The **TINN** collaborative project: an European investigation on pediatric and neonatal anti-infective drugs

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Do you think that the same drug formulation might be suitable for these two individuals?
# A usual clinical/management chart of a preterm neonate in NICU

**Federica M., very-low-birth-weight preterm neonate, born 02/10/2008**

**Birth Weight**: 795g.  
**G.A.**: 29 sett.  
**Day-of-life**: 12

<table>
<thead>
<tr>
<th>Medication</th>
<th>Route</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>i.v.</td>
<td>3 mg every 2nd day</td>
</tr>
<tr>
<td>Caffeine citrate</td>
<td>i.v.</td>
<td>8 mg/day</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>i.v.</td>
<td>0.6 mg x 3/day</td>
</tr>
<tr>
<td>Ampicilline+sulbactam</td>
<td>i.v.</td>
<td>55 mg x 2/day</td>
</tr>
<tr>
<td>Vitamin mixture</td>
<td>os</td>
<td>3 drops/day</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>i.v.</td>
<td>12 mg/day for 3 consecutive days</td>
</tr>
<tr>
<td>Vitamin E + Tocopherol</td>
<td>topic</td>
<td>ointment</td>
</tr>
</tbody>
</table>
How many of these drugs do you think are currently used in a compassionate, off-label way?

Unfortunately, ALL OF THEM
The case of IBUPROFEN

Federica’s mother’s headache or premenstrual syndrome

Federica’s life-threatening PATENT DUCTUS ARTERIOSUS (PDA)
A child is not a small adult!
A neonate is not a small child!
A preterm neonate is not a small neonate!

Therefore, a drug for a neonate is not just a small dose of a drug for adults!
Regulation 1901/2006 of the European parliament and the Council of Medicinal Products for Paediatric Use

- To increase availability of medicines authorized for children
- To increase the information on the use of medicinal products in the paediatric population

Entry in force 26 January 2007
Support will be given to studies dedicated to provide evidence for specific paediatric use of off-patent medicinal product currently used off-label. Studies include the assessment of pharmacokinetics (as well as data analysis and extrapolation by means of in silico models), efficacy and safety, and/or development of appropriate formulations.


Funding scheme: Collaborative Projects (Small or medium scale focused research projects with a maximum of € 6,000,000 /project
**EMEA’s Priority list**

**of off-patent drugs**

**with an objective of Public Health**

Priority points were assigned to conditions, based on:

- the **severity** of the disease,
- the paediatric age groups affected (with special priority to the **neonatal population***),
- the non-availability of treatment alternatives
- the high prevalence of the disease in the paediatric population
### The burden of neonatal SEPSIS: Antibiotic use in preterm neonates in USA
(data from the U.S. NICU national registry)

<table>
<thead>
<tr>
<th></th>
<th>Episodes</th>
<th>Incidence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Late-onset Sepsis</strong></td>
<td>1313 of 6215</td>
<td>21%</td>
</tr>
<tr>
<td>Antibiotic treatment</td>
<td>3459 of 6215</td>
<td>56%</td>
</tr>
<tr>
<td><strong>Early-onset Sepsis</strong></td>
<td>147 of 7606</td>
<td>1.9%</td>
</tr>
<tr>
<td>Antibiotic treatment</td>
<td>3652 of 7606</td>
<td>48%</td>
</tr>
</tbody>
</table>

**CONS**
- S. Aureus
- C. albicans
- E. coli

> 3 days
Infections in neonates

EMEA Priority-list: ciprofloxacin and fluconazole

- **Ciprofloxacin** is administered to treat neonates with sepsis caused by multiple resistant organisms, against which only ciprofloxacin is effective.

- **Fluconazole** is administered to prevent and/or treat neonates with invasive fungal infection, mainly candidiasis.

- Neonates are a High risk population
- Infection-related Mortality is High
- Health care problems (prematurity, hospitalizations, long-term sequelae, drug toxicities, etc)
- Lack of data on pharmacology (PK, dosage schedules..), clinical efficacy and toxicity
The burden of the disease in the EU: Neonatal Fungal Infections estimates

Fungi and Candida spp:

- Severe infections in **5 to 15% of all neonates <1500g**
- 20-50% mortality
- Up to 60% late neurodevelopmental impairment (permanent handicaps and disabilities)

- Management options:
  A- prevention → FLUCONAZOLE (→ off-label !!)
  B- treatment → AMPHOTERICIN B (→ off-label !!)
The burden of the disease in the EU: Neonatal Fungal Infections estimates (2)

