Invasive Fungal Infections (IFI) in Neonates

– The state of the art –

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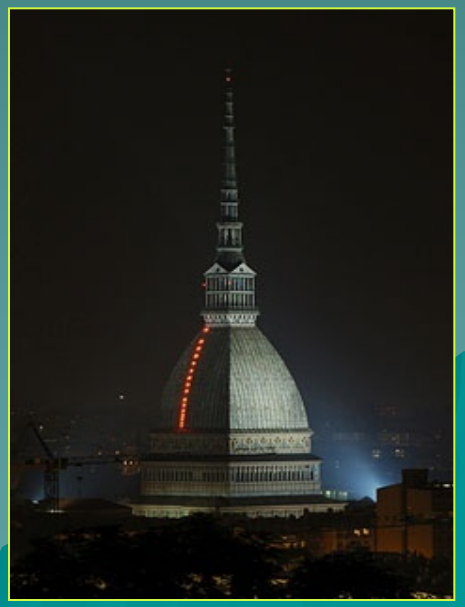
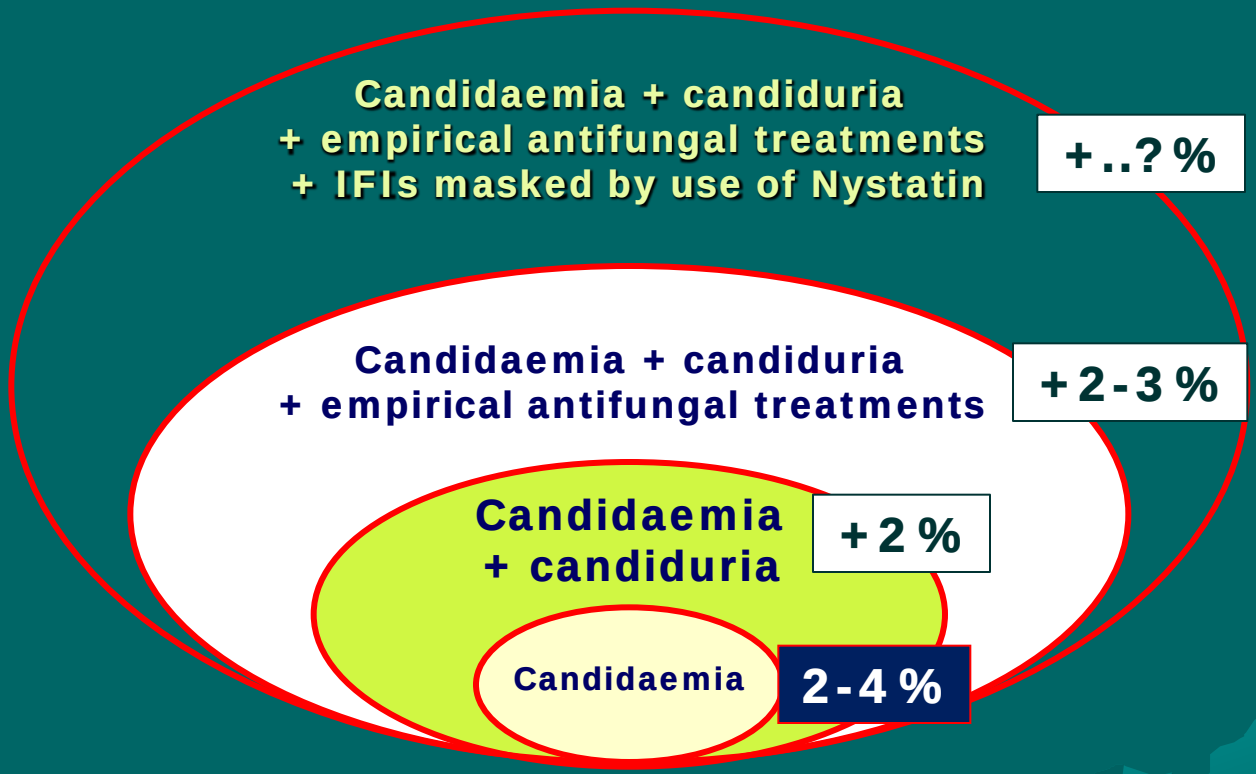


Do the data of neonatal IFI accurately reflect the real incidence?

