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RESEARCH ARTICLE

Medicines prescription patterns in European neonatal units

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Abstract
Background Hospitalized neonates receive the highest number of drugs compared to all other age groups, but consumption rates vary between studies depending on patient characteristics and local practices. There are no large-scale international studies on drug use in neonatal units. *Objective* We aimed to describe drug use in European neonatal units and characterize its associations with geographic region and gestational age. *Setting* A one-day point prevalence study was performed as part of the European Study of Neonatal Exposure to Excipients from January to June 2012. *Method* All neonatal prescriptions and demographic data were registered in a web-based database. The impact of gestational age and region on prescription rate were analysed with logistic regression. *Main outcome measure* The number and variety of drugs prescribed to hospitalized neonates in different gestational age groups and geographic regions. *Results* In total, 21 European countries with 89 neonatal units participated. Altogether 2173 prescriptions given to 726 neonates were registered. The 10 drugs with the highest prescription rate were multivitamins, vitamin D, caffeine, gentamicin, amino acids for parenteral nutrition, phytomenadione, ampicillin, benzylpenicillin, fat emulsion for parenteral nutrition and probiotics. The six most commonly prescribed ATC groups (alimentary tract and metabolism, blood and blood-forming organs, systemic anti-infectives, nervous, respiratory and cardiovascular system) covered 98% of prescriptions. Gestational age significantly affected the use of all commonly used drug groups. Geographic region influenced the use of alimentary tract and metabolism, blood and blood-forming organs, systemic anti-infectives, nervous and respiratory system drugs. *Conclusion* While gestational age-dependent differences in neonatal drug use were expected, regional variations (except for systemic anti-infectives) indicate a need for cooperation in developing harmonized evidence-based guidelines and suggest priorities for collaborative work.

Keywords Database · Europe · Exposure data · Infant · Neonatal pharmacotherapy · Neonatal unit

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Impacts on practice

- There is a need for commonly accepted European treatment guidelines for neonates, to ensure safe and appropriate medicines use in this patient group.
- There is a knowledge gap in neonatal medicines' use due to the lack of relevant international research in the field. Therefore, it is important to highlight the areas of neonatal pharmacotherapy in which the future research could be focused.
- There are significant regional variations within Europe in the consumption of most commonly used medicines in neonates.

Introduction

Medicines play a pivotal role in improving neonatal health and reducing mortality, and thus are widely used in neonatal units. A median of 3–11 medicines per neonate are given depending on the setting and gestational age (GA) [1, 2]. Most medicines administered to neonates are either off-label or unlicensed and the exposure of off-label/unlicensed medicines is the highest among preterms [1]. The use of medicines depends on underlying conditions, which are often associated with GA, medicines availability in a country and presence of evidence-based guidelines. Traditions and expert opinions could play a role as well [3, 4].

Medicine use among neonates has been poorly studied. The most comprehensive studies conducted in the United States have been based on national datasets [5, 6]. Hsieh et al. showed that antibiotics (ampicillin and gentamicin) were the most commonly used medicines, followed by caffeine, vancomycin and beractant, and the mean number of medicines per neonate was four [6].

Until now European studies have covered single countries or centres [7, 8] or only selected therapeutic groups such as antibiotics [9]. Lass et al. showed, that neonates in Estonia received similarly to US neonates most commonly antibiotics (gentamicin and ampicillin), followed by simethicone, heparin and fentanyl [7]. Median number of products used per treated child was also similar—four per a neonate.

Due to methodological variabilities between-country comparisons are complicated. Still, significant geographical differences in medicine use have been described [10]. Describing medicine use patterns is crucial in obtaining a comprehensive picture of the present situation and identifying priority areas for research. The European Study of Neonatal Exposure to Excipients (ESNEE) was a pan-European project that aimed to describe the use of pharmaceutical excipients in neonatal medicines. For this purpose data on medicine use in neonatal units were collected as previously described [11].

Aim of the study

In this sub-study of ESNEE we aimed to describe the use of medicines in European neonatal units and explore how geographic region and GA influence their consumption. We hypothesized that GA will influence medicine use regardless of region because underlying conditions depend on GA, and medicine use should not depend on region.

Ethics approval

Ethics Committee approval was obtained locally for participation in the study in compliance with national requirements ("Appendix" section). No consent for individual patients was sought, as the data were collected in routine clinical practice and anonymized before leaving the study sites.