- in EU (2007 Eurostat data) → 5,266,125 live births
- among them, 1.2% (= 60,000) are preterm neonates <1500g

translating into:

- up to 8,000 Invasive Fungal Infections
- up to 2,250 Deaths as a result of the Fungal Infection
- another 4,500 infants with permanent neurodevelopmental impairments, due to Neonatal Fungal Infection

every year in the EU
Luxembourg’s yearly live births = 6,000 to 6,500

Deaths or Permanent Disabilities due to Neonatal Fungal Infections in the EU = 2,250 + 4,500 = 6,750 every year

.....how can we save all Luxembourg’s infants?  
.....which is the way for decreasing the burden of the disease?
A Multicenter, Randomized Trial of Prophylactic Fluconazole in Preterm Neonates

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Cristiana Magnani, M.D., Gennaro Vetrano, M.D., Elisabetta Tridakalli, M.D.,
Giuseppina Corona, M.D., Chiara Giovannozzi, M.D., Daniele Farina, M.D.,
Riccardo Arisio, M.D., Franco Merletti, M.D., Ph.D., Milena Maule, M.D.,
Fabio Mosca, M.D., Ph.D., Roberto Pedicino, M.D., Mauro Stronati, M.D.,
Michael Mostert, M.D., and Giovanna Gomirato, M.D.,
for the Italian Task Force for the Study and Prevention of Neonatal Fungal Infections and the Italian Society of Neonatology

ISRCTN85753869 - http://www.controlled-trials.com/ISRCTN85753869/
“Crescere Insieme al S.Anna” Research Foundation.Torino

SIN (Italian Society of Neonatology)
GSIN (Italian Neonatal Infection Society)
This was the FIRST MULTICENTER, placebo controlled, randomized trial of fluconazole prophylaxis in 322 preterm neonates with birth weight <1500g.

- 8 tertiary NICUs in Italy
- Enrollment within 72 hours of birth
- Randomization 1:1:1 by center to three groups by means of computer-generated randomization lists:
  1. Group A1 → fluconazole 6 mg/kg
  2. Group A2 → fluconazole 3 mg/kg
  3. Group B → placebo
Primary objectives

- To evaluate the effectiveness and safety of fluconazole vs. placebo in the prevention of:
  - Candida colonization
  - Candida systemic infection

Adverse Effects Monitoring - Safety and Toxicity Surveillance

- Systematic monitoring of liver function tests: AST, ALT, γGT, bilirubin
- Serum levels measured at baseline, at 4 weeks, at 6 weeks and at discharge
### Results: FLUCONAZOLE either dosage (A1+A2) vs. PLACEBO

<table>
<thead>
<tr>
<th></th>
<th>FLUCONAZOLE n = (112+104) = 216</th>
<th>PLACEBO n = 106</th>
<th>R.R.</th>
<th>95% C.I.</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive Fungal Infections (%)</td>
<td>7/216 (3.2%)</td>
<td>14/106 (13.2%)</td>
<td>0.25</td>
<td>0.10</td>
<td>-0.59</td>
</tr>
<tr>
<td>Fungal Colonization</td>
<td>19/216 (8.8%)</td>
<td>31/106 (29.2%)</td>
<td>0.30</td>
<td>0.18</td>
<td>-0.51</td>
</tr>
<tr>
<td>All-cause Mortality prior to discharge</td>
<td>18/216 (8.3%)</td>
<td>10/106 (9.4%)</td>
<td>0.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality attributable to Fungi</td>
<td>0/216 (0%)</td>
<td>2/106 (1.9%)</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

This first, multicenter RCT shows that Fluconazole Prophylaxis in preterm VLBW neonates in NICU, with dosages of at least 3 mg/kg every second day, is safe and effective in reducing fungal infection and colonization.
Based on the data from the pilot Italian NEJM study of 2007, adoption of FLUCONAZOLE prophylaxis in the EU neonatal Units might translate into:

- **1,800 (instead of 8,000)** Invasive Fungal Infections
- **No Deaths (instead of 2,250)** due to the Fungal Infection
- **900 (instead of 4,500)** infants with permanent disabilities due to Neonatal Fungal Infection every year in the EU
With FLUCONAZOLE ➔
Deaths or Permanent Disabilities
due to Neonatal Fungal Infections
in the EU =
0 + 900 = **900 every year**
(instead of 6,750)

Luxembourg has been saved!
There are many major practical and ethical issues in relation to studying medicines in the vulnerable group of preterm and term neonates:

- Limited number of neonates with comparable diseases. They represent only a small part of the population as compared to older children and adults. In addition, diseases may affect only a small subcategory of patients; furthermore, neonates represent only a small proportion of the paediatric population in Europe.