The true burden of *Candida* infections in preterm neonates in NICU is likely higher

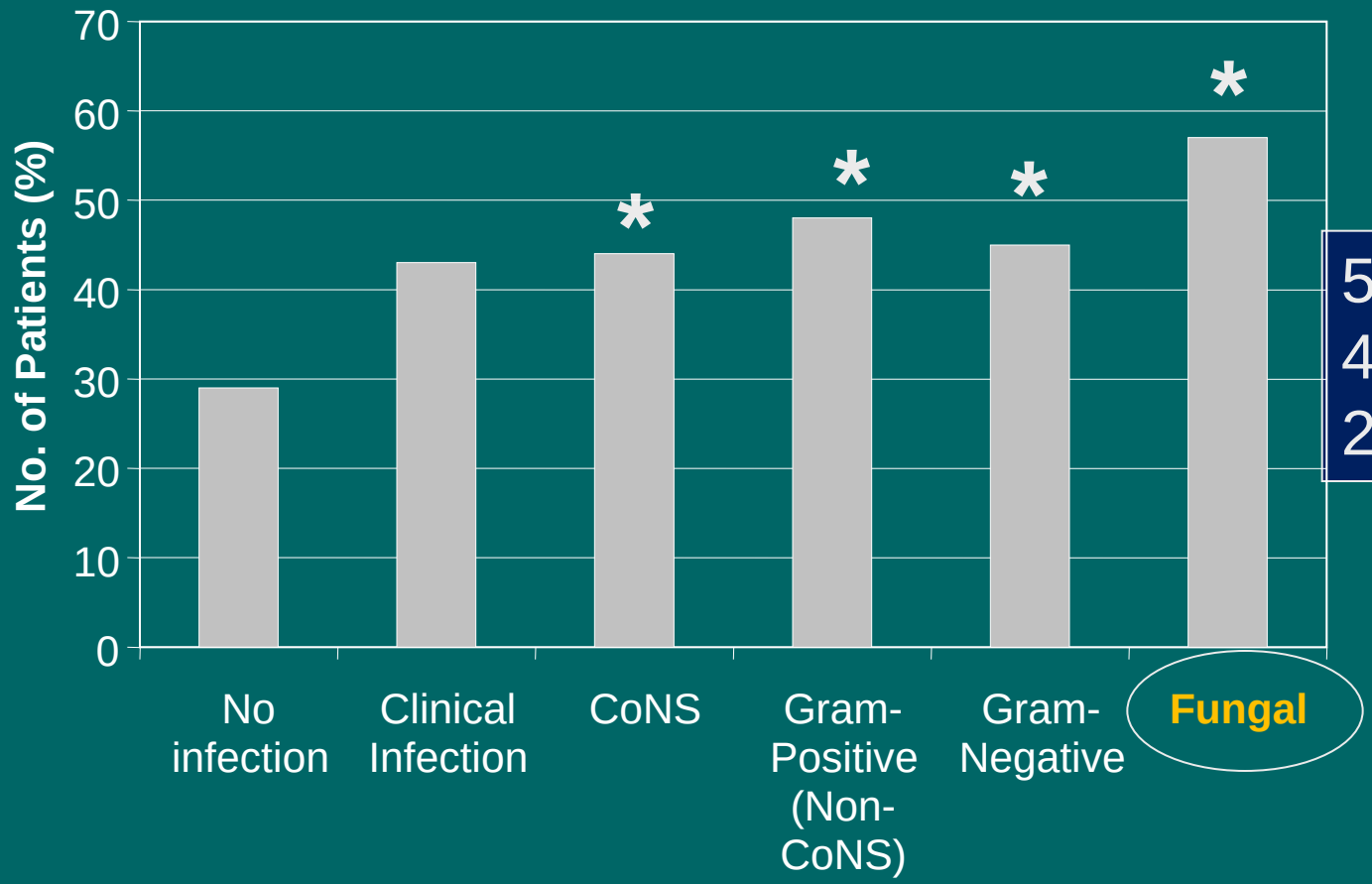
- Invasive Fungal infections (IFI) in neonates → 95% are *Candida* spp infections
- IFI in 7% of all preterm,VLBW neonates
- 74% of all IFI occurs in infants <1000g
- Huge variability of reported incidence rates of IFI among Settings: In the USA, in a survey including around 30 third level NICUs, IFI incidence in VLBWs varied from 2% to 25%!



TOTAL estimated, 'real-life' incidence → more than 9 %

1. Burwell LA, et al. *Pediatrics* 2006;118;e1019; 2. Fridkin SK, et al. *Pediatrics* 2006;117:1680–7;
3. Manzoni P, et al. *Arch Dis Child* 2009;94:983–7.

