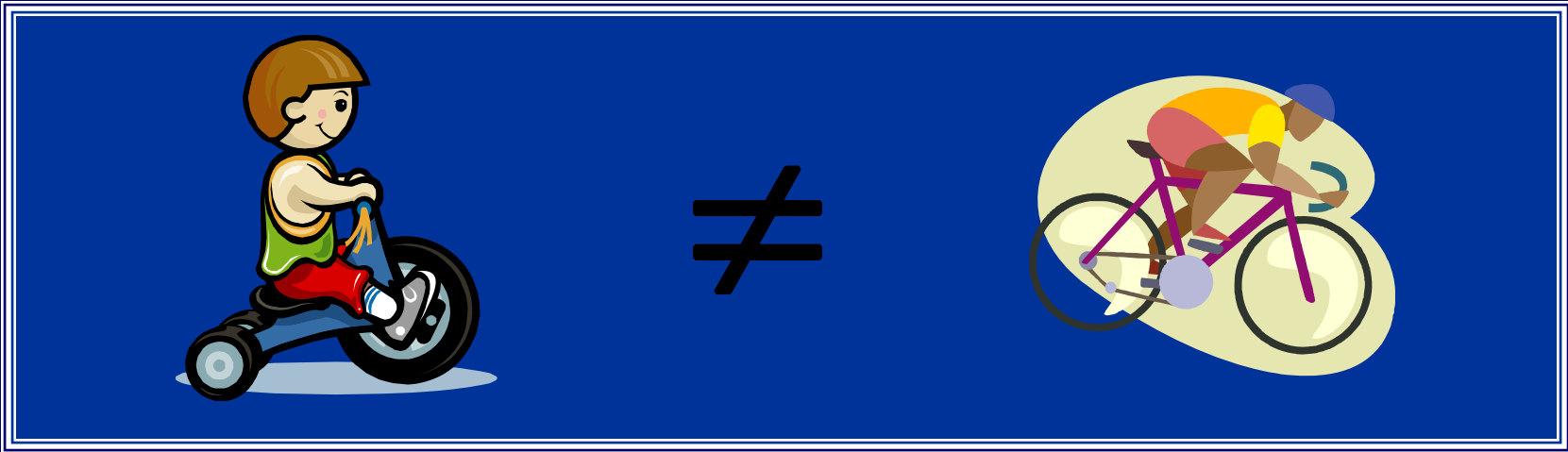


**Epidemiology/
Risk Factors**

Management

Prevention





Anatomic

- Primary barriers to defense in children (mucosa and integument) are fragile and easily colonized

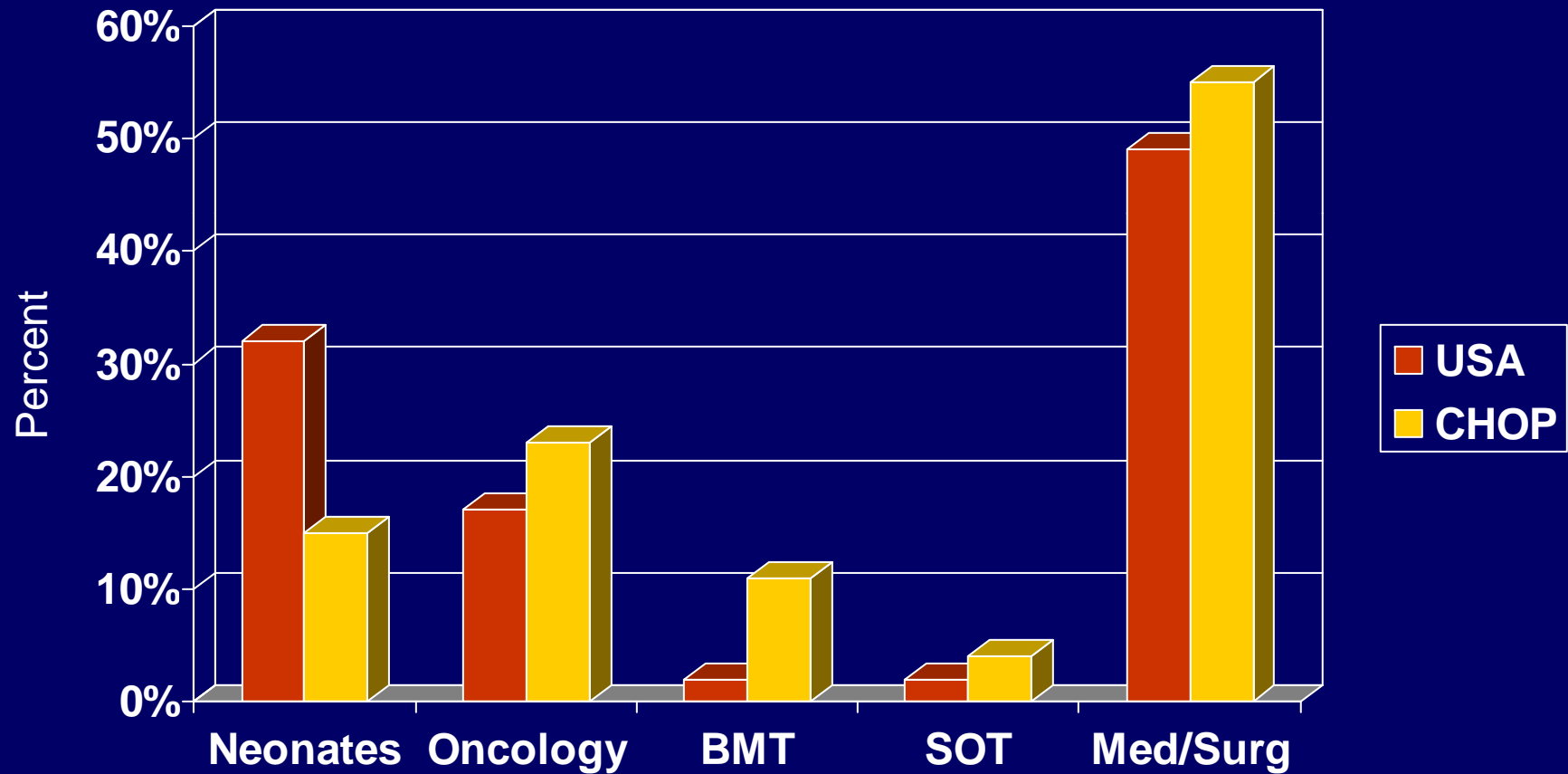
Physiologic

- Greater ability to tolerate more intensive treatments

Immunologic

- Functional immaturity of phagocytes and T lymphocytes
- Congenital immunodeficiencies

