

# ***INCIDENCE AND RISK FACTORS FOR INVASIVE CANDIDIASIS IN NEONATAL INTENSIVE CARE UNIT IN THE INSTITUTE OF NEONATOLOGY IN BELGRADE, SERBIA***

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## Clinical Microbiology of Bacterial and Fungal Sepsis in Very-Low-Birth-Weight Infants

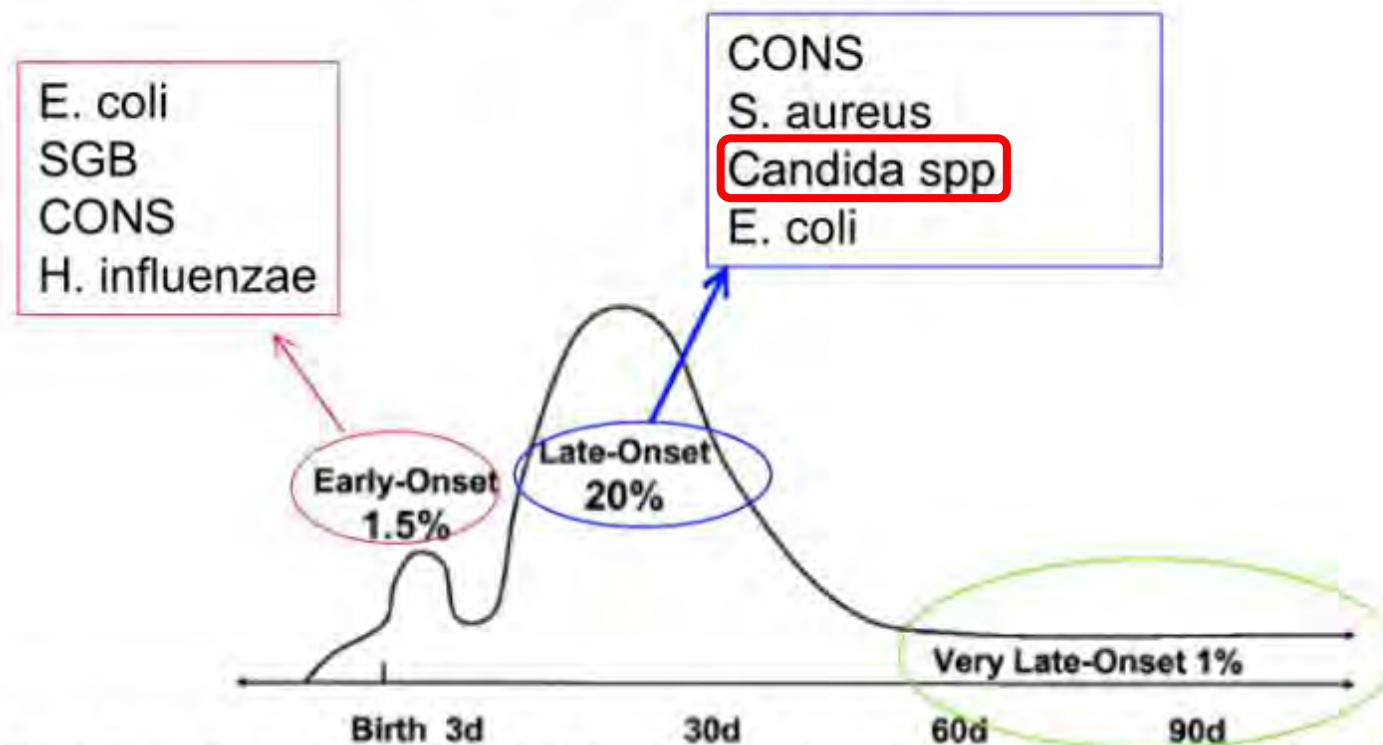


FIG. 1. Timing of bacterial and fungal sepsis in VLBW infants. Percentages indicate the approximate number of VLBW infants with septicemia. EONS usually occurs via ascent of organisms from the birth canal to the amniotic fluid, with or without rupture of amniotic membranes. LONS occurs with vertical and horizontal spread of organisms. While the vast majority of cases of sepsis in VLBW infants occur in the first 30 days of life, VLBW infants requiring prolonged intensive care are at risk for VLONS beyond 2 months of age.

# Neonatal invasive candidiasis (IC)

- *associated with significant mortality and morbidity, including neurodevelopmental impairment among survivors;*
- *clinical signs are non specific, and are often similar to the other infectious and non-infectious conditions;*
- *the reason why IC is underdiagnosed;*
- *there are no true data about its incidence.*

## *Incidence*

- 2.6-13.2% in VLBW (<1500g)
- 6.6-26.0% in ELBW (<1000g)



