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Antibiotic Use in a Cohort of Extremely Low Birth Weight Neonates: Focus on Off-Label Uses and Prescription Behaviour

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Abstract

Aim: To analyse antibiotic prescriptions in a cohort of extremely low birth weight neonates admitted to Italian level III Neonatal intensive Care Units. **Methods:** An online questionnaire was used to collect detailed information for each newborn. Antibiotic prescriptions were classified about their license status and compared with British National Formulary for Children (BNFC) and with a practical guide prepared by the Italian Society of Neonatology (ISN). **Results:** During the study period (May-July 2014) among 93 neonates admitted to 30 Italian Neonatal intensive Care Units, 56 (60%) received at least an antibiotic (92 prescriptions in total). Ampicillin, gentamicin and vancomycin were the antibiotics most commonly used for the prevention/treatment of bacterial infections. 56/92 antibiotic prescriptions (61%) resulted *off-label* mainly as regards dosing frequency, while 13 prescriptions (14%) regarded antibiotics used in absence of specific indication for newborns (meropenem, imipenem, piperacillin/tazobactam, clindamycin, clarithromycin). 50/56 neonates (89.3%) received at least one *off-label* antibiotic prescription. Differences have been observed in dosing regimens between current study and recommendations contained in BNFC, while prescriptions adhered more frequently to ISN indications. **Conclusions:** Our results confirm the high prevalence of *off-label* antibiotic use in ELBW neonates and underline a better adherence to indications based on clinical practice.

Keywords

Antibiotics, ELBW Neonates, *Off-Label* Use, Variability

1. Introduction

In the last decades, the survival of extremely low birth weight (ELBW) neonates

(BW ≤ 1000 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 [1] and in particular are vulnerable to bacterial and fungal infections (up to one third 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 [2].

Suspected infections are frequent in preterm newborns and the incidence of sepsis is inversely associated with BW [3]: this leads to a common use of antiinfectives in ELBW neonates in the first days of life often on a prophylactic basis [4]. If treatment is delayed, neonatal sepsis can be rapidly fatal, making optimal use of antibiotic essential. On the other hand, a prolonged antibiotic empirical therapy is associated to adverse effects (alteration of gut microflora, fungal colonization and subsequent invasive infection, necrotizing enterocolitis, late-onset sepsis and death) and could lead to unnecessary exposure causing a selective pressure for antibiotic resistance, especially in the case of late-onset infections [5]. Therefore, empirical therapy should be applied only when necessary at the best possible option [6] [7].

At this moment, a large variability in the use of antibiotics for the treatment of suspected/confirmed neonatal sepsis persists between different European Neonatal Intensive Care Units (NICUs) [8] [9] [10] [11] and most agents are still used in an *off-label* (OL) manner [12] [13] [14]. In fact, with some exceptions antibiotics are licensed for use in the neonate, but are frequently administered with different modalities particularly as regards dosage and frequency [9] [12] [13] [14] [15].

This paper is focused on antibiotic prescriptions in a cohort of ELBW neonates included in a multicentre study involving a representative sample of Italian NICUs [16], with the purpose to describe practices concerning prevention and treatment of bacterial infections, in particular the extent and nature of OL antibiotic use in this setting. Moreover, the prescription behaviour was compared with indications contained in the British National Formulary for Children (BNFC) 2016-2017 [17] and in a practical guide to the use of drugs in newborns [18] prepared by the Neonatal Pharmacotherapy Study Group (NPSG) of the Italian Society of Neonatology (ISN).

2. Patients and Methods

2.1. Study Design

A sub-analysis of a multicentre one-day study involving all 107 level III Italian NICUs was performed [16].

2.2. Data Collection and Analysis

For current analysis, data from each ELBW infant present in NICUs and receiv-

ing at least an antibiotic treatment in the day chosen within each ward between May and July 2014 were retrieved from data collected and recorded in an online questionnaire (Google form), after sought and information to local ethics committees.

Anonymised demographic data included date of birth, sex, gestational age (GA) and birth weight (BW), post-natal age (PNA), Apgar score, diagnosis. Moreover, all information about each antibiotic administered during the day chosen was retrieved**:** formulation, route of administration, individual dosing regimen (unit dose and dosing interval)**,** length of therapy, indication for use, tolerability. As personal identifying data of the infants could neither directly or indirectly be attributed to a specific individual and the study design did not affect the healthcare of the included patients, a formal written consent for participation in this study was not obtained.

For each antibiotic, the licensed or OL use was determined according to the *Italian Drug Compendium* 2013. This classification was based on information derived from product data sheets (package insert, Summary of Product Characteristics).