Methods

A multicentre, single-day point prevalence study (PPS) was performed as detailed elsewhere [2, 9, 11]. The study aimed to cover all 27 European Union countries plus Iceland, Norway, Serbia and Switzerland. All general neonatal, intermediate and neonatal intensive care units (NICU) and also mixed paediatric and NICUs with more than 50% of admissions of neonates (age of ≤ 28 days) were eligible for participation. The eligible units were contacted by the ESNEE consortium's national lead contacts who were asked to include as many hospitals and units as possible. All units that agreed to participate, were involved in the study.

Data collection was performed in a web-based database within one day, chosen by the unit, within three fixed two-week study periods from January 01st to June 30th, 2012. All neonates present at 8am in the neonatal unit and receiving prescriptions on the study day were included and demographic data was recorded.

The participating countries were divided according to the United Nations Statistics Division [12] European geographical regions—East (Bulgaria, Hungary, Romania), North (Estonia, Ireland, Latvia, Lithuania, Norway, United Kingdom), South (Greece, Italy, Malta, Portugal, Serbia, Slovenia, Spain), West (Austria, Belgium, France, Netherland, Switzerland) (Fig. 1). Participating hospitals were divided based on teaching status (teaching/non-teaching) and units were classified according to the units' level of care: level 1 offering basic neonatal care; level 2 offering high dependency care, short term intensive care and low birth weight care and level 3 offering comprehensive intensive care including extremely low birth weight neonates [13].

Based on strong non-linear correlation (Spearman's rank correlation rho = 0.918) between GA and bodyweight we chose GA to classify neonates based on their development. Neonates were categorized based on GA to extremely preterm (22–27 weeks), very preterm (28–31 weeks), late preterm (32–36 weeks) and full-term (≥ 37 weeks) [14].

All prescriptions excluding blood products, glucose and electrolyte solutions, vaccines, nursery care topical