Candidiasis: Incidence



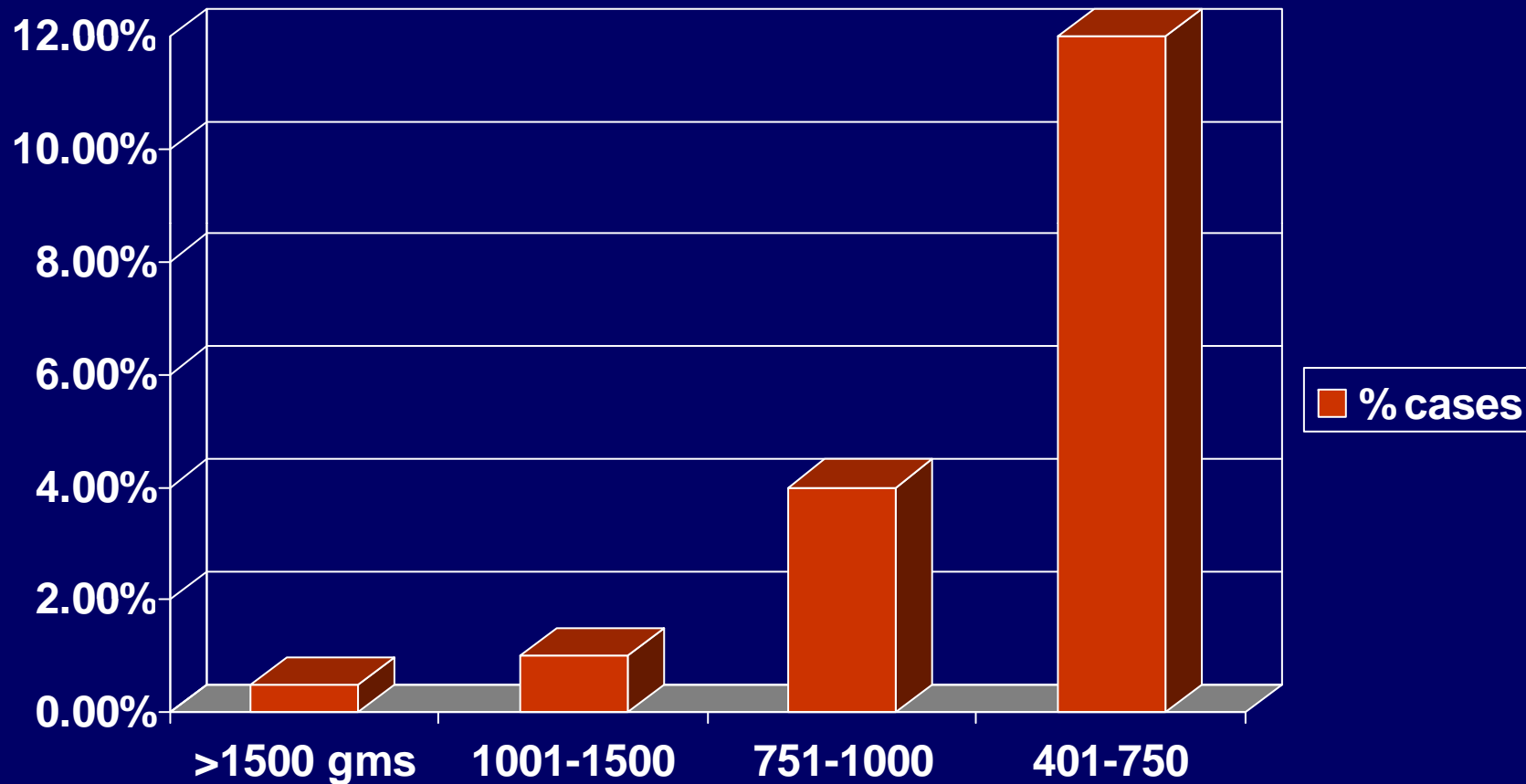
Zaoutis T, *PIDJ* 2004

Zaoutis, et al. *CID* 2005

Epidemiology

- 3rd most common cause of late-onset neonatal sepsis – 12.2% of cases
- Incidence/100,000 admissions – 2000 National Data
 - Neonates 150 (95% CI:130,160)
 - Older Children 43 (95% CI: 35,52)
 - Adults 30 (95% CI:26-34)
- US National Nosocomial Surveillance System Hospitals (NNIS) from 1995 to 2004
 - 128 NICUs (130,523 neonates)
 - 1997 cases of Candidemia
 - Median 7.5% (IQR: 4.6, 13.5%)