Antibiotic prescriptions were classified into three groups: 1) antibiotics following the marketing authorization (*on-label* prescriptions); 2) antibiotics with no information for use in neonatal population (*off-label* for age); 3) antibiotics licensed for use in neonates, but *off-label* for dose, frequency, route of administration, length of therapy and clinical indication.

In addition, every prescription was compared with the BNFC 2016-2017 [17], commonly accepted as one of the few dosing references, and with a practical guide proposed by the NPSG, containing information about all medicines commonly used in NICU and available both as book [18] and online to all Italian neonatologists. Dosing recommendations for ELBW infants were based not only on BW, but also on GA and/or PNA.

Data were collected in a database and summarized using standard descriptive methods. Categorical variables related to prescription behaviour were compared by χ^2 analysis: statistical significance was defined as $p \leq 0.05$.

3. Results

3.1. General Data

Among the 36 NICUs participating to the multicentre study (34% of all Italian level III NICUs, comprising hospital and academic wards) [16], 30 wards admitted ELBW neonates: each NICU participating in this study recorded a median number of six charts (range 2 - 22) and should be considered representative of the regional distribution and of the number of beds/ward (in every case > 4, with a maximum of 36 beds in some cases).

3.2. Patient Data

A total of 93 ELBW neonates were treated with at least one drug in the day cho-

sen. As specified in Table 1, 52 were male, 50 with a G.A. between 26 and 28 weeks and 39 with a BW between 601 and 800 g: 21/93 (22.6%) were small for gestational age (SGA). On the day chosen for data collection, the median PNA

Table 1. Baseline characteristics of ELBW infants.

PARAMETER	PATIENTS (n = 93)
Male gender	52 (56%)
Gestational age (wks)	
23 - 25 wks	29 (31.2%)
26 - 28 wks	50 (53.8%)
29 - 32 wks	14 (15%)
Birth weight (g)	
400 - 600 g	17 (18.3%)
601 - 800 g	39 (41.9%)
801 - 1000 g	37 (39.8%)
Small for gestational age	22 (23.7%)
Apgar score 1st min	
≤3	23 (24.7%)
4 - 6	47 (50.6%)
7 - 10	23 (24.7%)
Apgar score 5th min	
≤3	6 (6.5%)
4 - 6	15 (16.1%)
7 - 10	72 (77.4%)
Suspected/proven infections	46
-Bacterial	44
-Fungal	2
Sepsis	19
-Bacterial	12
-Fungal	7
Anemia	32
Cardiovascular problems	15
Gastrointestinal problems	30
Respiratory problems	76
Other	11
Endotracheal intubation at birth	7
Mechanical ventilation	9
O_2 supplementation	4
Phototherapy	2
Catheterization	22
Surgical intervention	2

was 2 weeks (range: 0 - 28 days).

3.3. Prescription Data

Among a total of 367 drug prescriptions (54 different medicines), 92 regarded antibiotics given to 56/93 (60%) neonates: in 89/92 cases the antibiotic was administered intravenously (mostly by infusion). Ampicillin, gentamicin, amikacin and vancomycin were the antibiotics most commonly used for the prevention/treatment of bacterial infections (56/92, 61% of all antibiotic prescriptions). In 36% of cases (33/92 prescriptions) a coadministration of ampicillin and gentamicin was applied. In other cases, neonates were treated with vancomycin (14/92 prescriptions, 15% of cases) or with a broad-spectrum antibiotic such as ceftazidime, cefotaxime, ceftriaxone, imipenem, meropenem, clarithromycin (15/92 prescriptions, 16% of cases). The mean duration of treatments was 5 - 7 days in case of suspected infections, >10 days (mean 12 - 14 days) when the infection was proven or a diagnosis of sepsis was made.

3.4. *Off-Label* Prescriptions

50/56 ELBW neonates (89.3%) received at least one OL antibiotic prescription.

Prescriptions related to 20 different antibiotics, analysed according to their license status, are reported in Table 2. Some differences have been observed taking into account the birth weight of neonates, with a higher but not significant percentage of *on-label* prescriptions in newborns with a BW < 800 g ($p = 0.583$, NS).

The only antibiotics used according indications were ampicillin/sulbactam, cefotaxime and ceftriaxone, piperacillin and teicoplanin (23/92 prescriptions, 25%). 13 prescriptions (14%) regarded five antibiotics (meropenem, imipenem, piperacillin/tazobactam, clindamycin, clarithromycin) used in absence of a specific indication for use in the neonatal population. 56/92 antibiotic prescriptions (61%) resulted *off-label*, mainly as regards dosing frequency, while in few other cases prescriptions deviated for dose or formulation.