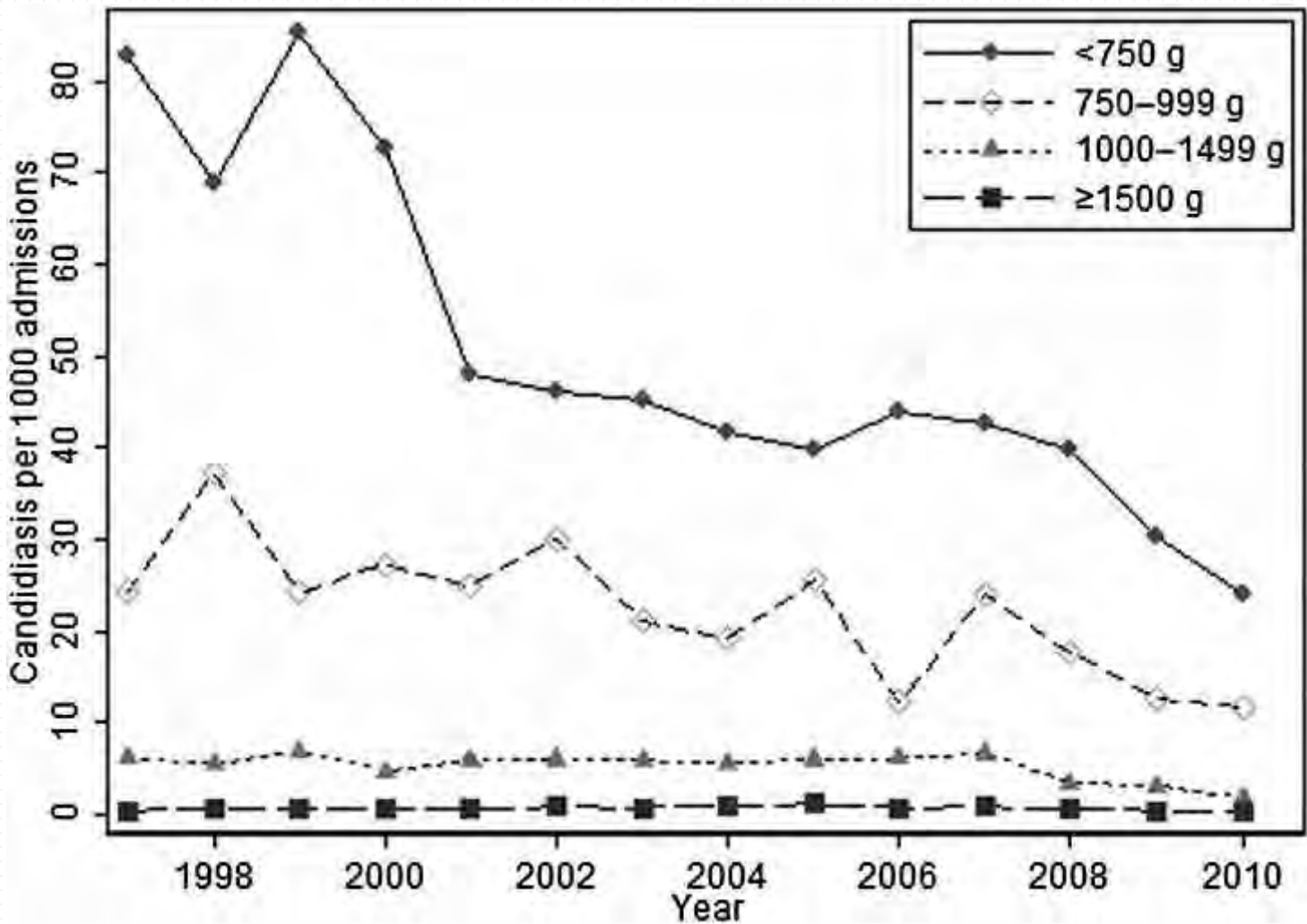
## *Incidence*

*Invasive candidiasis in hospitalized infants appears to be decreasing.*

- *Fluconazole prophylaxis;*
- *reduced use of broad-spectrum antibiotics;*
- *empirical antifungal therapy;*
- *and improved care of central venous catheters*

*have contributed to the declining incidence of invasive candidiasis.*

Candidiasis by year and birth weight



↓ 3.6 → 1.4/1000

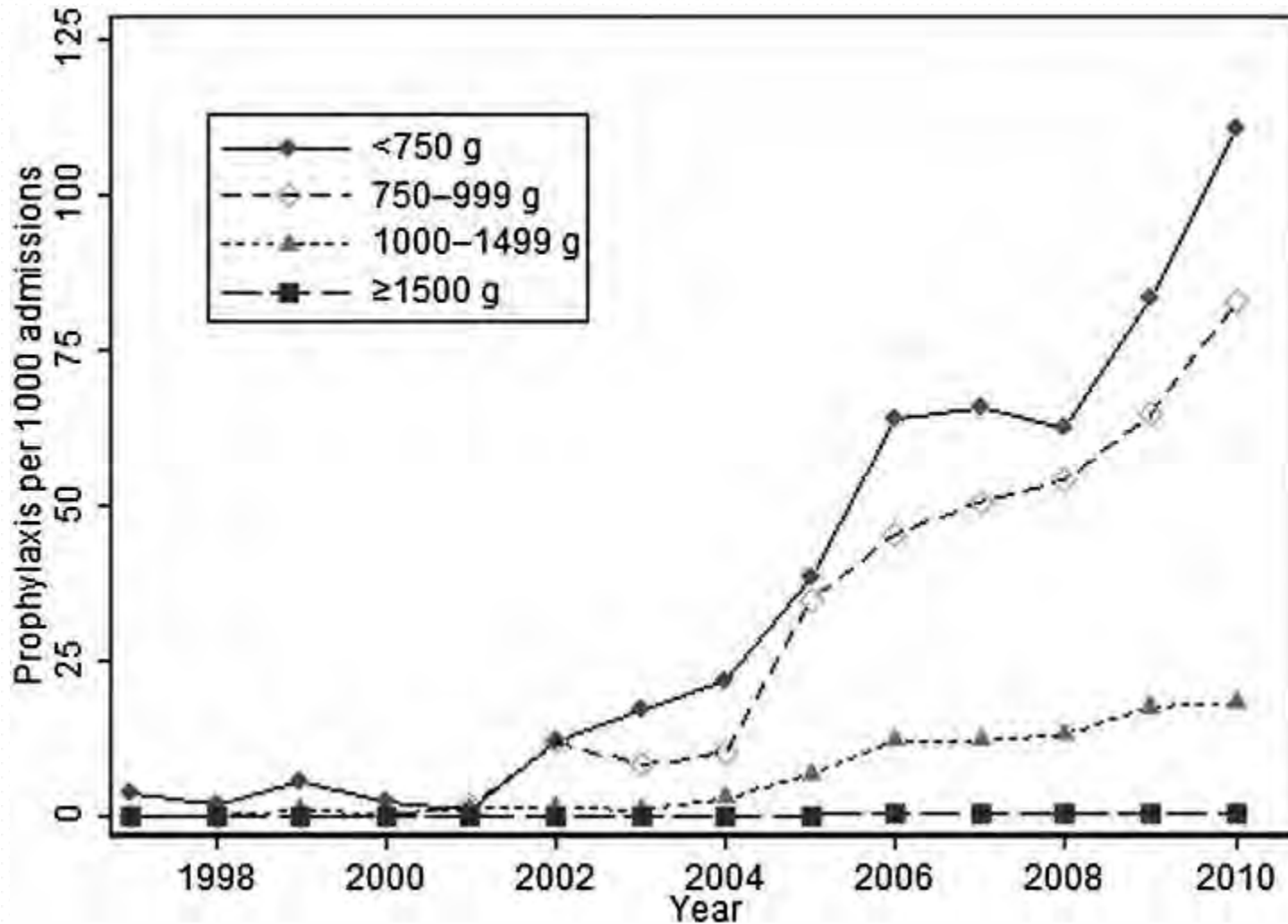
↓ 24.2 → 11.6/1000 (750-999g)