Neonatal Candidiasis: Incidence and Birth Weight



Stoll BJ, et al *Pediatrics* 2002

Benjamin DK et al. *Pediatrics* 2005

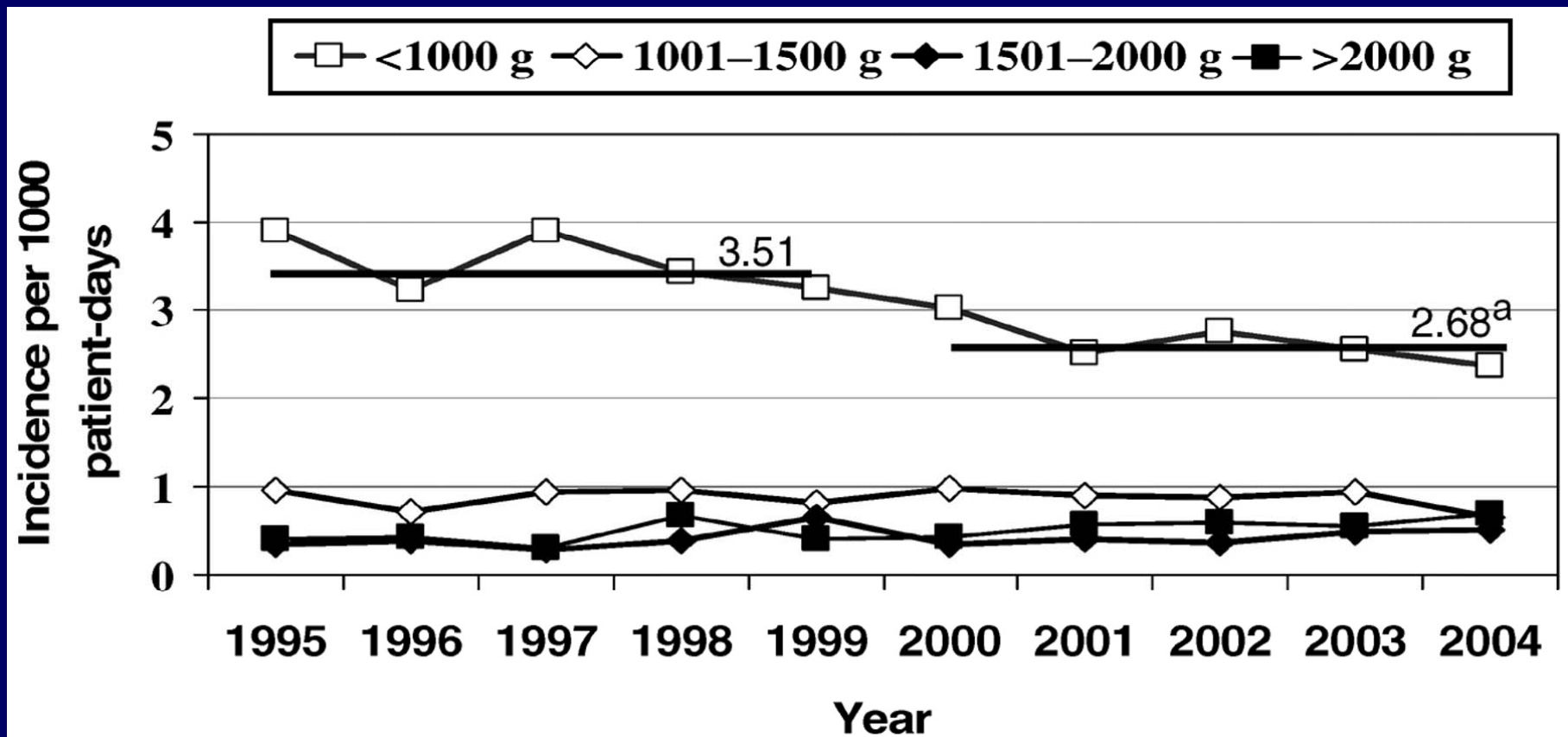
Benjamin DK, et al. *Pediatrics* 2003

Risk Factors

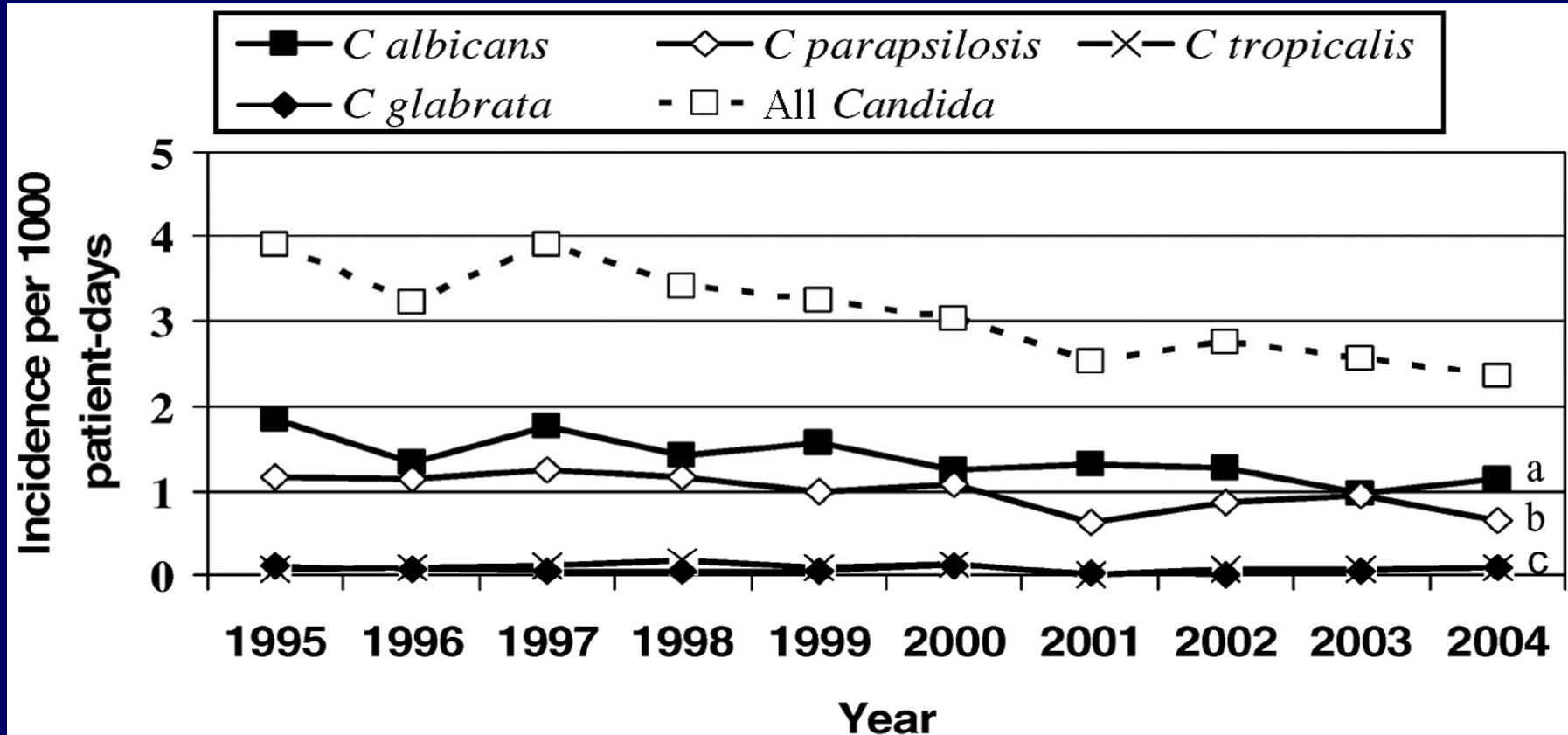
- Gestational age
- Prolonged rupture of membranes
- H₂ blockers
- Intubation
- Third-generation cephalosporins
 - Carbapenems and other broad-spectrum antibiotics
- Hyperalimentation
 - Lack of enteral feeding
- Central venous catheters

1. Saiman L, et al. *Pediatr Infect Dis J*. 2000;19:319-324. 2. Linder N, et al. *J Hosp Infect*. 2004;57:321-324. 3. Makhoul IR, et al. *Clin Infect Dis*. 2005;40:218-224. 4. Feja KN, et al. *J Pediatr* 2005; 147:156-161. 5. Benjamin DK, et al. *Pediatrics*. 2003; 112:543-547. 6. Benjamin DK, et al. *Pediatrics*. 2006;117:84-92. 7. Manzoni P, et al. *Pediatrics*. 2006;118:2359-64.