Poor outcomes after Neonatal IFI: higher burden of Neurodevelopmental Impairment after IFI in infants <1000g



57% fungal
44% bacterial
28% no sepsis

*P≤0.001 vs. no infection

Stoll, *JAMA* 2004

Poor outcomes after Neonatal IFI: negative Neurodevelopmental performances at 20 months of age in survivors from neonatal IFI by *Candida* spp

Data from 4,589 ELBW neonates in the US neonatal network

Outcome	Candidiasis %	Controls %	P
Bayley MDI < 70	48.4	29.7	<.001
Bayley PDI < 70	31.5	19.8	<.001
Cerebral Palsy	13.6	5.8	<.001
Visual impairment	23.5	13.5	<.001
Blindness	1.9	0.6	.03
Hearing impairment	10.5	2.9	<.001
Deafness	6.2	1.3	<.001
Mental retardation	57.2	35.8	<.001

Benjamin et al. , Pediatrics 2006

Best management → PREVENTION!!
Outline of all possible preventative strategies

- **Neonatal management:**
  - Breastfeeding – fresh human milk
  - Hygiene measures
  - Cautious CVC management
  - Enhancing enteric microbiota composition with use of probiotics
  - H2-blockers, steroids and 3rd generation cephalosporin restrictions

- **Pharmacological prophylactic interventions:**
  - Bioactive substances (Bovine Lactoferrin)
  - Probiotics
  - Non-absorbable antifungal agents preventing gut colonisation: Nystatin
  - Specific antifungal prophylaxis: **fluconazole**

ADC-FNN Online First, published on January 20, 2015 as 10.1136/archdischild-2012-303350

Update on the management of *Candida* infections in preterm neonates

P Manzoni,[1] M Mostert,[2] E Castagnola[3]

The state-of-the-art

Box 2 Key issues in the management of systemic fungal infections in neonates: summary

1. Consider any premature infant with microbiological or clinical evidence of invasive candidiasis as having disseminated disease.
2. Indirect diagnostic tests (eg, 1–3-β-D-glucan) are not yet validated for clinical use in neonatal settings.
3. Two antifungal treatment strategies are possible: targeted therapy or empirical/pre-emptive/diagnostic-driven treatment.
4. Information on local epidemiology and fungal ecology is mandatory and pivotal to guide initial therapeutic choices.
5. Consider penetration of antifungal drugs in sanctuaries and target the CNS and the Candida bio-films.
6. Consider colonisation status.
7. Consider the central venous catheter status and the possibility/probability that bio-films have formed.
8. Assess and rule out possible end-organ localisations.
9. Consider previous exposure to antifungal prophylaxis, if any, and switch to a different antifungal class.

Fluconazole prophylaxis prevents invasive *Candida* infections in preterm infants

- Meta-analysis of 11 studies[1]
  - 7 retrospective, 4 RCTs

Fluconazole prophylaxis reduces:[1]

- The chance of developing IFI in high-risk infants <1000g by 91%
  (OR 0.09; 95% CI 0.04 to 0.24; p=0.0004)
- The chance of developing IFI in all infants <1500g by 85%
  (OR 0.15; 95% CI 0.08 to 0.26; p<0.0001).
- The overall mortality rate by 26% (11% vs. 16.3%)
  (OR 0.74; 95% CI 0.58-0.95; P=0.017)
- The *Candida*-related mortality by 96% (virtually eliminated)
  (OR 0.04; 95% CI 0.01 to 0.31; p=0.006)
- No effect on developmental long-term outcomes assessed[2]
- Ecological safety data available up to 8 years:
  - No shifts towards fluconazole-resistant spp[3]
  - No selection of resistant strains[4]

1. Kaufman DA, Manzoni P. *Clin Perinatol* 2010;37:611–28; 2. Kaufman DA, et al. *J Pediatr* 2011;158:759–65
3. Manzoni P, et al. *Pediatr Infect Dis J* 2008;27:731–7; 4 Kaufman DA NeoReviews 2011;12:e381–e92..

Summary of pending, unresolved issues with neonatal IFI (1)

- Blood culture may often be negative → need for empiric treatment
- Frequent end-organ localisations and high risk of CNS involvement → poor NeuroDevelopm outcomes → better to treat with the most potent and wide-spectrum antifungal available (to avoid/limit poor outcomes) : ***"Hit fast, Hit hard" strategy***
- Causative fungal agents → 99% *Candida spp.* , but 5–10% are inherently resistant to fluconazole → avoid Fluco for treatment
- **Neonates have a p**rolonged need for CVC → high risk of hub colonisation + biofilms → choose a drug active on biofilms (not Fluco !!)