↓ 82.7 → 23.8/1000 (<750g)

Sofia Aliaga et al. Pediatrics 2014;133:236-242



## Fluconazole prophylaxis by year and birth weight

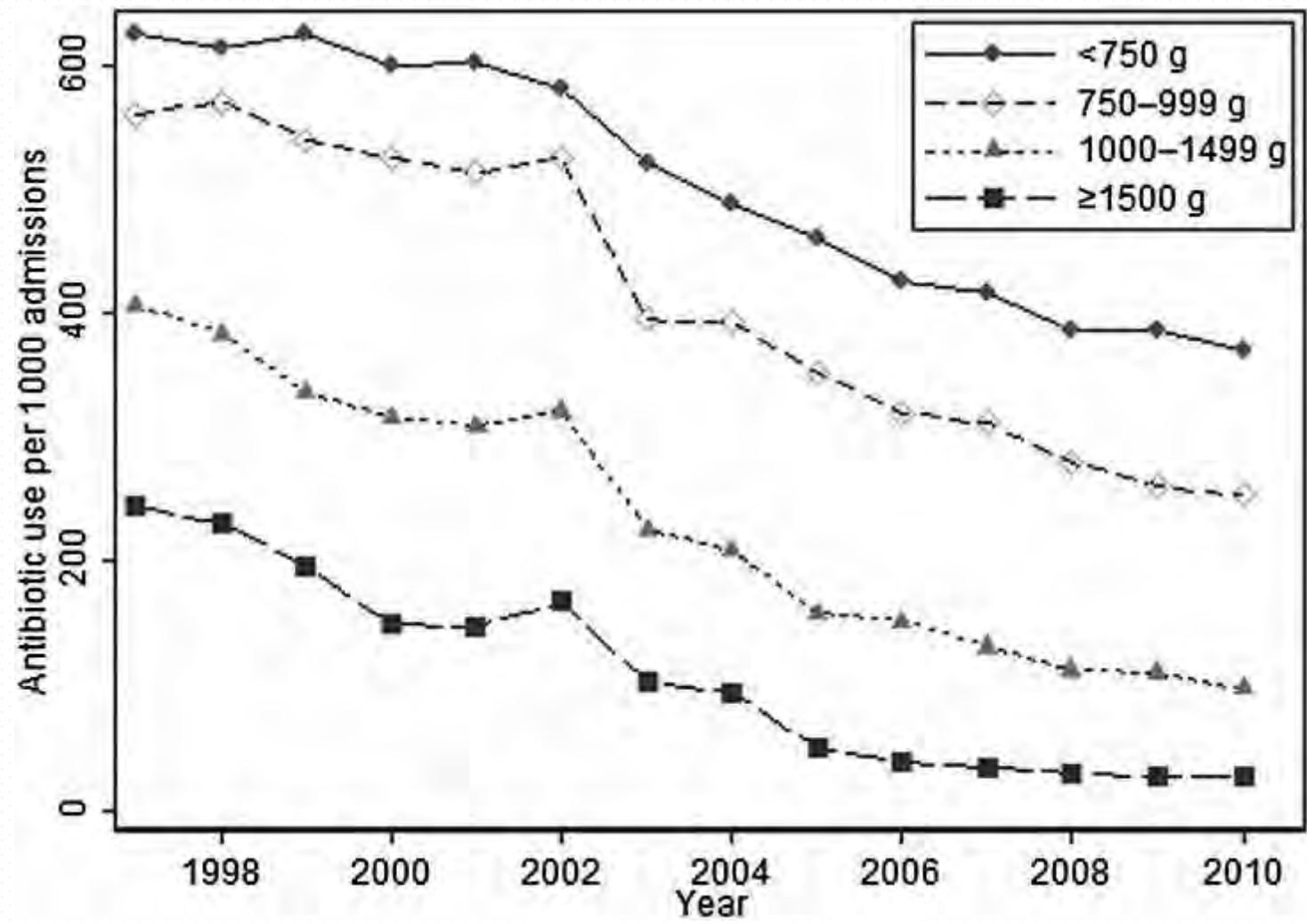


Sofia Aliaga et al. Pediatrics 2014;133:236-242

↑ 0.1 → 7.4/1000

↑ 3.8 → 110.6/1000 (<750g)