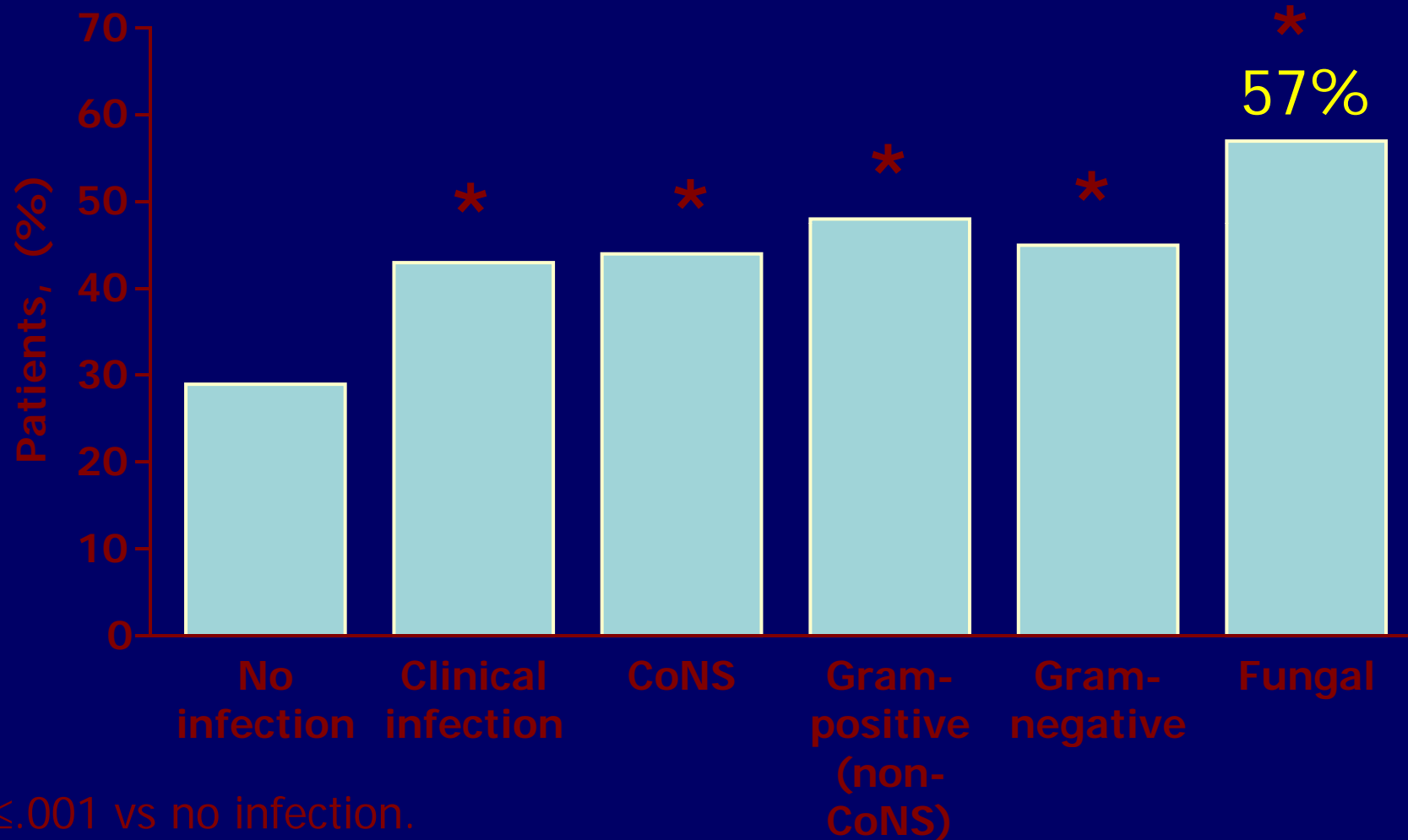
Neonatal Candidiasis: Incidence over Time



Neonatal Candidiasis: Incidence over Time by Species



Neurodevelopmental Outcomes and Bloodstream Infection in Infants <1000 g



* $P \leq .001$ vs no infection.

Attributable Outcomes

	Mortality (95% CI)	LOS (95% CI)	Cost (95% CI)
Neonatal < 1000 g	12% (5.5, 18.3)	3 (-5, 9)	39,045 (1,374 - 76,715)
Neonatal > 1000 g	- 4 % (-9.8, 1.4)	16 (8,24)	122,302 (80,457 - 164,148)

9

Clinical Vignette

- 26-week, 620-gram infant
- Extubated to CPAP on day of life (DOL) 2
- Enteral feedings started DOL 3
- DOL 15
 - Apnea
 - Hypotension
 - Platelet count fell from 165,000 to 70,000
- Blood, Urine and CSF sent for culture
 - Broad spectrum antibiotic therapy started

Should Empiric Antifungal Therapy Be Initiated?

- Review of 49 cases with fungal sepsis (Makhoul IR, Pediatrics 2001)
 - No mortality in 35 VLBW infants with fungal sepsis
 - Attributed this outcome to empiric therapy with amB
- Pre-post intervention study (Procianoy RS. Eur J Pediatr)
- <1500 g or “Very Sick NICU patient”
- Clinical signs of infection plus
 - Vancomycin and/or 3rd generation cephalosporin x 7 days
 - And 1 of the following: TPN, Mechanical ventilation, Postnatal steroids, H2 blocker, *Candida* rash or thrush
- Eliminated *Candida*-related mortality
 - 11 of 18 (61%) - No empiric therapy
 - 0 of 6 (0%) - Empiric therapy

Should Empiric Antifungal Therapy Be Initiated?