Hence, ideal antifungal drugs for neonates must have:

- Significant activity against biofilms
- Significant activity against *C. glabrata, C. tropicalis* and *C. krusei* (because they may survive prophylactic fluconazole)
- Ability to be used in mono-therapy, good tolerability, No interactions

Summary of pending, unresolved issues with neonatal IFI (2)

- Fluconazole is widely used for prophylaxis, but not authorized;
- RCT of fluco prophylaxis are no more feasible/ethical

  → ***how can we find a solution?***

- Micafungin is authorized, but effective dosages are likely different than those in the label

  → ***how can we find a solution?***

- Studies on "Old" antifungals (e.g., Ampho B, Liposomal Ampho, etc) are not supported by Pharma as they are not rentable in neonatology

  → ***how can we find a solution?***

- Superiority trials for new antifungals are impossible to perform in preterm neonates owing to limted numerosity, but nonetheless new antifungals would be welcome
- The outcome to measure for neonatal trials should be "survival free from NDI at 20 months", and not "survival", "clearance of infection", or similar other indicators

  → ***how can we find a solution?***

Thank you for your attention !

Neonatology and Neonatal Research Foundation
"Crescere insieme al Sant'Anna"
www.fondazionesantanna.org

See you in TORINO 2016

5th INTERNATIONAl NEONATOLOGY CONFERENCE

September 2016

www.iccn2014.eu

Disclosure slide

Conflicts of interest in the last 5 years

- Acted as an advisor or consultant for BIOSYNEXUS Inc., USA, and ASTELLAS US.
- Served as a paid speaker or chairman for ABBVIE, USA and ASTELLAS, UK

KEY ISSUES for TREATMENT of Neonatal IFI :
what to do when prophylactic fluconazole is not given, or when it does not work

Consider the specific characteristics of neonatal SFI

- Prolonged need for CVC → high risk of hub colonisation + biofilms
- Blood culture may often be negative → need for empiric treatment
- Frequent end-organ localisations and high risk of CNS involvement
- Causative fungal agents → 99% *Candida spp.* (*Aspergillus spp.* very uncommon in neonates), 5–10% inherently resistant to fluconazole

Optimal rescue strategy → *"Hit fast, Hit hard"*

- Treat with the most potent and wide-spectrum antifungal available (to avoid/limit poor outcomes)

Ideal antifungal drugs for neonates must have:

- Significant activity against biofilms
- Significant activity against *C. glabrata*, *C. tropicalis* and *C. krusei* (because they may survive prophylactic fluconazole)
- Ability to be used in mono-therapy
- Good tolerability
- No pharmacological interactions

- The Echinocandins are the most appropriate class of antifungal agents to date available to address the specific neonatal needs
- Micafungin is the only antifungal agent to date approved for neonatal use in Europe

	Micafungin[1]	Caspofungin[2]	Anidulafungin[3]
Invasive candidiasis	**Yes**	Yes	Yes
Neutropenic patients	**Yes**	Yes	No
Paediatric patients	**Yes**	≥ 12 months	No
Neonates	**Yes**	**Limited data**	**No**
Prophylaxis in HSCT patients or expected neutropenic patients			
Adults	**Yes**	No	No
Paediatric patients	**Yes**	No	No
Neonates	**Yes**	No	No

1. MYCAMINE® (micafungin) powder for solution for infusion SPC. Astellas Pharma Ltd. September 2011
2. CANCIDAS® (caspofungin) powder for concentrate for solution for infusion SPC. Merck Sharp & Dohme Limited. September 2011
3. ECALTA® (anidulafungin) powder and solvent for concentrate for solution for infusion SPC. Pfizer Limited. August 2011

Probiotics in neonates

Probiotics are beneficial in promoting a 'good' enteric microbiota in preterm neonates, preventing colonisation by many pathogens including the various *Candida* spp[1]

Which probiotic products ?