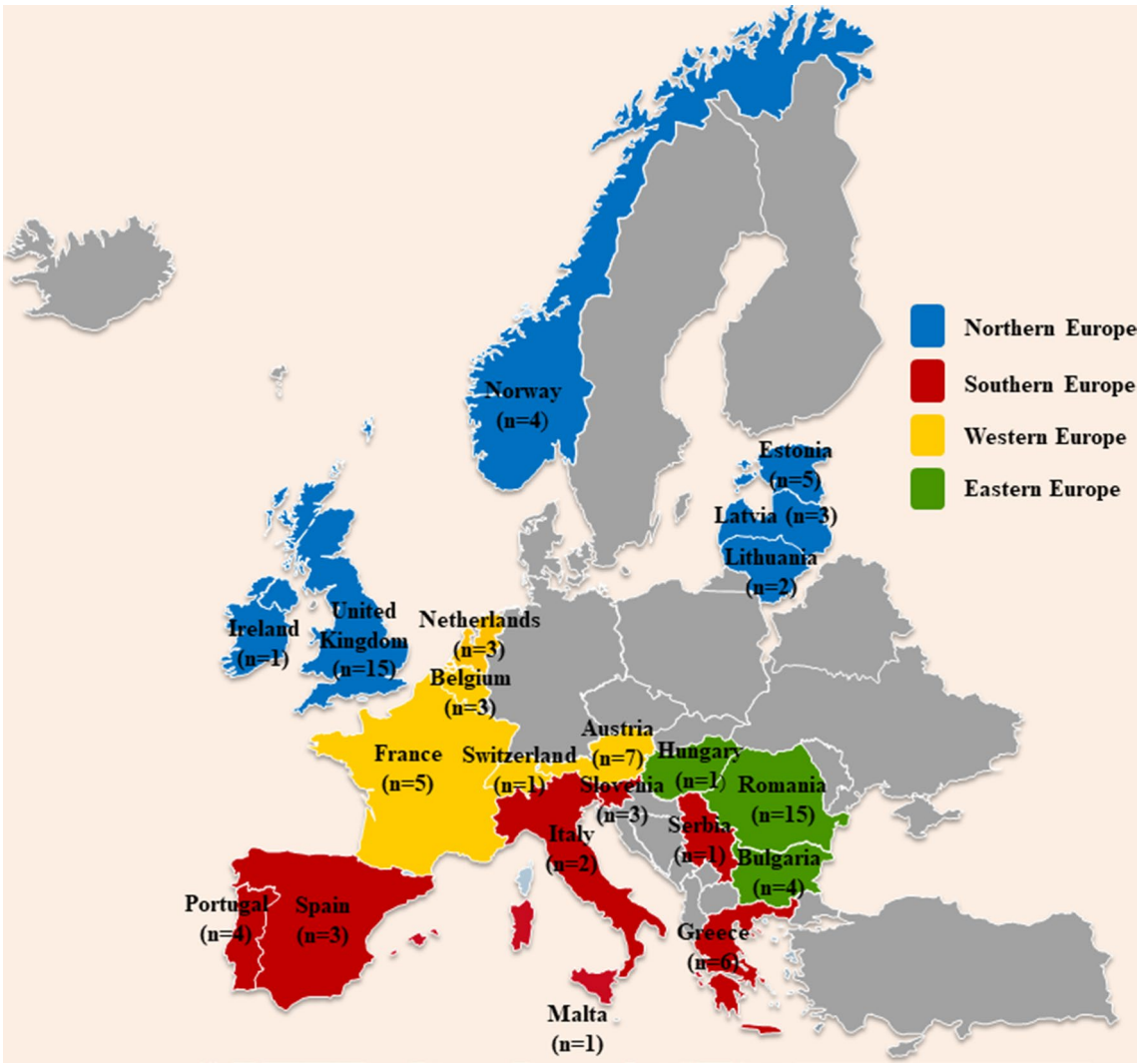

Fig. 1 Participating countries by European region—blue color indicates Northern, yellow Western, green Eastern, and red Southern European region. Number of neonatal units participating from each country is shown in parentheses. European regional distribution according to the United Nations Statistics Division [12]. (Color figure online)

agents, herbal medicines and enteral nutrition including breast milk fortifiers, were collected. For every medicine trade name, active pharmaceutical ingredient (API), dose and route of administration were registered.

The prescriptions were analysed based on the World Health Organization Anatomical Therapeutic Chemical (ATC) classification system [15] according to the level 1 (main anatomical), 3 (pharmacological subgroup) and 5 (chemical substance). Prescription rates (number of prescriptions per 100 admissions) were calculated for frequently used medicine groups (by ATC level 1 and 3) and APIs (ATC level 5) for all GA groups and geographical regions. Formulations that consist only one vitamin (e.g. vitamin D, phytomenadione) were analysed separately. All multivitamin products (enteral and parenteral formulations) were analysed as group named "multivitamins". Different vitamins in multivitamin compositions (e.g. vitamin D) were not calculated separately.

Statistical analysis

Statistical software R (version 3.1.1.) was used. Potential confounders were chosen based on logistic regression analysis, where GA, region, hospital teaching status and department level were included. As teaching status and department level were not significant in univariate analysis, these confounders were excluded from further analyses.

The prescription (yes/no) of therapeutic group (ATC level 1) or therapeutic subgroup (ATC level 3) were analysed using uni- and multivariate logistic regression. Separate models were used for each of the six most commonly used therapeutic groups and the 12 most commonly used

subgroups. Vitamins, minerals and probiotics were excluded from therapeutic subgroup analyses as these groups have the smallest evidence base for use.

GA group and geographical region were used as exploratory factors and the Eastern region and extremely preterm neonates as reference groups. As the main outcomes in uni- and multivariate analyses were similar, we only present the results of multivariate analysis. The results of univariate analysis are given in "Appendix" section (Table 6).

Results

Study population

Out of 31 invited countries, 21 participated with 89 units from 73 hospitals; both relatively evenly distributed between regions. The characteristics of participating units are described by Nellis et al. [11].

Data of 726 patients of whom almost two-thirds were preterm neonates (n = 477, 65.7%), were collected. The proportional distribution of neonates based on GA varied significantly between regions, with the highest representation of extremely preterms in the West (21%) and of term neonates in the East (52.4%) (Table 1).

The distribution of neonates based on level of maturity is shown in Table 2.

Prescriptions

In total 2173 prescriptions with median number of 2 prescriptions per neonate [interquartile range (IQR) 1–4] were registered.