Multivariable Analysis of Predictors of Candidemia

Variable	Category	OR	95%CI	Points
Gestational age	≥28 wk	Referent		
	25-27 wk	2.02	(1.52-3.05)	1
	<25 wk	4.15	(3.12-6.12)	2
Thrombocytopenic	Value ≥150	Referent		
	Value <150	3.56	(2.68-4.74)	2
Cephalosporin or carbapenem	No	Referent		
	Yes	1.77	(1.33-2.29)	1

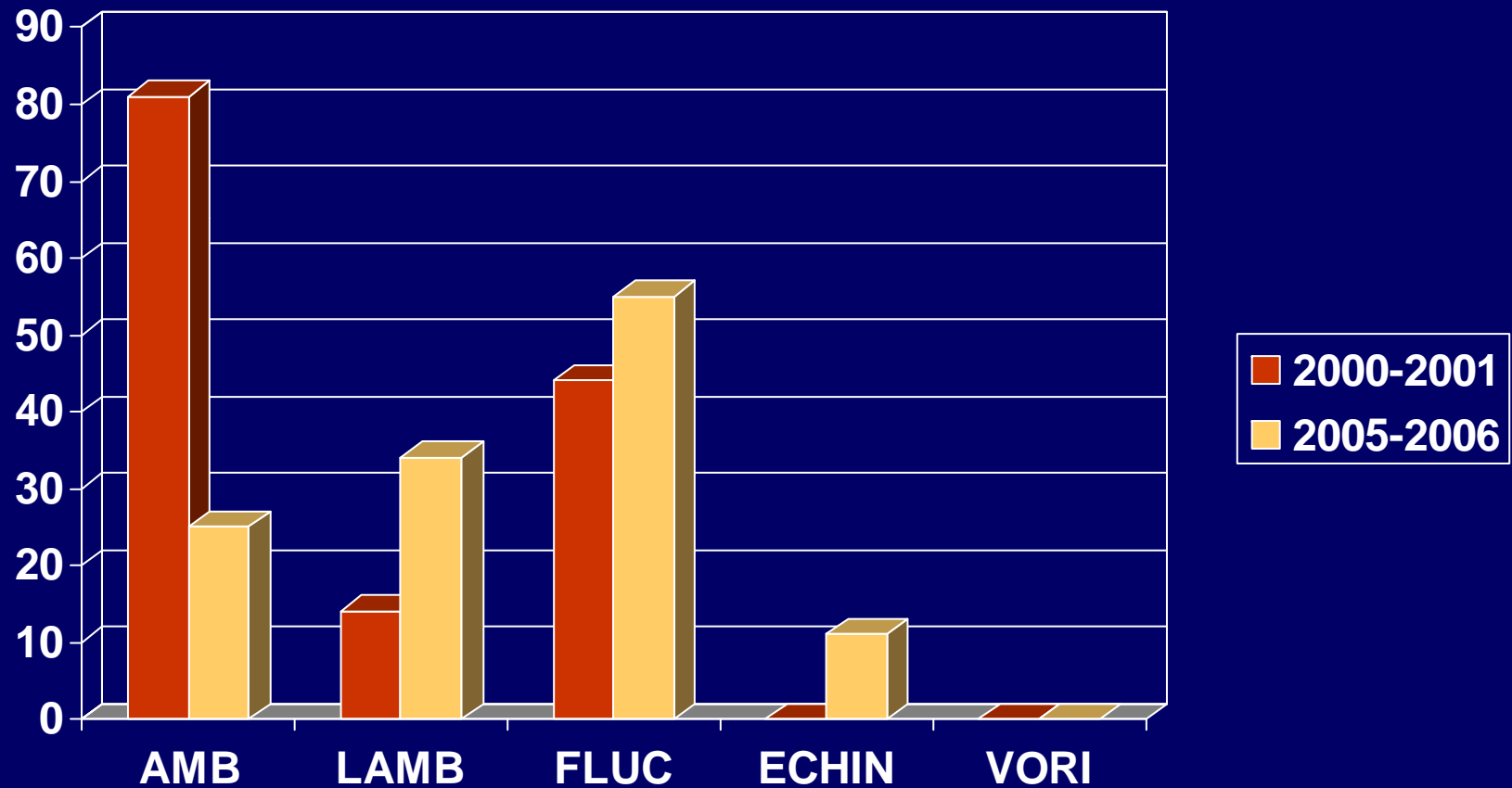
Need for Empiric Antifungal Therapy: Clinical Predictive Model

Score	Candidemic	Not Candidemic	Sensitivity	Calculated Specificity	LR(+)	LR(-)
0	4	2882	1	0		
1	47	6626	99%	14%	1.15	0.08
2	79	5155	85%	47%	1.62	0.31
3	77	3112	63%	71%	2.18	0.52
4	82	2233	41%	85%	2.78	0.70
5	59	877	17%	96%	4.10	0.87

Selection of Antifungal Agent

- IDSA Guidelines for the Treatment of Neonatal Candidiasis
- AmB deoxycholate 1 mg/kg (A-II)
 - Test dose not required; may contribute to delayed clearance
 - Tolerated well with limited effect on creatinine
- Lipid formulations at 3- 5 mg/kg (B-II)
- Fluconazole 12/mg/kg (B-II)
- Echinocandins should be used with caution
 - Caspofungin 25 mg/m² once daily similar levels to adult dose of 50 mg/day⁴
 - Micafungin 5-7 mg/kg in neonates > 1000 grams similar levels to adults receiving 100 mg and 150 mg

Candidiasis: Neonatal Antifungal Therapy



Does removal of the catheter improve outcomes?

- Prompt removal is associated with:
 - Lowered mortality rates
 - Shorter duration of candidemia
 - Reduced end-organ dissemination
- Intravascular catheter removal is strongly recommended (A-II)

Chapman RL. *Pediatr Infect Dis J.* 2000;19:822-827; Karlowicz MG, et al. *Pediatrics.* 2000;106:E63; Noyola DE, et al. *Clin Infect Dis.* 2001;32:1018-1023; Benjamin DK, et al. *Pediatrics.* 2006;117:84-92.

Does Removal of the Catheter Improve Outcomes?