*Broad-spectrum antibacterial antibiotic use by year and birth weight*



↓ 275.4 → 48.5/1000

Sofia Aliaga et al. Pediatrics 2014;133:236-242



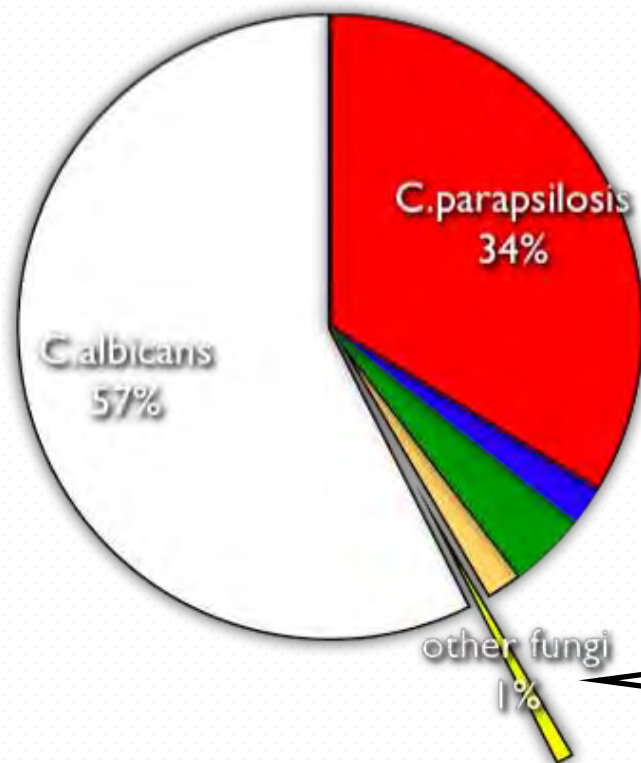


# Fungal Infection in neonates and infants in NICU: basic facts - *the “90% rule”*

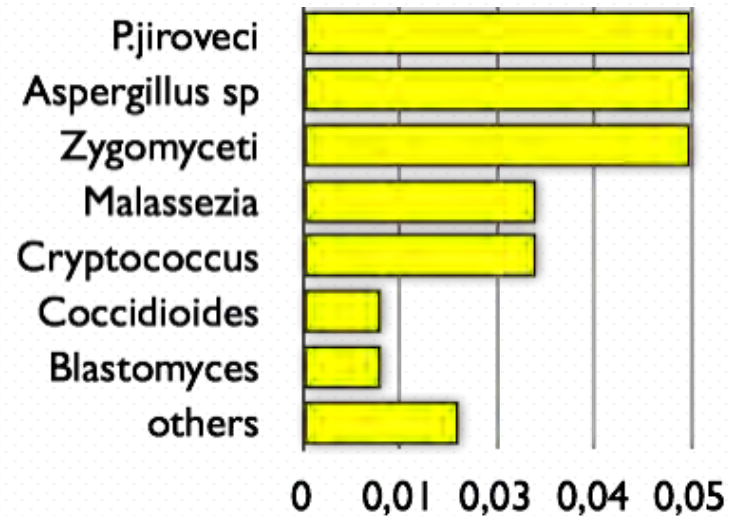
- **90% occur in extreme premature neonates**  
→ *that is, less than 1500g and/or less than 32 weeks gestational age (GA) at birth*
- **90% are caused by *Candida spp***  
→ *other Fungi are very uncommon*
- **90% originate from nosocomial acquisition**  
→ *Infections deriving from maternal vertical transmission are a minority of cases*

# Etiology of invasive fungal disease in NICU

- C.parapsilosis
- C.glabrata
- C.tropicalis
- other Candida
- other fungi
- C.albicans



**Other fungi → sporadic cases and microepidemics because of local factors**

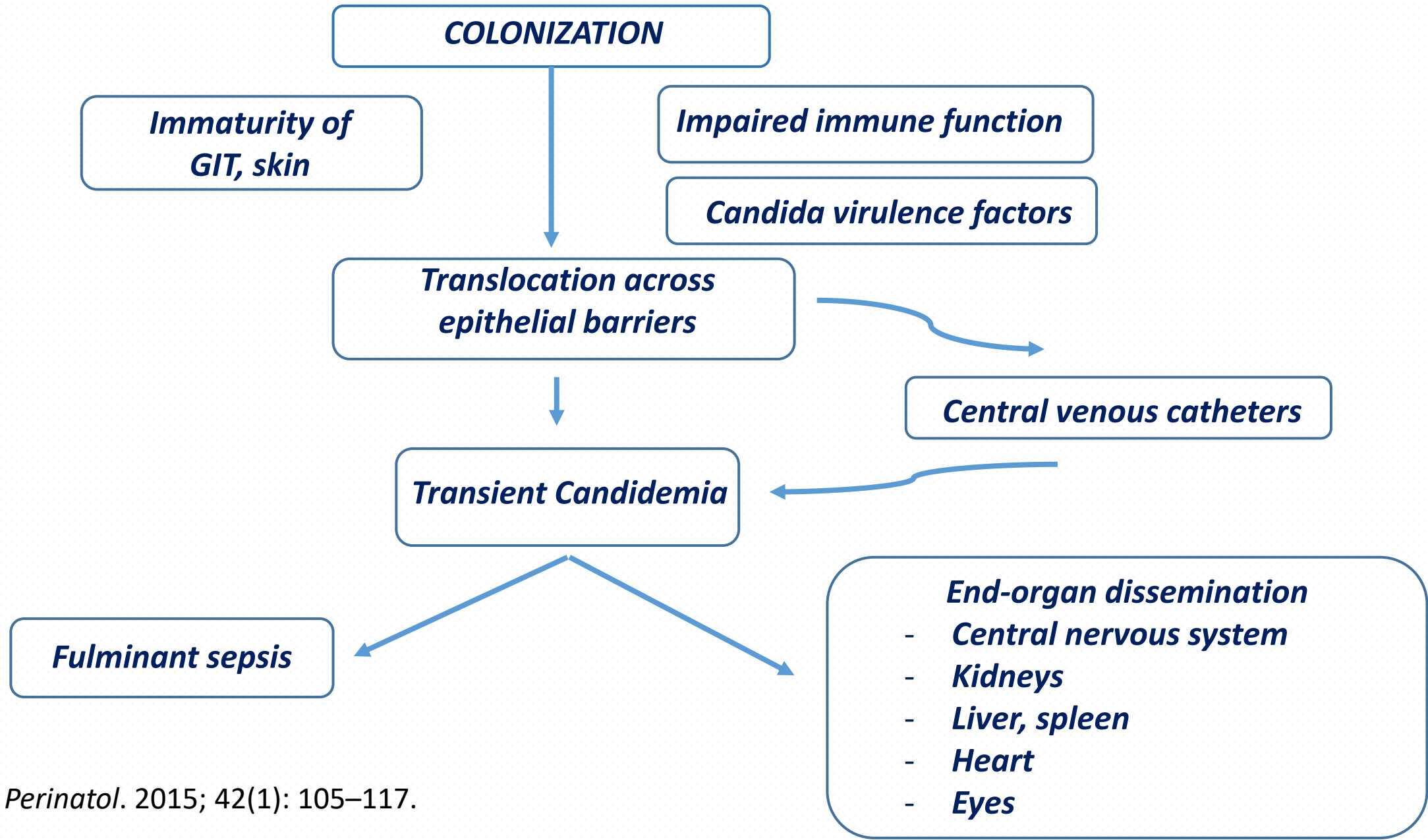


## **Risk factors**, *associated with significant morbidity and mortality*

1. *Extreme prematurity*
2. *Neonatal intensive care unit (NICU)*
3. *Broad spectrum antibiotics*
4. *Central venous catheter*
5. *Prior bacterial bloodstream infection*
6. *Necrotizing enterocolitis (NEC)*
7. *Lack of enteral feedings*
8. *Use of H2-blockers*
9. *Duration of mechanical ventilation*
10. *Steroids*
11. *Complicated gastrointestinal (GI) disease*



## ***Patophysiology of invasive candidiasis in premature neonates***



# Prophylactic fluconazole is effective in preventing fungal colonization and infection in preterm neonates: a multicenter, randomized trial in Italy



The NEW ENGLAND  
JOURNAL of MEDICINE

Manzoni P, Stolfi I, Pugni L, Decembrino L, Magnani C, Mosca F, Vetrano G, Tridapalli E, Corona G, Giovannozzi C, Farina D, Merletti F, Maule M, Pedicino R, Stronati M, Mostert M, Gomirato G

on behalf of The Italian Task Force for the study and prevention of Neonatal Fungal Infections; the Italian Society of Neonatology