- Need for adapted formulations.

- Need for suitable methodological approaches for clinical trials.

- Limited number of trained investigators with expertise in neonatal clinical trials.

- Inadequate critical mass of investigators in any single European country.

- Lack of adequate drug monitoring programs in this population.

- Major ethical issues.
Only **european networks** may address major health problems in Neonatal and Preterm neonates populations

..and thus.....
Merci prof. Evelyne Jacqz-Aigrain !
This consortium brings together 16 partners (3 private companies and 13 laboratories) from 7 Member States of the European Union.

It is coordinated by the National Institute for Health and Medical Research (INSERM, Prof. Evelyne Jacqz-Aigrain, Paris-FRANCE)
TINN = Treat Infections In Neonates

- 7 countries
- 16 partners
- 74 participants

- Score: 15.5/16
- 5,200,000 €
- 5 years
The TINN project aims at conducting two clinical trials in the groups of preterm and term neonates.

- Evaluation of the pharmacokinetics, efficacy and safety of ciprofloxacin in preterm and term neonates.
- Evaluation of the pharmacokinetics, efficacy and safety of fluconazole in preterm and term neonates.

The final objective is to validate Pediatric Investigations Plans (PIPs) for the two drugs and apply for a Pediatric Use Marketing Authorization (PUMA).
Tinn is a European research network (Collaborative Project) coordinated by the National Institute for Health and Medical Research (INSERM, Prof. Evelyne Jacqz-Aigrain, Paris - FRANCE) and by the University of Nottingham (Prof. Imti Choonara, UK). This consortium brings together 16 partners, including 3 private companies and 13 laboratories, from 7 Member States of the European Union. It is supported by the European Commission under the Health Cooperation Work Programme of the 7th Framework Programme.
TINN Workpackages

- WP1: Co-ordination and Management of the Consortium
- WP2: Preclinical studies: juvenile animal models and *in silico* experiments
- WP3: Ciprofloxacin trial
- WP4: Fluconazole trial
- WP5: Ethics and Safety
- WP6: Organisation and monitoring of the trials
- WP7: Diffusion of information
The TINN investigation project

- Ciprofloxacin
- Fluconazole

PIP: Paediatric Investigation Plan
PUMA: Paediatric Use Marketing Authorisation
With PUMAs obtained for Ciprofloxacin and Fluconazole, all preterm neonates in the E.U. will have increased hopes to survive the prematurity and to enter into the adult society free from major disabilities.

All the members of the TINN Consortium feel deeply committed towards this task, and greatly appreciate the E.U. support.
Merci pour l’attention!

Neonatology and Neonatal Research Foundation
“Crescere insieme al Sant’Anna”

Please visit
www.fondazionesantanna.org
www.fondazionesantanna.it/turinneonatologyconference.htm

paolomanzoni@hotmail.com
Limitedly only to the infections caused by fungi, the use of prophylaxis with fluconazole, one of the two drugs that our network will study, would allow decrease of fungal infection to 1,800 (instead of 8,000); none of the infected infant would die, so saving 2,250 lives; and only 900 of the survivors (instead of 4,500) would have neurodevelopmental impairment. Similar figures may be applied for the estimated improvement in neonatal health achievable with the use of Ciprofloxacin. The combined perspective of using both “new” drugs in the EU would ultimately translate into approximately 6,750 neonatal deaths avoided yearly, and into an excess of approximately 8,000 handicapped children newly entered into the social security system every year.
Partners

- **France**: CIC network, French Society of Neonatology,
- **Belgium**: Neonat
- **Nederlands**: Neonat
- **Danemark**: Neonat
- **UK**: Pharmacovigilance / Ethics
- **Italy**: Epidemiology / Neonat
- **Germany**: Pharmacogenetics
- **Sweden**: Pharmacology, Neonat
- **SME**: EPMC Pharma, ClinInfo
- **Inserm Transfer**
- **Teddy, Paedifon**
The partners of the TINN project agreed to work simultaneously on the two drugs in a unique collaborative project as:

- the two medicines have common features. They
  - are used off-patent in all European countries
  - are administered to cure rare infectious diseases
  - are prescribed in identical groups of preterm and term neonates with high risk infection
  - are administered from dosage forms designed for adults or older children

- are therefore used in a unique clinical setting of neonatal intensive care
- the two medicines are not properly evaluated in neonates. They
  - require data on pharmacokinetics, efficacy and safety
  - and therefore, require specialists in paediatric methodology, pharmaceutics, pharmacokinetics, neonatologists trained in clinical evaluations