Cohort study of 320 infants with candidemia

Prompt (<24 h) vs. delayed

- All cases of candidemia
 - Mortality 21% vs. 37% ($P=.024$)
 - Combined mortality + neurodevelopmental impairment (NDI) ($P=.01$)
 - No difference for NDI alone (45% vs. 63%) ($P=.08$)
 - No difference in time to clearance (5 vs 7.3 d)
- *Catheter removal and species*
 - *C. albicans*: 35% vs. 48%
 - *C. parapsilosis*: 10% vs. 31%

Does Removal of the Catheter Improve Outcomes?

Variable	No.	OR	95%CI
Catheter removal			
Early (within 1 day)	57	Reference	
Late	132	2.69	1.25-5.79
Gestational age			
<u>≥ 25</u> weeks	83	Reference	
< 25 weeks	106	3.91	1.85-8.29
Gender			
Female	94	Reference	
Male	95	2.30	1.09-4.84

When is the Bloodstream Clear of *Candida*?

- Duration of candidemia often prolonged
- Up to 10% of neonates will have positive blood cultures > 14 days
- 21% of infants with *Candida* BSI will have intermittent negative cultures between positive cultures
- Daily cultures should be performed until 3 or more documented negative cultures
- New central access could be placed >2 days after 3rd culture documenting clearance
- Duration of therapy: 3 weeks

End-Organ Dissemination

- Meta-Analysis
- Prevalence of:
 - Endophthalmitis 3% (IQR: 0-17%)
 - Meningitis 15% (IQR: 3-23%)
 - Brain Abscess or Ventriculitis 4% (IQR: 3-21%)
 - Endocarditis 5% (IQR: 0-13%)
 - Renal Candidiasis
 - By renal ultrasound 5% (IQR: 0-14%)
 - Positive urine culture 61% (IQR: 40-76%)
 - Lumbar puncture and eye exam recommended (B-III)
 - Imaging if persistently positive cultures

Antifungal Prophylaxis (FP) in Preterm Infants

Let's look at the data.....

Oral Prophylaxis - Nystatin

- One RCT to date
 - 67 intubated infants, birth weight < 1250 g
 - Bloodstream infection
 - 0/33 (0%) vs. 2/34 (6%) placebo, $P=.16$
 - UTI
 - 2/33 (6%) vs. 10/34 (29%) placebo, $P=.01$
- 1988-2006
 - A few retrospective reports of nystatin failure when initiated after colonization was detected

Oral Prophylaxis - Nystatin

- Prospective quasi-randomized study
 - Oral nystatin prophylaxis (NP) reduced the invasive candidiasis in ELBW and VLBW infants ($P=.004$)
 - Controls 36%
 - In colonized infants 14%
 - NP started at birth 3.6%

Fluconazole Prophylaxis Studies

- Randomized Placebo Controlled studies
 - Kicklighter 2001 (Colonization Study)
 - Kaufman 2001
 - Parikh 2007
 - Manzoni2007 (Multicenter RCT)
- Randomized Controlled studies
 - Kaufman 2005 (Dosing schedule comparison study)
- Non-randomized with historic retrospective controls
 - Bertini 2005
 - Healy 2005 and 2008
 - Manzoni2006
 - Uko 2006
 - Aghai 2006
 - Weitkamp 2008

Fluconazole Prophylaxis: Randomized Placebo-Controlled Trials

3 mg/kg with IV access up to 6 weeks

Study	N	FP	Placebo	P
Kaufman 2001	100 <1000 g	0 of 50 (0%)	10 of 50 (20%)	0.008
Subanalysis				
Subgroup <24 wks	9	0 of 4 (0%)	4 of 5 (80%)	0.04
Subgroup ≥24 wks	91	0 of 46 (0%)	6 of 45 (13%)	0.01

Fluconazole Prophylaxis: Randomized Placebo-Controlled Trials

- Multicenter, randomized, controlled trial
- 1:1:1 randomization
- 3 mg/kg, 6 mg/kg, or placebo

Study	N	FP	Placebo	P
Manzoni 2007 (<i>NEJM</i>)	322 <1500 g	7 of 216 (3.2%)	14 of 106 (13.2%)	<.0001

3 mg/kg and 6 mg/kg BOTH equally effective

* <1000 g (P=.02)

* <27 weeks (P=.007)

Analysis of Randomized Controlled Trials

- Efficacy
 - Cochrane Review 2007
 - Typical relative risk: 0.23; 95% confidence interval, 0.11, 0.46
 - Number needed to treat of 9 (95% confidence interval 6, 17)

Fluconazole Prophylaxis Retrospective Studies

Study	N (BIRTH WEIGHT)	FP	Control Group	P
Healy 2005	446 (<1000 g)	3 of 240 (1%)	15 of 206 (7%)	.001
Manzoni 2006	129 (<1000 g)	1 of 72 (1.4%)	13 of 57 (22.8%)	<.0001
	336 (1000-1500 g)	3 of 153 (2%)	9 of 183 (4.9%)	.009
Bertini 2005	255 (<1500 g)	0 of 136 (0%)	9 of 119 (7%)	.003
Uko 2006	384 (<1500 g)	2 of 178 (1.1%)	13 of 206 (6.3%)	.007
Aghai 2006	277 (<1000 g)	0 of 140 (0%)	9 of 137 (6.6%)	<.006

Aghai ZH, et al. *J Perinatol.* 2006;26:550-555; Bertini G, et al. *J Pediatr.* 2005;147:162-165; Healy CM, et al. *J Pediatr.* 2005;147:166-171; Manzoni P, et al. *Pediatrics.* 2006;117:e22-32; Uko S, et al. *Pediatrics.* 2006;117:1243-1252

Adverse Events

- No increase in other infections
 - Bacteremia
 - Necrotizing enterocolitis
- Long-term outcomes (mean 14 months)
 - No effect on growth
 - No effect on cholestasis or other liver disease
 - No increase in adverse neurodevelopmental outcomes

Fluconazole Prophylaxis: Cholestasis

Retrospective studies:

Study	Cholestasis	FP	Control	P
Aghai 2006	db >2 Discharge	43% 6.7%	8.8% 3.6%	<0.001 0.54
Uko 2006	db db >5 4%	0.6 (0-19) 12%	0.9 (0-21) 0.015	<0.001