	<b><i>Fluconazole n=(112+104) =216</i></b>	<b><i>Placebo n=106</i></b>	<b><i>R.R.</i></b>	<b><i>95% C.I.</i></b>	<b><i>P-value</i></b>
<b>Total invasive fungal infections (IFI; %)</b>	<b>7/216 (3.2%)</b>	<b>14/106 (13.2%)</b>	<b>0.25</b>	<b>0.10-0.59</b>	<b><u>0.001</u></b>
<b>Overall colonization</b>	<b>19/216 (8.8%)</b>	<b>31/106 (29.2%)</b>	<b>0.30</b>	<b>0.18-0.51</b>	<b><u>&lt;0.0001</u></b>
Overall mortality	18/216 (8.3%)	10/106 (9.4%)			0.83
Mortality attributable to fungi	0/216 (0%)	2/106 (1.9%)			0.10

**FLUCONAZOLE either dosage (3mg/kg or 6mg/kg every 2nd day) vs. PLACEBO**

*N Engl J Med* 2007;356:2483–95

## Original Investigation

# Effect of Fluconazole Prophylaxis on Candidiasis and Mortality in Premature Infants

## A Randomized Clinical Trial

Daniel K. Benjamin Jr, MD, PhD; Mark L. Hudak, MD; Shahnaz Duara, MD; David A. Randolph, MD, PhD; Margarita Bidegain, MD, MHS-CL; Gracías T. Mundakel, MD; Girija Natarajan, MD; David J. Burchfield, MD; Robert D. White, MD; Karen E. Shattuck, MD; Natalie Neu, MD, MPH; Catherine M. Bendel, MD; M. Roger Kim, MD; Neil N. Finer, MD; Dan L. Stewart, MD; Antonio C. Arrieta, MD; Kelly C. Wade, MD; David A. Kaufman, MD; Paolo Manzoni, MD; Kristi O. Prather, MPH; Daniela Testoni, MD, MHS; Katherine Y. Berezny, MPH; P. Brian Smith, MD, MPH, MHS; for the Fluconazole Prophylaxis Study Team

- ✓ **Multicenter RCT**
- ✓ **362 infants <750g**
- ✓ **6mg/kg Fluconazole twice weekly vs placebo**

	Fluco	Placebo	95%CI	P-value
<b><i>Invasive Candidiasis</i></b>	3%	9%	-11 to -1	<b>0.02</b>
Death (any cause)	14%	14%	-7 to 7	0.98
Death OR Candidiasis	16%	21%	-13 to 3	0.24
Neurodevelopmental Impairment – composite at 18-22 months c.a.	31%	27%	-10 to 7	0.60



# *Prophylactic systemic antifungal agents to prevent mortality and morbidity in very low birth weight infants (Review)*

*Cleminson J, Austin N, McGuire W.*

**Objectives:** *To assess the effect of prophylactic systemic antifungal therapy on mortality and morbidity in very preterm or very low birth weight infants.*

*15 eligible trials enrolling a total of 1690 infants. These trials were generally of good quality.*

**Keyfindings:** *The overall analysis showed a reduction in the risk of severe fungal infection in infants who received systemic antifungal prophylaxis, but did not show a difference in the risk of death. This trials did not assess the risk of long-term problems, including disabilities.*

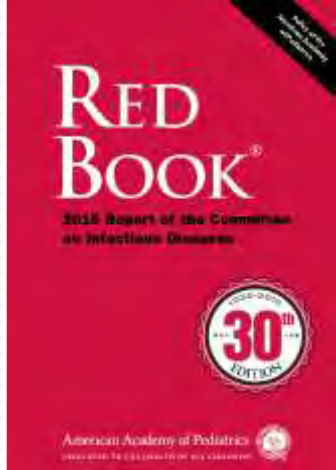
**Conclusions:** *There is evidence from some good-quality trials that giving antifungal drug regularly for the first 4-6 weeks after birth reduces the number of infants who develop severe infection. There is not yet any convincing evidence that death or disability rates are affected.*

## ***Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America***

*What Are the Recommendations for Prophylaxis in the Neonatal Intensive Care Unit Setting?*

### ***Recommendations***

In nurseries with high rates (>10%) of invasive candidiasis, intravenous or oral fluconazole prophylaxis, 3-6mg/kg twice weekly for 6 weeks, in neonates with birth weights <1000g is recommended (*strong recommendation; high-quality evidence*).



*Fluconazole prophylaxis is recommended for extremely low birth weight infants cared for in neonatal intensive care units with moderate (5%–10%) or high ( $\geq 10\%$ ) rates of invasive candidiasis.*

*The recommended regimen for extremely low birth weight neonates is to initiate fluconazole treatment intravenously during the first 48 to 72 hours after birth at a dose of 3 mg/kg, and administer it twice a week for 4 to 6 weeks, or until intravenous access no longer is required for care.*