RCTs	Probiotic used	Primary outcome	Results in probiotic group	Results in placebo group	P-value
Manzoni et al, Clin Infect Dis 2006	**Lactobacillus rhamnosus GG**	*Candida* gut colonisation in <1500g neonates	23.1%	48.8%	0.01
Romeo et al, J Perinatol 2011	**Lactobacillus reuterii**	*Candida* gut colonisation in <2500g neonates	7.1%	22.9%	0.01
Romeo et al, J Perinatol 2011	**Lactobacillus rhamnosus GG**	*Candida* gut colonisation in <2500g neonates	10.7%	22.9%	0.01

1. Manzoni et al, J Mat Fet N Med 2009.

LACTOFERRIN prevents sepsis by all pathogens, including *Candida spp*

	LF combined N=304	PLACEBO N=168	R.R.	95% C.I.	p-value
Late-onset sepsis (all agents)	5.3%	17.3%	0.28	0.16–0.50	<0.001
LOS by Gram-positive	1.2%	5.4%	0.21	0.07–0.82	0.02
LOS by Gram-negative	3.4%	6.5%	0.48	0.35–0.98	0.05
Candida enteric colonisation	17.1%	13.9%			*0.43*
Candida systemic infection	0.8%	5.4%		0.09–0.77	0.009
Rate of progression from *Candida* colonisation to infection	7.8%	41.9%	0.29	0.09–0.89	0.02
Mortality attributable to *Candida* spp	0%	1.2%			0.50

JAMA®

Manzoni P, et al. *JAMA* 2009;302:1421–8;
Manzoni P, et al. *Pediatrics* 2012;129:116–23.

The New England Journal of Medicine

N Engl J Med, Vol. 345, No. 23 · December 6, 2001

FLUCONAZOLE PROPHYLAXIS AGAINST FUNGAL COLONIZATION AND INFECTION IN PRETERM INFANTS

DAVID KAUFMAN, M.D., ROBERT BOYLE, M.D., KEVIN C. HAZEN, PH.D., JAMES T. PATRIE, M.S., MELINDA ROBINSON, R.N., AND LEIGH GOODMAN DONOWITZ, M.D.

Study Design

- Prospective, randomised, double-blind clinical trial over a 30-month period
- 100 preterm **ELBW** infants (ventilated, or with CVC) randomly assigned to intravenous **fluconazole** (3 mg/kg every second day) or placebo during the first 6 weeks of life
- Weekly surveillance cultures from all patients

	Fluconazole	Placebo	95% C.I	P
Fungal colonisation	22%	60%	0.18–0.56	0.002
Invasive fungal infection	0%	20%	0.04–0.36	0.008

Conclusions

Patterns of sensitivity to fluconazole of fungal isolates did not change during the study period. No adverse effects of fluconazole treatment were documented

“Prophylactic IV fluconazole during the first six weeks of life in ELBW infants is effective in preventing fungal colonisation and infection”

Kaufman D, et al. *N Engl J Med* 2001;345:1660–6.

Manzoni P, Stolfi I, Pugni L, et al

(on behalf of The Italian Task Force for the study and prevention of Neonatal Fungal Infections)

Prophylactic fluconazole is effective in preventing fungal colonisation and infection in preterm neonates: a multicenter, randomised trial in Italy

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

The NEW ENGLAND JOURNAL of MEDICINE

	Fluconazole N=216	*Placebo n=106*	*R.R.*	*95% C.I.*	*P-value*
Total invasive fungal infections (IFI; %)	7/216 (3.2%)	14/106 (13.2%)	0.25	0.10-0.59	0.001
IFI caused by natively fluconazole-resistant *Candida* spp	1/7	1/14			>0.99
Overall colonisation	19/216 (8.8%)	31/106 (29.2%)	0.30	0.18-0.51	<0.0001
Colonisation by natively fluconazole-resistant *Candida* spp	3/216 (1.4%)	2/106 (1.9%)			0.67
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

Manzoni P, et al. *N Engl J Med* 2007;356:2483–95.

Candida spp distribution in preterm neonates[1]

- *C. albicans* 58%
- *C. parapsilosis* 34%
- *C. tropicalis* 4%
- *C. glabrata* 2%
- *C. lusitaniae* 2%
- *C. krusei* 0.2%

Mortality and fungal species in preterm neonates[2]

Organism	Deaths / nr. of isolates	Mortality rate
C. albicans	63/147	**42.9 %**
C. parapsilosis	25/127	**19.7 %**
C. tropicalis	0/3	**0.0 %**
Other *Candida* spp	8/25	**32.3 %**

1. Fridkin SK, et al. *Pediatrics* 2006;117:1680–7;
2. Benjamin DK, et al. *Pediatrics* 2006;117:84–9.