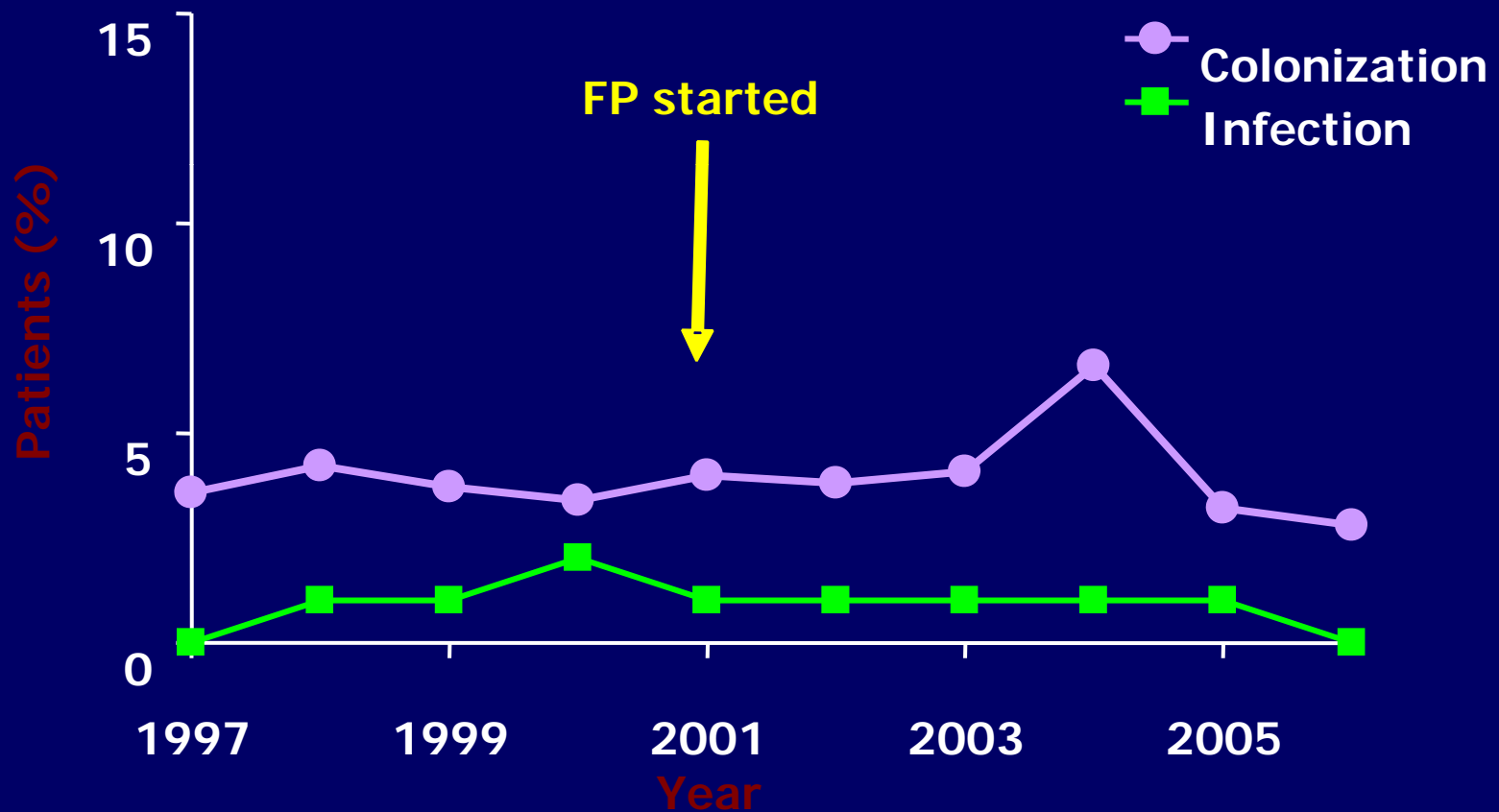
Randomized placebo controlled trials:

Study	FP	Placebo	P
Kaufman 2001	NO DIFFERENCE		0.34
Manzoni 2007			

Fluconazole Prophylaxis: Resistance

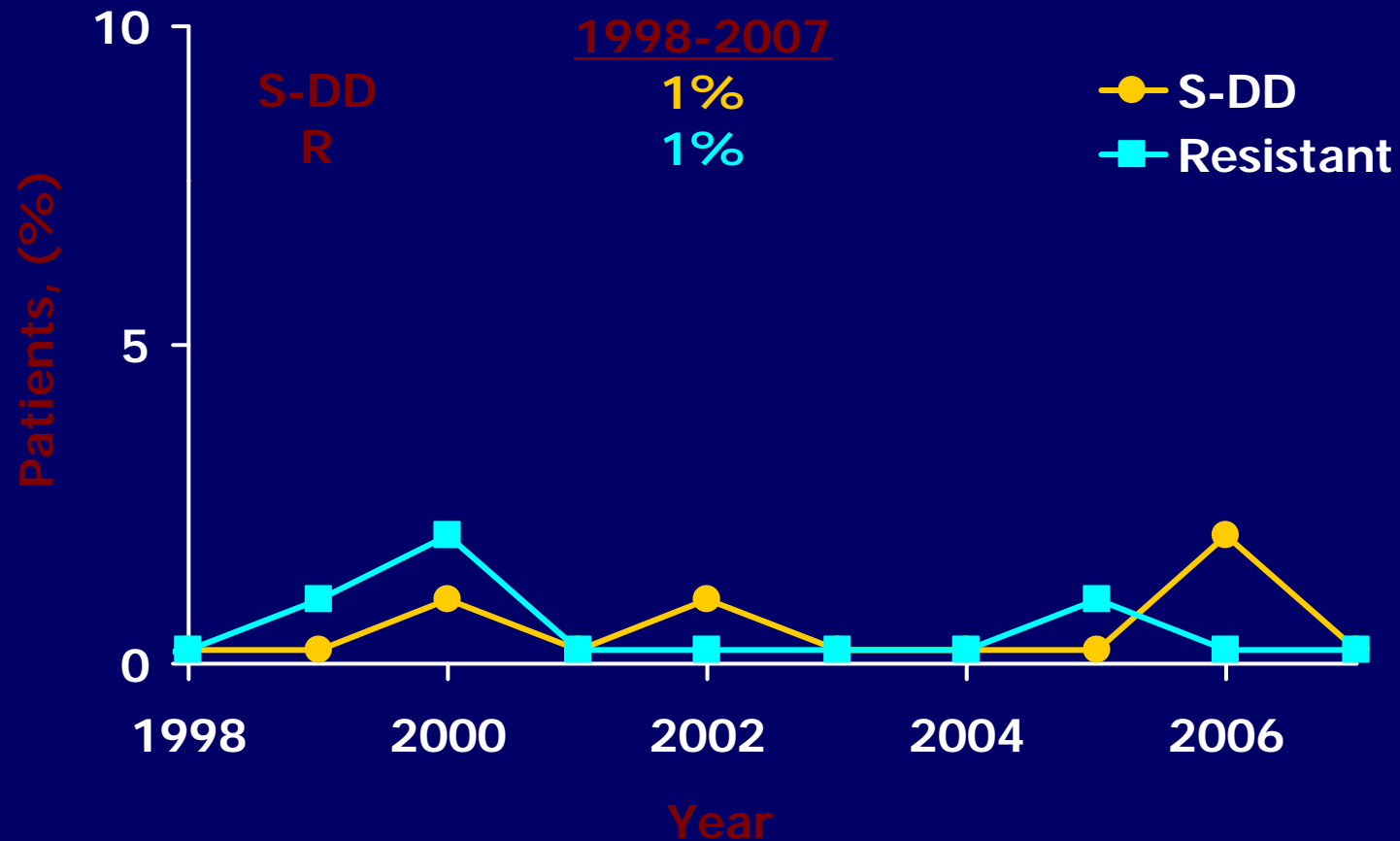
- No significant resistance in 1232 FP treated patients
 - During 4 - 6 week prophylaxis periods for any patient
 - During 24 - 36 month study periods for all patients
- No increase of candidemia due to *C glabrata* or *C krusei*