The six most commonly prescribed medicine groups (based on ATC level 1) accounted for 98% of all prescriptions. Medicines, most commonly prescribed were medicines for alimentary tract and metabolism (ATC group A, 31%), systemic anti-infectives (J, 26%), medicines for blood and blood-forming organs (B, 24%), nervous (N, 11%), respiratory (R, 3%) and cardiovascular system (C, 3%). The variations in most commonly used medicine groups according to GA and geographical region are presented in Figs. 2, 3 and Table 5.

The most commonly used medicines based on ATC level 5 were multivitamins, followed by vitamin D and caffeine. Among the ten most commonly used APIs were

Table 1 Distribution of participants based on geographic region

	Geographic region				Total	*p* value
	East	North	South	West		
No (%) of participating hospitals	16 (21.9)	26 (35.6)	18 (24.7)	13 (17.8)	73 (100)	NS
No (%) of participating units	20 (22.5)	30 (34)	20 (22.5)	19 (21)	89 (100)	NS
No (%) of neonates receiving any prescription during the study period	185 (25.5)	274 (37.7)	143 (19.7)	124 (17.1)	726 (100)	$p < 0.001$
Distribution of children in gestational age groups, n (%):						$p < 0.001$[a]
Extremely preterm	8 (4.3)	40 (14.6)	10 (7.0)	26 (21.0)	84 (11.6)	
Very preterm	29 (15.7)	69 (25.2)	28 (19.6)	36 (29.0)	162 (22.3)	
Late preterm	51 (27.6)	87 (31.8)	54 (37.8)	39 (31.5)	231 (31.8)	
Term neonates	97 (52.4)	78 (28.5)	51 (35.7)	23 (18.5)	249 (34.3)	
Distribution of neonates based on neonatal units' level of care[d], n (%)						$p < 0.001$[b]
Level 1	7 (3.8)	0 (0.0)	0 (0.0)	4 (3.2)	11 (1.5)	
Level 2	54 (29.2)	61 (22.3)	18 (12.6)	11 (8.9)	144 (19.8)	
Level 3	124 (67.0)	213 (77.7)	125 (87.4)	109 (87.9)	571 (78.7)	
Distribution of neonates based on hospital teaching status, n (%)						$p < 0.001$[c]
No	47 (25.4)	34 (12.4)	7 (4.9)	33 (26.6)	121 (16.7)	
Yes	138 (74.6)	240 (87.6)	136 (95.1)	91 (73.4)	605 (83.3)	

p values from Chi squared test; NS—not significant at $\alpha = 0.05$. Percentages may not sum to 100 because of rounding

[a]Significant differences in neonates' distribution into GA groups between regions e.g. the proportion of term neonates in the Eastern region and the proportion of extremely preterm neonates in the Western region are significantly higher compared to other regions

[b]Significant differences in the distribution of department levels between regions—the proportion of Level 1 and Level 2 hospitals was the highest in the Eastern region

[c]Significant differences in the distribution of participating units' teaching statuses between regions—the proportion of teaching hospitals was higher in the Southern and Northern region compared to the Eastern and Western region

[d]Level 1—special neonatal care; Level 2—high dependency care, short term intensive care, low birth weight neonates; Level 3—provides continuous life support and comprehensive intensive care for extremely high risk neonates [13]

Table 2 Distribution of study population according to level of maturity

	Extremely preterm neonates	Very preterm neonates	Late preterm neonates	Term neonates	Total	*p* value
No of patients admitted	84	162	231	249	726	< 0.001
Sex, male[a]	47	93	142	129	411	NS
Proportional distribution (%) of neonates by region						< 0.001
East	9.5	17.9	22.1	39	25.5	
North	47.6	42.6	37.7	31.3	37.7	
South	11.9	17.3	23.4	20.5	19.7	
West	31	22.2	16.9	9.2	17.1	
Birth weight (grams) median (IQR)	830 (686–940)	1340 (1140–1580)	1980 (1718–2310)	3340 (2960–3680)	1993 (1356–3006)	< 0.001
Apgar score at 1 minute[b] mean ± SD	5.3 ± 2.4	6.3 ± 2.4	7.4 ± 1.9	7.9 ± 1.9	7.1 ± 2.3	< 0.001
GA weeks[c] median (IQR)	26 (25–27)	30 (28–31)	34 (33–35)	39 (38–40)	34 (30–38)	< 0.001
Postnatal age on study day morning (days) median (IQR)	15 (7–21.5)	13 (7–20)	10 (5–18)	4 (1–15)	10 (3–18)	< 0.001