As specified in Table 3, in the current study *off-label* prescriptions resulted >60%, relatively low as regards vancomycin (35.7%) and ceftazidime (33.3%), >90%

Table 2. Antibiotic prescriptions in ELBW infants analysed according to their license status (χ^2 test, NS = not significant).

	Total prescriptions (n = 92)	400 - 600 g (n = 20)	601 - 800 g (n = 35)	801 - 1000 g (n = 37)	Significance
On-label prescriptions	23 (25%)	6 (30%)	10 (29%)	7 (19%)	**NS**
Prescriptions in absence of neonatal indications	13 (14%)	1 (5%)	5 (14%)	7 (19%)	**NS**
Off-label prescriptions	56 (61%)	13 (65%)	20 (57%)	23 (62%)	
Frequency	46	8	19	19	**NS**
Dose	8	4	1	3	
Formulation	2	1	-	1	

Table 3. Analysis of *off-label* (OL) antibiotic prescriptions of the current study in comparison with ISN practical guide.

	Total prescriptions (n = 92)	OL prescriptions (n = 56)	Reason	No adherence to ISN protocol (n = 18)	Deviation
Ampicillin	18	17 (94.4%)	OL for frequency (12 - 24 h)	2 (11.1%)	Frequency
Gentamicin	15	15 (100%)	OL for frequency (18 - 36 - 48 h) or dose (2.5 mg/kg)	5 (33.3%)	Frequency
Vancomycin	14	5 (35.7%)	OL for frequency (18 - 24 h)	2 (14.3%)	Frequency
Amikacin	9	9 (100%)	OL for frequency (8 - 24 - 36 h) or dose (15 mg/kg)	6 (66.7%)	Dose or frequency
Ceftazidime	3	1 (33.3%)	OL for dose (150 mg/kg/day)	1 (33.3%)	Frequency
Metronidazole	3	3 (100%)	OL for frequency (48 h)	1 (33.3%)	Frequency
Netilmicin	3	3 (100%)	OL for frequency (48 h) or formulation (collyrium)	1 (33.3%)	Frequency
Oxacillin	1	1 (100%)	OL for frequency (12 h)	-	-
Tobramycin	1	1 (100%)	OL for formulation (collyrium)	-	-
Miocamicin	1	1 (100%)	OL for frequency (24 h)	-	-

for the other antibiotics (in particular ampicillin, aminoglycosides and metronidazole). Compared to the ISN practical guide, only about 20% of prescriptions deviated and differences mainly regarded frequency of administration: the adherence was >80% for ampicillin and vancomycin.

As regards the four antibiotics most commonly prescribed in Italian NICUs to ELBW infants (ampicillin, gentamicin, amikacin, vancomycin), differences have been observed in dosing regimens between current study and recommendations contained in BNFC, particularly as regards ampicillin and gentamicin (Table 4).

4. Discussion

Bacterial infections account for a major part of neonatal morbidity and mortality worldwide [2] and antibiotics are extensively prescribed in neonates admitted to NICUs, particularly in ELBW infants [19].

The current analysis of data, regarding a subpopulation of ELBW infants enrolled in a nation-wide study comprising about one-third of all Italian level III NICUs [16], confirms the existence of different approaches between Italian NICUs towards the prevention and management of infections in ELBW neonates, resulting in a large variability in antibiotic use and in a high number of *off-label* prescriptions.

In detail, from our data different prescription behaviour emerge by the comparison with indications contained in BNFC and ISN practical guide, with a major adherence to local guidelines.

The large variability in antibiotic use undoubtedly derives from the difficult standardization of treatments in this neonatal subpopulation characterized by immaturity and rapid physiologic changes in the first postnatal weeks, but also by the lack of a unique source for prescribing guidance. This heterogeneity was

Table 4. Dosing regimens of the four more frequently used antibiotics in ELBW infants admitted to Italian NICUs in comparison with BNFC and ISN guide (intravenous infusion).