Colonization and Infection with *C glabrata* or *C krusei* Species



Colonization During and After FP

Susceptible-Dose-Dependent and Resistant Isolates



Treatment of Invasive Candidiasis in Fluconazole Prophylaxis Studies

- All studies used amphotericin B primarily for treatment of infections
 - Both AmB deoxycholate or lipid preparations
 - This decreases overall unit exposure to fluconazole
 - May have intermittently eliminated less susceptible or resistant fungi

Changes in fluconazole susceptibility over time among bloodstream isolates of *C. parapsiolsis*

Time Period	No. of Isolates	MIC (mg/liter) ^a			% of isolates at MIC (mg/liter of:		
		Range	50%	90%	≤8	16-32	≥64
1990-1994	7	0.5-2	1		100	0	0
1999-2000	7	1-16	2		86	14	0
2001-2002	12	2-64	8	64	50	33	17
TOTAL	26	0.5-64	2	16	73	19	8

^a 50%, MIC at which 50% of the isolates are inhibited; 90%, MIC at which 90% of the isolates are inhibited.

Fluconazole Prophylaxis Costs

- Fluconazole prophylaxis is cost effective.
- Uko et al. examined the cost with fluconazole prophylaxis and showed a significant cost benefit of \$516,702 over 18 months in their NICU.
- The pharmacy costs of one dose is approximately \$18, making the cost of a 4 to 6 week course (8 to 12 doses) between \$144 and \$216 per patient.

Impact of Prevalence on Decision to Administer Prophylaxis

Incidence < 1000 grams

center	incidence	6 weeks	Reduce	Risk Difference	NNT	NNT Death
Low	0.0%	0.0%	0.0%	0.0%	>250	>750
Low	1.2%	1.0%	0.2%	0.8%	126	379
Low	2.1%	1.8%	0.4%	1.4%	69	207
Moderate	4.4%	3.7%	0.7%	3.0%	33	100
Moderate	6.7%	5.7%	1.1%	4.5%	22	66
High	10.7%	9.1%	1.8%	7.3%	14	41
Danger	17.9%	15.2%	3.0%	12.1%	8	25

Fluconazole Prophylaxis: Who and How?

- In nurseries with high rates of invasive candidiasis, fluconazole prophylaxis may be considered in neonates with birth weights less than 1000 grams (A-I)
- Antifungal drug resistance, drug-related toxicity, and neurodevelopmental outcomes should be observed (A-III)
- 3 mg/kg IV fluconazole
 - Similar efficacy and less risk for resistance compared to higher doses
 - While they require IV access
 - Starting on DOL 1; First 6 weeks of life
 - Twice weekly dosing
- Use of different antifungal for treatment or empiric therapy
- AAP survey 34% of neonatologists used prophylaxis

Summary

- An important cause of morbidity and mortality
- Empiric therapy and catheter removal improve outcomes
- Amphotericin B is drug of choice for treatment
- Prophylaxis with fluconazole is effective in high-risk neonates
- More studies needed to determine long term impact of fluconazole on developing neonate



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About the International PFN

Dedicated to Understanding Pediatric Fungal Invasive Infections and Antifungals Through Global Collaboration

PFN Pediatric Fungal Network
 The incidence of pediatric invasive fungal disease is increasing. Coordinated clinical and laboratory investigative efforts have enhanced our understanding of fungal disease and improved the treatment of adult patients. However, most of these efforts have not incorporated children and neonates. Pediatric exclusion has limited our knowledge of the epidemiology and pathophysiology of pediatric fungal disease and has resulted in a paucity of data regarding the safety and efficacy of pediatric antifungal therapy. Previous pediatric cooperative models in other disciplines, including the Children's Oncology Group and the Pediatric AIDS Clinical Trials Group, have successfully advanced our understanding and treatments of other childhood diseases.

The multi-center International Pediatric Fungal Network (PFN) was created to gain a complete understanding of the scope and character of pediatric fungal infections in order to improve the care of our patients. The primary mission of the PFN is to increase the knowledge of pediatric invasive fungal infections and discern any undescribed characteristics or outcomes unique to pediatric patients through a coordinated network of scientific investigation. In addition to advancing our understanding of the fundamental epidemiology of pediatric invasive fungal infections, the PFN will serve as an effective vehicle of cohesive investigators and centers to conduct ground-breaking diagnostic and therapeutic clinical trials focused on pediatric fungal infections, diagnostic surrogates, and antifungals. Clinical information on patients is captured through a secure electronic portal to maximize efficiency of data collection and analysis. Investigators are linked through conference calls and meetings to both plan future studies and analyze results.

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