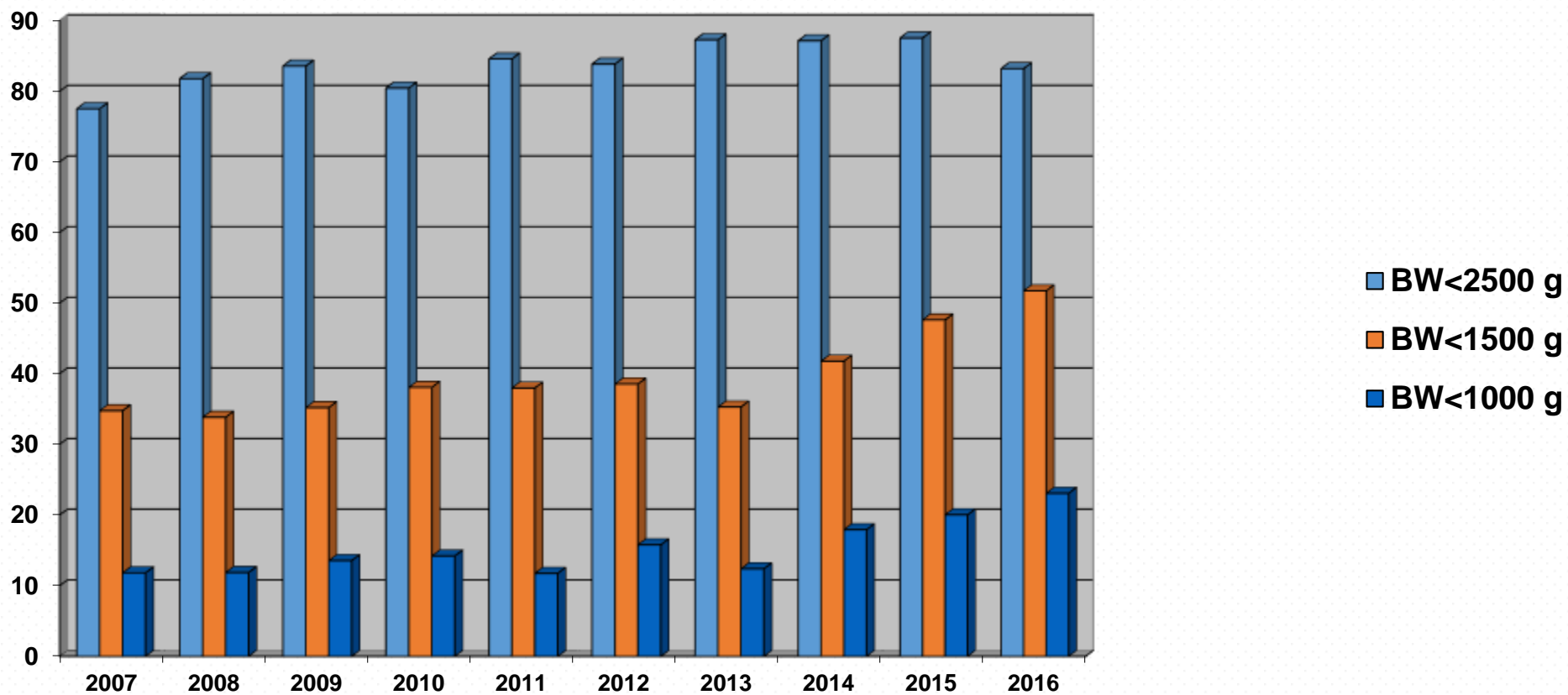


## *Institute of neonatology, Belgrade*

- *Tertiary hospital, outborn babies*
- *800 admissions/year*
- *>50% babies GA < 32wk*
- *NICU 550 babies*
- *MV 430 babies*