Antibiotic	GA (wks)	PNA (days)	Unit dose (mg/Kg)			Dosing interval (h)		
			Current Study	BNFC	ISN guide	Current Study	BNFC	ISN guide
Ampicillin (n = 18)	≤27 wks		50 (100*)			6 - 12		
	28 - 32 wks		50 (100*)			12 - 24		
		<7 days		30 (60 - 100*)			12	
		7 - 20 days		30 (60 - 100*)			8	
		21 - 28 days		30 (60 - 100*)			6	
	≤29 wks	0 - 28 days			50 (100*)			12
	30 - 32 Wks	0 - 14 days			50 (100*)			12
		>14 days			50 (100*)			8
Gentamicin (n = 15)	≤27 wks		2.5 (5*)			24 - 36 - 48		
	28 - 32 wks		2.5 (5*)			18 - 24 - 36 - 48		
		<7 days		5*			36	
		7 - 28 days		5*			24	
	≤29 wks	0 - 14 days			2.5			24 - 36
		≥15 days			2.5			18 - 24
	30 - 32 wks	0 - 7 days			2.5			18
		≥8 days			2.5			12 - 18
Vancomycin (n = 14)	≤27 wks		10 - 15*			6 - 8 - 12 - 18 - 24		
	28 - 32 wks		10 - 15*			12		
	<29 wks			15			24	
	29 - 32 wks			15			12	
	≤29 wks	0 - 14 days			10 - 15*			18
		>14 days			10 - 15*			12
	30 - 32 wks	0 - 14 days			10 - 15*			12
		>14 days			10 - 15*			8
Amikacin (n = 9)	≤27 wks		7.5 (15*)			8 - 24 - 36		
	28 - 32 wks		7.5 (15*)			12 - 24 - 36		
		0 - 28 days		7.5 (15*)			12 - 24	
	≤28 wks	0 - 24 days			7.5			24
	29 - 32 wks	0 - 7 days			7.5			12
		≥8 days			7.5			8

*serious infections or sepsis.

previously underlined by some authors as regards dosage schemes of gentamicin, vancomycin and ciprofloxacin [8] [12] [13] [14] [15] and by other authors [20] who compared antibiotic prescriptions in a NICU with recommendations contained in three commonly used reference sources (Pediatric Dosage Handbook, Neonatal Drug Formulary and Neofax), detecting divergent information on dosage schemes in preterm newborns. More recently, dosage regimens of antibiotics were analysed in French NICUs and a considerable inter-centre variability was observed, with doses and/or dosage frequency varying

significantly for 12 antibiotics (aminoglycosides, vancomycin, penicillin G, oxacillin and cloxacillin, ceftazidime, imipenem/cilastatin, clindamycin and metronidazole) [9]. The same variability has been observed in 89 NICUs of 21 different European countries: from the analysis of 586 antibiotic prescriptions referred to 37 different systemic antibiotics, deviations from BNFC dosage recommendations have been observed between European countries, with the use of higher doses for antibiotics well tolerated and of lower doses when safety concerns were evident [10].

Off-label drug use is a common practice in neonatal care [21] and in many situations this is the only therapeutic alternative due to the lack of availability of suitable licensed/labelled drugs.

As regards antibiotics, the most commonly prescribed medications in NICUs, the high prevalence of *off-label* prescriptions in newborns derives in some cases by a lack of registered clinical trials [22], leading to absence of indication for use in this paediatric subpopulation. Despite some encouraging initiatives (such as the introduction of the European Paediatric Regulation) have been taken with the aim to reduce the use of *off-label*/unlicensed drugs in the paediatric population [23], new antibiotics approved in the last years in the EU have been rarely studied in the newborn (only 6/31 pediatric clinical trials enrolled neonatal population) [24] and very few labelling changes specific for the neonatal population have been introduced [25]. More frequently, in presence of indication for use in neonates *off-label* prescriptions are due to deviations from information contained in data sheets that rarely reflects clinical practice.

Our data, regarding a cohort of ELBW neonates where antibiotics were given on the basis of a diagnosis of bacterial sepsis (12 neonates) or of a suspected/proven bacterial infection (44 newborns), are in line with previously published results on *off-label* antibiotic use [9] [12] [13] [14]: only about one-fourth of prescriptions followed the terms of the marketing authorization and more than 80% of newborns received at least one *off-label* antibiotic prescription, with a 75% prevalence for use of antibiotics *off-label* for dosage schemes or for age (no indication in preterm infants).

As regards dosage schemes, the choice of the interval in administering antibiotics have important efficacy and safety concerns in newborns: if the dosing interval is too long antibiotic concentrations may drop below the MIC, while if the dosing interval is too short the antibiotic may accumulate in the body causing toxicity. Extended dosing intervals rather than divided doses are more commonly used in preterm newborns, even if supported by limited data [26]. This approach, based on the conviction of potentially less toxicity, results also by our data and the deviation from indications reported in data sheets translates in a better adherence to ISN recommendations, derived by clinical practice, that take into account both gestational age and postnatal age.

In our cohort of ELBW neonates, the combination ampicillin+gentamicin was the most commonly applied regimen (33/56) for an empirical therapy of early-onset infections, in some cases (15/56) substituted with a unique broad-spectrum antibi-

otic (ceftazidime or another cephalosporin, meropenem or imipenem, clarithromycin).

