Antibiotics and antifungals in VLBW infants

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Abstract

Very low birth weight infants are particularly vulnerable to bacterial and fungal infections. This leads to a common use of antiinfectives, often on a prophylactic basis. Due to the limited available information and the lack of guidelines, the use of antibacterials and antifungals in preterm newborns admitted to Neonatal Intensive Care Units is characterized by a large variability and these drugs are frequently given with different modalities, particularly as regards dosage and frequency, and in an off-label manner. This article provides an updated overview of the current situation on the use of antiinfectives in prematures, by reporting information derived by an analysis of the literature.

Keywords

Preterm newborn, antibiotics, antifungals, off-label use.

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How to cite

Introduction

In the last decades, the survival of very low birth weight (VLBW) infants (BW < 1,500 g) has improved dramatically due to advances in perinatal and neonatal care and better understanding of their physiopathology [1]. These neonates, characterized by a great immaturity, are more exposed to risks to develop different morbidities such as respiratory problems, patenty of ductus arteriosus, NEC, IVH and ROP [2]. In particular, VLBW infants are vulnerable to bacterial and fungal infections (up to one fourth develop hospital-acquired infections) due to the immaturity of the immune system and to predisposing factors such as maternal chorioamnionitis, ventilator care, catheterization and total parenteral alimentation [3]. This leads to a common use of antiinfectives, often on a prophylactic basis [4]. As regards antibiotics, a prolonged empirical therapy is associated to adverse outcomes and could lead to unnecessary exposure causing a selective pressure for antibiotic resistance, therefore it should be applied only when necessary at the best possible option [5-8]. Antifungal prophylaxis is currently applied in different NICUs with successful results and fluconazole is the recommended drug for neonates lower than 1,000 g and/or 27 weeks’ gestation or less in nurseries [9, 10], mortality rates associated to candidemia ranging from 40 to 50% in these subjects [11].

At this moment, a large variability in the use of antibacterials and antifungals for the treatment of suspected/confirmed neonatal sepsis persists among European NICUs [12, 13] and most agents are still used in an off-label manner [14-16]. With some exceptions, antibiotics are licensed for use in the neonate, but are frequently administered with different modalities particularly as regards dosage and frequency [17, 18]. First-line treatment of fungal infections includes amphotericin B, fluconazole or micafungin. However, information on pharmacokinetics and doses in prematures are still limited and these drugs are frequently used in an off-label manner, being micafungin the only antifungal reporting information for use in preterm newborns [19].

In this article an updated overview of the use of antibiotics and antifungals in preterm newborns admitted to NICUs will be presented, by analyzing the literature available in particular as regards the current research situation and the off-label use of these drugs.

Antibiotics

The incidence of infections is higher in the neonatal period than at any time of life and management of early-onset and late-onset bacterial infections, accounting for the major part of mortality and morbidity in VLBW infants [5], is an everyday challenge for neonatologists.

The basic treatment of neonates with suspected/proven bacterial infections has not substantially changed over the last years, but the increasing problem of multidrug-resistant bacteria encourage the development and subsequent approval of new antibiotics for use in preterm newborns, particularly vulnerable to bacterial infections [3].

Important initiatives have been adopted both in Europe and the USA to favour a rapid development of drugs, comprised antibiotics, to be safely used in neonates. These initiatives comprise the introduction of the Paediatric Regulation n. 1901 on 26 January 2007 [20] and of the FDA Safety and Innovation Act in 2012 to advance neonatal drug studies [21], the preparation by EMA of a priority list of off-patent drugs (comprising antibiotics) with the highest need for studies in preterm and term neonates [22], the funding of some projects by the EU [23].

Despite these encouraging initiatives, new antibiotics approved in the last years in the EU rarely have been studied in the preterm newborn.

Some authors [24] analyzed new antibiotics for paediatric use by reviewing a decade of regulatory trials submitted to EMA from 2000, before and after the introduction of the European Paediatric Regulation. As regards the 11 antibiotics newly approved for use in the adult, 31 clinical trials enrolling also children were identified in Europe, but many of these trials did not provide a neonatal subset analysis (only 6/31 involve neonatal population), some studies have been prematurely terminated and others are apparently active but still not recruiting patients (Tab. 1).