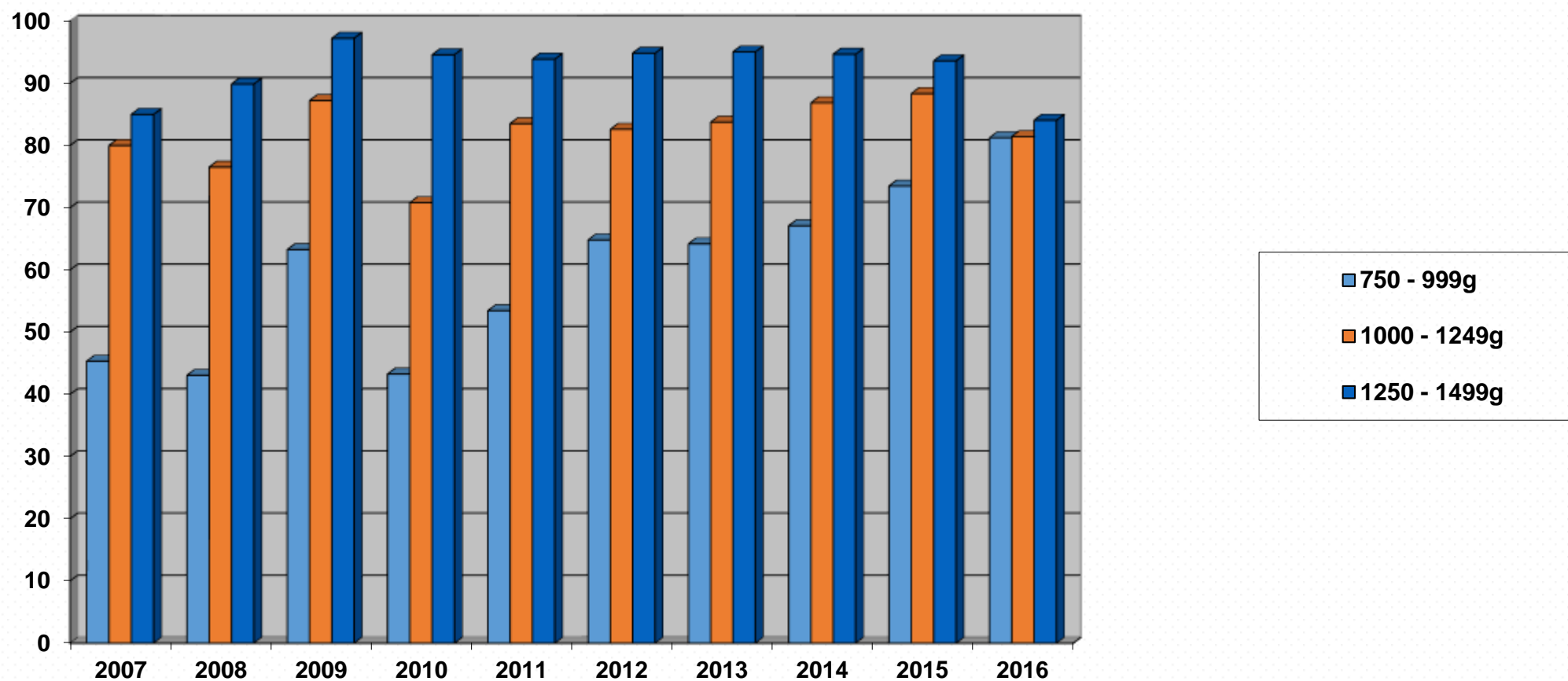


## *Institute of neonatology, Belgrade*





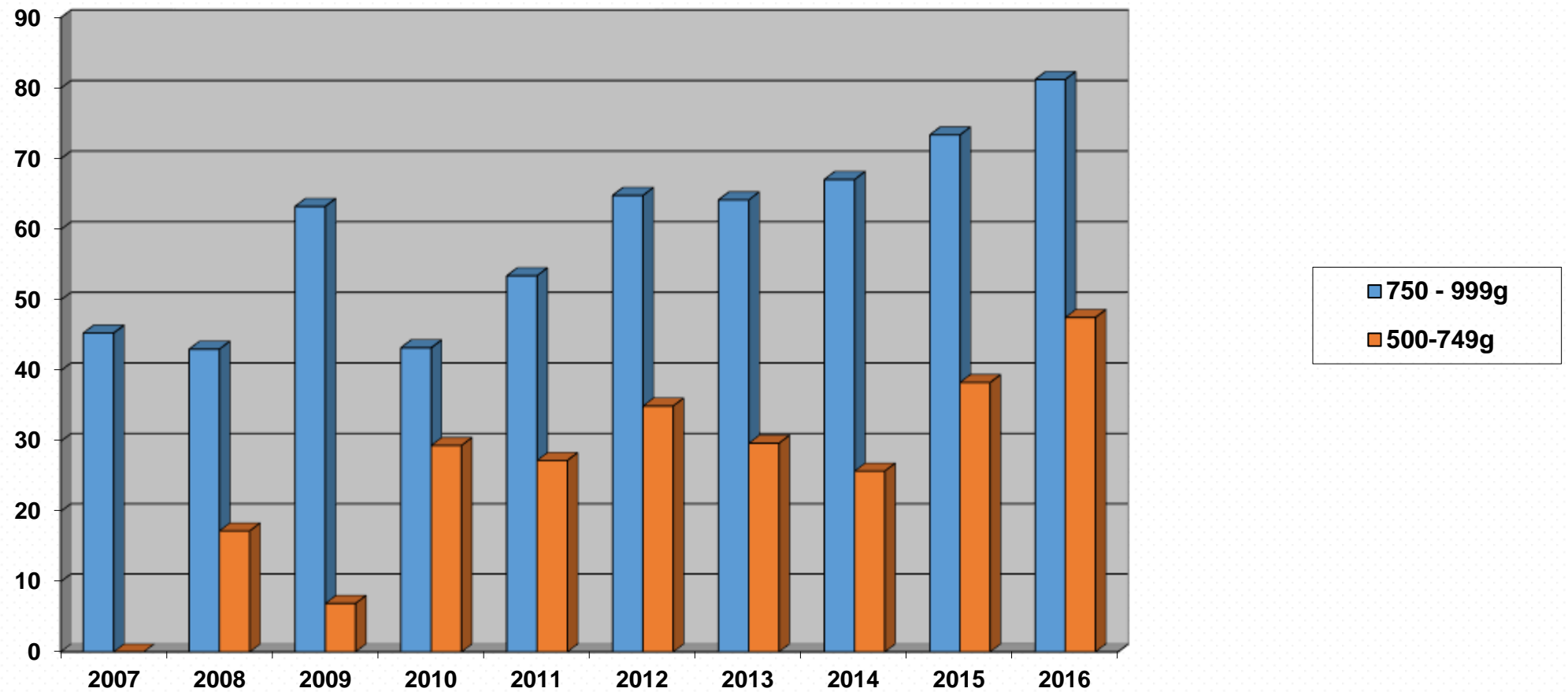
*Outcome of VLBW babies*







*Outcome of ELBW babies*



## *Institute of neonatology, Belgrade*



- *fluconazole prophylaxis*  
*3mg/kg IV twice a week*
- *From June 2016.*  
*on admission GA<28wk, BW<1000g*



## *INCIDENCE AND RISK FACTORS FOR INVASIVE CANDIDIASIS IN NEONATAL INTENSIVE CARE UNIT IN THE INSTITUTE OF NEONATOLOGY*

### ***Objectives:***

- *to determine the incidence of IC based on positive blood culture (Candida) and*
- *to analyze the risk factors for developing IC*



## ***Methods:***

- *Retrospective analysis of the incidence of IC in newborns treated in the Institute of neonatology from January 2010 to December 2016*
- *Diagnosis of IC was based on positive blood culture for Candida*

## ***Methods:***

- *As risk factors we analysed:*
  - ✓ *mode of delivery*
  - ✓ *perinatal asphyxia (APN)*
  - ✓ *prematurity*
  - ✓ *NICU*
  - ✓ *central venous catheter (CVC)*
  - ✓ *mechanical ventilation (MV)*
  - ✓ *use of antibiotics (AB)*
  - ✓ *total parenteral nutrition (TPN)*
  - ✓ *GI disorders*
  - ✓ *probiotic*
  - ✓ *fluconazole prophylaxis*