Ampicillin prescriptions resulted almost all *off-label* (94.4%) for frequency (12 - 24 h instead of 8 h), while deviated by the suggested ISN recommendations in only 11% of cases. The most common dosage scheme applied was 50 mg/kg every 12 h and this suggests a discrepancy between generic information contained in data sheets (100 mg/kg/daily divided in three doses) and how this antibiotic is effectively given to newborns taking into account the characteristics of the patient and the indication (prophylactic or therapeutic use and severity of the infection) as specified in ISN guide: 50 - 100 mg/kg every 8 - 12 h in preterm newborns depending both on gestational age and postnatal age.

The same differences in dose and frequency of administration also regard gentamicin and other aminoglycosides (netilmicin and amikacin). Aminoglycosides have been licensed with the recommendation to divide the total daily dose into two administrations, while in clinical practice (ISN indications) it is preferred to adopt once-daily dosing or longer intervals in the first days of life (in particular for GA ≤ 29 weeks), as demonstrated in some clinical trials [27] and also suggested by BNFC and by the National Institute of Health and Care Excellence [28]. From our data, dosage schemes of these antibiotics resulted variable among NICUs (12 different combinations), with often the application of longer intervals of administration (36 - 48 h) and consequently lower total daily doses: this may reflect a "fear" of known adverse effects, such as nephrotoxicity, preferring to reduce the risks by limiting dosage as previously reported [13]. This different prescription behaviour was previously underlined in a UK [15] and French survey [9] and by other authors who compared antibiotic prescriptions related to 110 newborns admitted to some NICUs in the UK, Italy and Greece: the number of *off-label* prescriptions resulted significantly higher in Italy and Greece (92% compared to 63% in the UK), mostly regarding gentamicin and amikacin given at different total daily doses or frequency [13].

Some prescriptions (14/92) regarded vancomycin, a narrow-spectrum antibiotic usually administered for late-onset sepsis caused by Gram-positive bacteria in neonates presenting cardiorespiratory instability and in areas where methicillin-resistant *Staph. aureus* is prevalent [5]. Although it has been used for >50 years, the dosing regimen remains a challenge in NICU [29] and also for this antibiotic the use in clinical practice results variable [9]. In our NICUs, 36% of prescriptions resulted *off-label* as regards frequency: every 18 - 24 h in preterm infants < 30 weeks (as partially suggested by ISN guide and BNFC), while data sheets generically reports every 8 - 12 h based only on postnatal age.

Finally, the use of antibiotics in absence of a specific indication in the neonatal population regarded five antibiotics (mainly meropenem, but also in specific situations imipenem, piperacillin/tazobactam, clindamycin and clarithromycin) and was cautious (in total 13 prescriptions, 14%) mainly referred to ELBW neonates with a higher BW: this kind of use was applied only in one case in presence

of a BW < 600 g, where meropenem (20 mg/kg every 8 h) was given after diagnosis of late-onset sepsis. Although meropenem has been widely successfully used to treat severe infections such as sepsis and meningitis ≥ 3 months of life [30], until now it has not yet been registered for use, at least in Italy, in the neonatal population.

This survey, despite some limitations (in particular the self-report nature of the study and the number of ELBW neonates included) that do not allow a more accurate analysis of the data, confirms the high prevalence of *off-label* prescriptions and the variability in the use of antibiotics in ELBW neonates. The reasons for this high variability in dosage schemes of antibiotics in newborns are multiple. First, high quality data is lacking for many antibiotics, being current guidelines mainly based on expert opinion and small studies rather than on large clinical trials [9]. Additional difficulties derive from changes in the pharmacokinetics of antibiotics in the first weeks of life [31]. Other reasons regard problems in adoption and dissemination of evidence-based knowledge [27] [31].

Given the paucity of data available on this neonatal sub-population, our recording and analysis of antibiotic prescriptions in a cohort of ELBW neonates could be a first step to introduce a data collection system useful to harmonize prescription behaviour.

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Contributions of Author Statement

Rocco Agostino and Laura Cuzzolin defined the study and the online questionnaire, Laura Cuzzolin performed the analysis of the data and wrote the first draft of the manuscript, Rocco Agostino critically reviewed the manuscript.

Conflicts of Interest

The authors declare that they have no conflict of interest in connection with this article

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Abbreviations

ELBW—Extremely Low Birth Weight
NICU—Neonatal Intensive Care Unit
BNFC—British National Formulary for Children
NPSG—Neonatal Pharmacotherapy Study Group
ISN—Italian Society of Neonatology