In a systematic review [25] the authors analyzed all randomized controlled trials (RCTs) involving neonates and antibiotics used in the last 15 years. A total of 35 trials (involving 13 different antibiotics) were evaluated: most of these studies have been conducted nationwide and hospital-based. RCTs of antibacterial agents to prevent or treat infections in neonates resulted poorly designed and reported, underlying the difficulties in conducting studies in neonates. There was no increase in the number and quality
of RCTs over the years. Gentamicin was the most frequently studied antibiotic (11 RCTs).

In an interesting paper published last year [26], the authors tried to quantify progress made in neonatal studies and neonatal information in product labelling as a result of recent legislation. By reviewing FDA databases between 1997 and 2010, 28 drugs examined in 41 different studies included also neonates and lead to 24 related labelling changes (6% on a total of 406 paediatric labelling changes made during the study period) while among 4 of the products studied in neonates that did not obtain a labelling change 3 regarded antibiotics (ophthalmic ciprofloxacin, ofloxacin and gatifloxacin). Among these 24 labelling changes, only 11 (46%) implied an approval for use in neonates and only one regarded antibiotics (linezolid). The remaining 13 labelling changes (54%), comprising linezolid for CNS infections and caspofungin, reported the statement “safety and effectiveness have not been established”. The number of neonates enrolled in the studies was relatively small.

Another aspect that need a deepen analysis regards how antibiotics, the most commonly prescribed medications in NICUs, are used in preterm newborns. In fact, antibiotics are frequently used with different modalities [17, 18] and in an off-label manner [14, 16].

Some authors [15] examined data on antibiotic use in some NICUs and paediatric wards of three European countries (UK, Italy, Greece). During a two-week study period, 110 neonates (62 in the UK, 38 in Italy and 10 in Greece) admitted to 4 NICUs received a total of 290 antibiotic prescriptions, among which 218 (75%) resulted off-label mainly for deviations from doses and/or frequency (42.8%), rarely for age (12 episodes regarding mostly meropenem, but also imipenem and ciprofloxacin). The antibiotics most frequently prescribed at doses other than those recommended were aminoglycosides (gentamicin and amikacin): compared to UK Units, in Italy differences consisted in the administration of a lower total daily dose or different fractioning, while in Greece higher doses were significantly more commonly used.

Within the TINN European project set up under the FP7 programme, some authors [12] focused their attention on ciprofloxacin, included in the EMA’s priority list of off-patent products with the highest need for studies in neonates. Questionnaires on the current use of this antibiotic from 189 European NICUs were analyzed. Ciprofloxacin was used only in 25% of NICUs in cases of culture-proven bacterial sepsis due to multidrug-resistant organisms: dosages varied enormously between countries and between NICUs and the most commonly used regimen was 20 mg/kg/day (10-15-20-25-30-45 mg/kg/day). No guidelines on the use of ciprofloxacin for sepsis were found.

In another paper [27], the same authors analyzed the use of ciprofloxacin in Italian NICUs. Data were obtained from 38 Italian NICUs. Only 5 wards (13%) used ciprofloxacin i.v. at different dosages: 20 mg/kg/day (12 h intervals) or 10 mg/kg/day (8-12 h intervals).

As part of the FP7 TINN2 Project, a survey [28] was undertaken to evaluate the role of azithromycin, the drug of choice used off-label throughout Europe, in preventing BPD and Ureaplasma spp. colonization. 167 NICUs of 28 different European countries adhered to the survey: four countries (UK, Italy, France and Spain) covered 44% of the data (74/167 Units). Prematurity (G.A. ≤ 28 weeks) and high oxygen requirements were the two major perceived risk factors for BPD and 66.4% of NICUs identified the presence of Ureaplasma spp. as an increased risk of BPD. The estimated rate of Ureaplasma spp. colonization in neonates < 28 weeks gestation ranged between 25% and 50% and an antibiotic treatment was applied in 79 NICUs (47%). In case of proven infection, azithromycin was used in 27% of NICUs in 12 countries, but the most widely used

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**Table 1.** Antibiotics approved in the EU during the period 2000-2012: information about paediatric population (modified from: Garazzino et al., 2013 [24]).