[a]Data not available for 1 neonate

[b]Data not available for 22 neonates

[c]Full gestation weeks

p values from Chi squared test; NS—not significant at α = 0.05

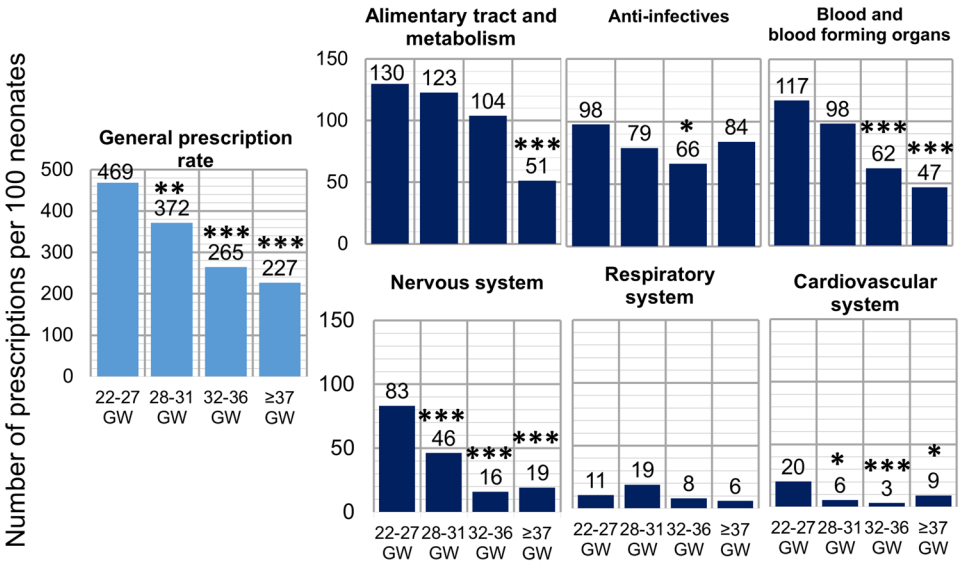

Fig. 2 Distribution of prescriptions based on GA group (Statistical analysis was made using Poisson regression analysis). Alimentary tract and metabolism (ATC group A), anti-infectives (J), blood and blood forming organs (B), nervous system (N), respiratory system (R), cardiovascular system (C). GW—gestational weeks: 22–27 GW—extremely preterm, 28–31 GW-very preterm, 32–36 late preterm, ≥ 37 full-term neonates. ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$; Reference group—extremely preterm neonates (22–27 GW)

three systemic anti-infectives—gentamicin, ampicillin and benzylpenicillin (Table 3).

The forty most commonly prescribed medicines are listed in Table 7.

Medicine use and GA

There was a significant downwards trend in medicine use with increasing GA. The prescription rate among extremely