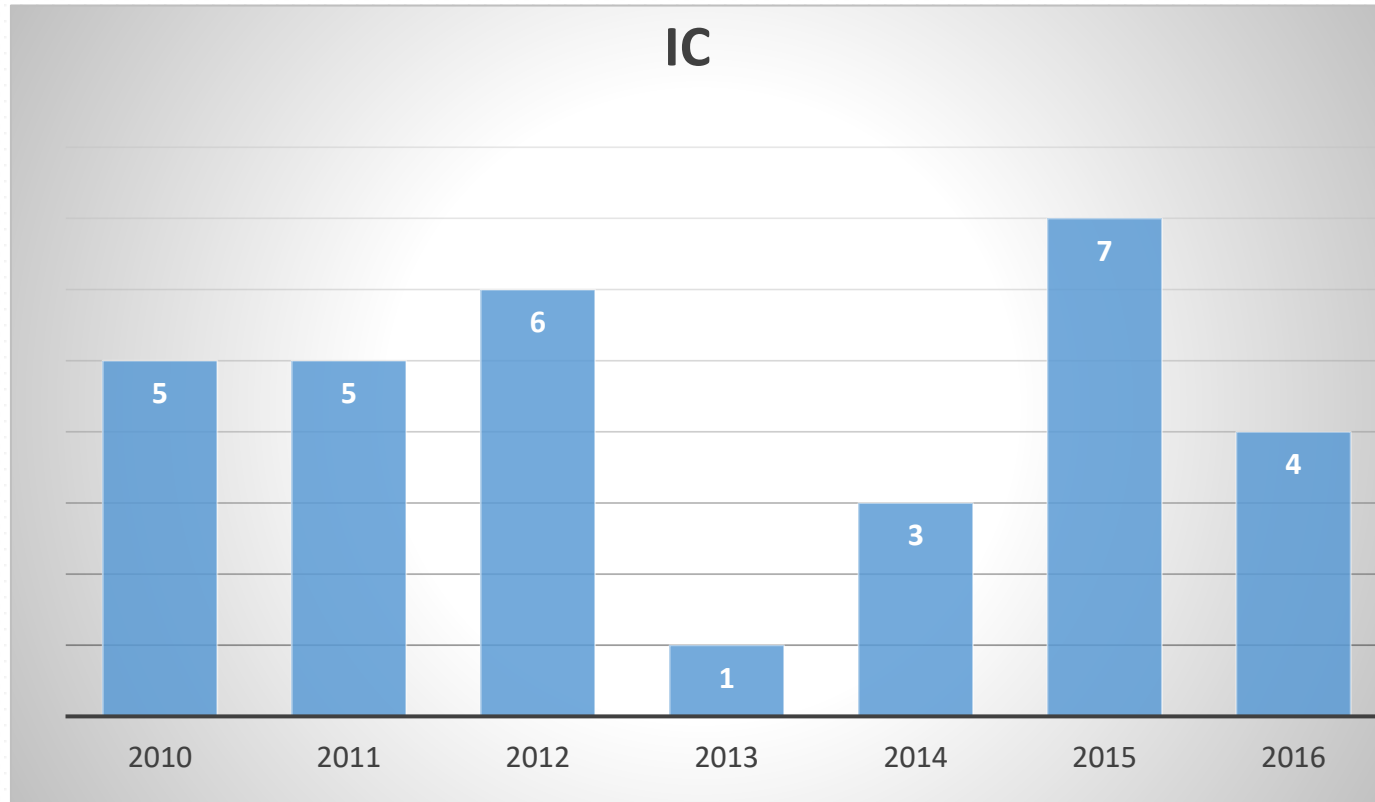
**Results:**

- *In this period we treated 5804 newborns,  
51.2% were of gestational age (GA)  $\leq 32$  weeks;*
- *Sepsis was diagnosed in 1245 (21.5%);*
- *IC was diagnosed (isolation of Candida) in 31 (0.5%) newborns.*

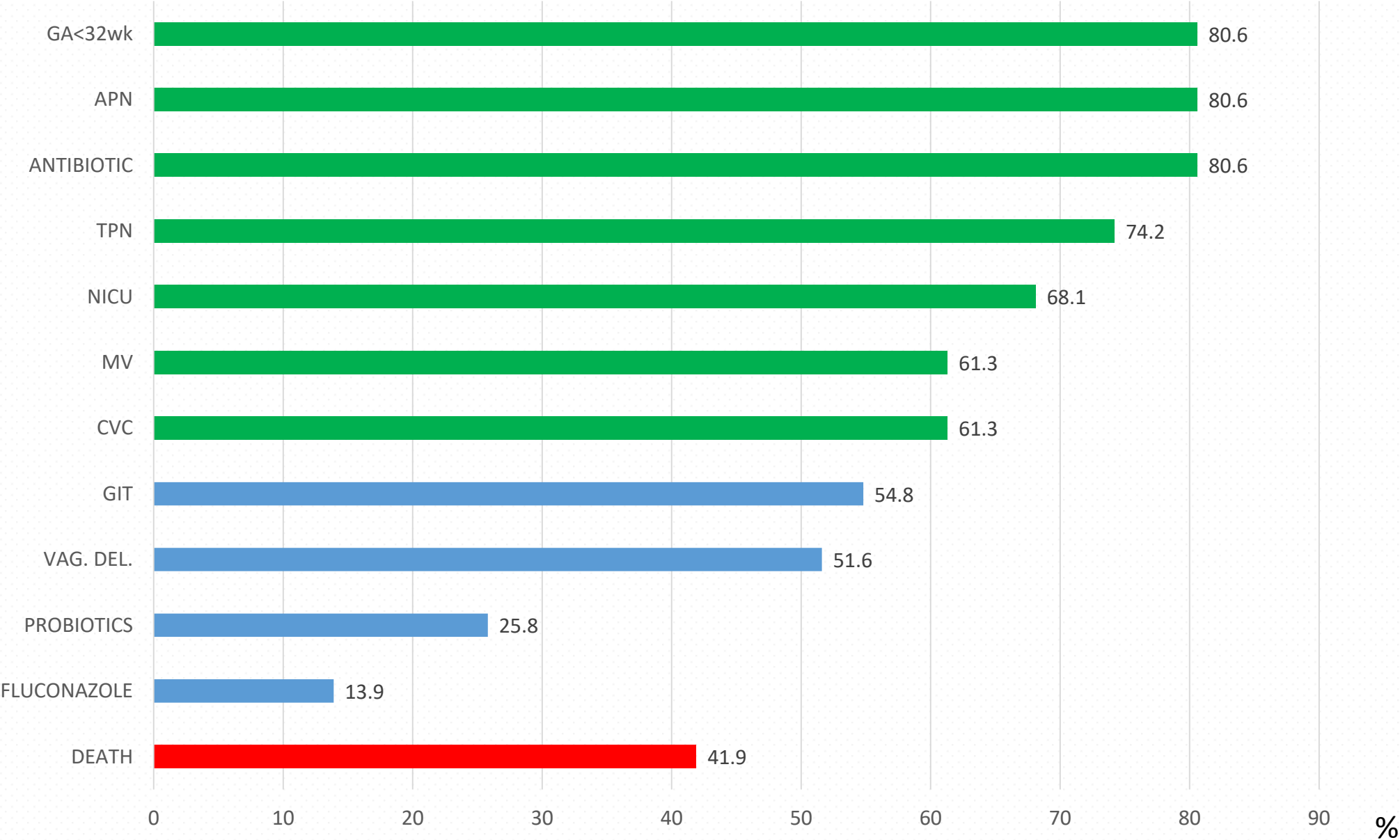




*Number of IC/year*



*INCIDENCE AND RISK FACTORS FOR INVASIVE CANDIDIASIS IN NEONATAL INTENSIVE CARE UNIT IN THE INSTITUTE OF NEONATOLOGY*



2017. 1 case

- *26wk, 850g, AS 2, PROM 90h*

- *Admission DOL 4*

*MV, ICH gr III, PDA, Sepsis (Klebsiella pneumoniae)*

- *DOL 8      BC: Candida albicans*

## **Conclusion:**

- Incidence of IC, based on the positive blood culture, in the period 2010-2016 was **0.5%**.
- Risk factors: **prematurity, antibiotics, perinatal asphyxia, TPN, NICU**
- **High mortality rate (41.9%)**
- As blood culture has low sensitivity for diagnosis of IC, we need other diagnostic biomarkers of infection, in order to improve sensitivity and specificity