<table>
<thead>
<tr>
<th>Drug</th>
<th>EU approved indications in children</th>
<th>Paediatric Trials n = 31</th>
<th>PIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aztreonam lysine</td>
<td>None</td>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td>Ceftaroline fosamil</td>
<td>No</td>
<td>2 0-18 years</td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td>None</td>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td>Doripenem</td>
<td>None</td>
<td>2* + 3 0-18 years</td>
<td></td>
</tr>
<tr>
<td>Ertapenem</td>
<td>Children &gt; 3 months</td>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td>Fidaxomicin</td>
<td>None</td>
<td>1* 0-18 years</td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td>None</td>
<td>2* + 3 0-18 years</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>None</td>
<td>1* + 3 &gt; 3 months</td>
<td></td>
</tr>
<tr>
<td>Retapamulin</td>
<td>Children &gt; 9 months</td>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>None</td>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td>Tigecyclin</td>
<td>None</td>
<td>2 8-18 years</td>
<td></td>
</tr>
</tbody>
</table>

* neonatal population.

PIP: Paediatric Investigation Plan.
macrolide was erythromycin (30/79 NICUs, 38%) particularly in the UK, Germany and Switzerland.

**Antifungals**

Invasive fungal infections are associated with high morbidity and mortality in neonates, with the highest incidence in VLBW and ELBW infants [29]: *Candida spp.* colonization, the main risk factor for the development of invasive candidiasis, results three times more common in neonates born < 26 weeks of gestation or with a birth weight < 750 g [30].

Antifungals currently used in the newborn for the treatment of fungal infections, mainly caused by *Candida spp.*, are polyene compounds (amphotericin B and lipid preparations), triazoles (fluconazole) and echinocandins (micafungin and caspofungin) [5, 19].

Fluconazole, approved by EMA for the treatment of candidiasis in term newborns and included in the EMA’s priority list of off-patent products with the highest need for studies in neonates, is emerging as the agent of choice for antifungal prophylaxis. However, its routine use in VLBW is controversial as regards its real efficacy in preventing *Candida spp.* infections, but also concerns including neurodevelopemental toxicity and emergence of drug resistance [31, 32]. Despite these controversies and the lack of license status for preterm newborns, the Scientific Societies support antifungal prophylaxis with fluconazole at a dose of 3-6 mg/kg/day, dosage used varied significantly in different NICUs, with wide ranges in the unit dose (3-6-12-20 mg/kg) and frequency (24-48-72 h). Transformed into total daily doses, the reported data ranged from 1 to 20 mg/kg/day, with 34% of NICUs administering ≤ 4 mg/kg/day and 49% ≥ 6 mg/kg/day.

In another paper [27], the same authors analyzed the use of fluconazole in Italian NICUs. Data were obtained from 38 Italian NICUs. 30 NICUs (79%) declared using fluconazole for prophylaxis in subjects < 1,500 g. Differences were found between NICUs in the dosage schemes: 3-6 mg/kg every 24-48-72 h. Average duration of prophylaxis ranged from 10 to 45 days. 17 NICUs administered fluconazole for treatment (cases of sepsis with identification of *Candida spp.*). Treatment schemes also varied between NICUs: 3-6-12 mg/kg/day, mostly i.v., average duration of therapy 10-30 days.

As regards the other antifungals, micafungin is the only drug authorized for neonatal use by EMA, with reliable published body of evidence regarding pharmacokinetics, efficacy and safety in newborns [19]. Amphotericin B formulations are a valid alternative, but the lack of data in neonates and its potential toxicity suggest that this antifungal should be used only as a second line [34].

**Conclusions**

Despite some recent important initiatives adopted both in the USA and Europe [20-23], antiinfective therapy in preterm newborns results already complicated by limited clinical testing and prescribing information for this patient population, confirming the widespread use of antiinfectives in an off-label manner [14-16]. Moreover, a great variability in the use of these drugs among NICUs has been reported [12, 17, 18]. Undoubtedly, it is extremely difficult to standardize antibiotic and antifungal treatments in VLBW and ELBW infants, as the choice of the empirical treatment depends on the clinical context and local epidemiology. However, other factors could contribute to the different clinical approaches in the treatment of bacterial and fungal infections such as the lack of evidence-based guidelines [12].

For all these reasons, preterm newborns admitted to NICUs, who represent the most vulnerable paediatric subpopulation, remain a group of patients at increased risk not only of
ineffective antiinfective treatments, but also of adverse drug reactions and medication errors [35, 36]. As suggested by some authors [37], only a strong collaboration among all those dealing with drug use in neonates as well as a harmonization of interventions will ensure that this patient population do not remain therapeutic orphans.

Declaration of interest

The Author declares that there is no conflict of interest.

References