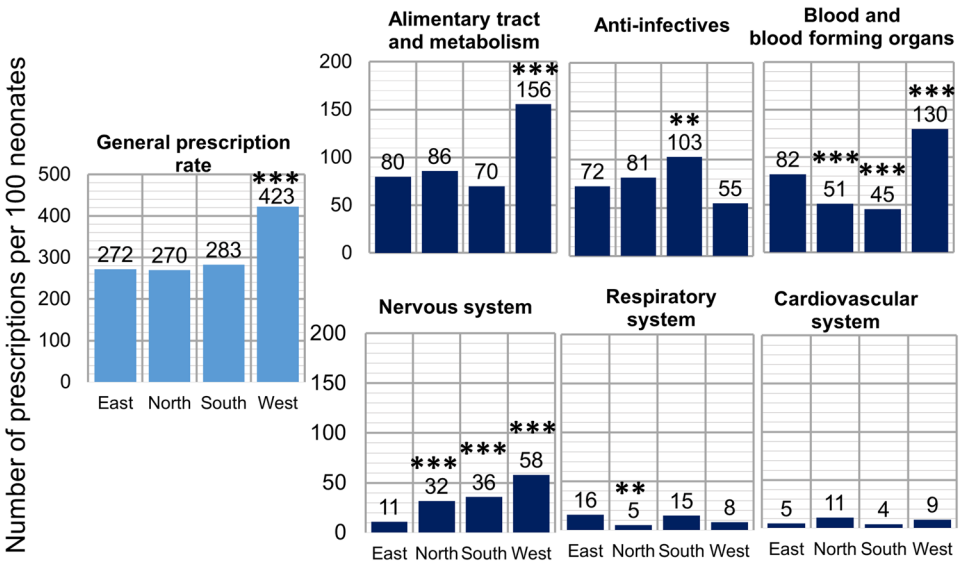

Fig. 3 Distribution of prescriptions based on geographical region (Statistical analysis was made using Poisson regression analysis). Alimentary tract and metabolism (ATC group A), anti-infectives (J), blood and blood forming organs (B), nervous system (N), respiratory system (R), cardiovascular system (C). ***$p<0.001$; **$p<0.01$; *$p<0.05$; Reference group—Eastern region

Table 3 Prescription rates (prescriptions per 100 admissions) of most frequently used medicines (based on ATC level 5) according to GA and geographic region

	Total	Gestational age group				Geographic region			
		Extremely preterm	Very preterm	Late preterm	Term	East	North	South	West
Multivitamins	33	43*	46*	45*	10	5	33*	31*	74*
Vitamin D	19	24	19	23*	14	23*	18	13	23
Caffeine	19	60*	43*	6	1	2	22	20	37*
Gentamicin	18	19	12	16	24*	11	25*	23*	7
Amino acids for parenteral nutrition	18	31*	25*	19*	7	19	12	20	24
Phytomenadione	13	6	9	3	26*	30*	7	1	13
Ampicillin (/+sulbactam)	12	5	10	19*	11	20*	3	26*	6
Benzylpenicillin	12	12	10	8	15*	3	24*	2	8
Fat emulsion for parenteral nutrition	11	24	18	10	3	7	7	8	30*
Probiotics	8	19	13	7	2	5	6	3	23
Iron	8	17	17	7	1	9	3	6	20
Heparin	7	19	7	6	4	2	9	4	15
Folic acid	7	7	13	10	1	5	9	4	7
Aminophylline	6	7	14	6	0	14	1	10	0
Vancomycin	5	12	6	3	4	4	4	9	7

This table does not contain medicines which were not included among 15 most commonly used medicines in general (e.g. fluconazole and nystatin were common among extremely preterm neonates, but not in other GA groups)

*The three most commonly used medicines in each group are marked with an asterisk

preterms was two times higher than term neonates (469/100 vs. 227/100, respectively) (Fig. 2, Table 5).

The list of commonly used APIs varied between GA groups. Caffeine was the most commonly used medicine among extremely preterms and frequently used among very preterms, however, it was rarely used among late preterm and term neonates as expected. Multivitamins were more commonly used among preterms compared to term neonates. Vitamin D was used with similar frequency among preterms (Table 3), but slightly less among term neonates.

Anti-infectives' prescription rate was the highest among extremely preterms, who received most commonly gentamicin (19/100), fluconazole (18/100), nystatin (13/100), vancomycin (12/100) and benzylpenicillin (12/100). The use of fluconazole and nystatin was lower among very preterms

Table 4 Multivariate logistic regression analysis

ATC level 1	ATC level 3 (frequently used active ingredients, arranged by frequency of use)	Gestational age group				Geographic region			
		Extremely preterm (reference) OR (95% CI)	Very preterm OR (95% CI)	Late preterm OR (95% CI)	Term OR (95% CI)	East (reference) OR (95% CI)	North OR (95% CI)	South OR (95% CI)	West OR (95% CI)
Alimentary tract and metabolism (A)	(Multivitamins, vitamin D, antidiarrheal microorganisms)	1	0.95 (0.49–1.81)	0.63 (0.34–1.16)	0.16 (0.09–0.3)*	1	0.93 (0.62–1.41)	0.71 (0.44–1.14)	3.28 (1.81–5.94)*
Anti-infectives (J)		1	0.55 (0.32–0.95)*	0.48 (0.29–0.81)*	0.74 (0.44–1.25)	1	1.03 (0.7–1.52)	1.65 (1.06–2.58)*	0.66 (0.4–1.09)
	Penicillins (J01C) (ampicillin, benzylpenicillin, amoxicillin)	1	1.18 (0.62–2.23)	1.47 (0.8–2.68)	1.75 (0.95–3.2)	1	1.68 (1.09–2.6)*	1.35 (0.82–2.23)	0.99 (0.56–1.74)
	Aminoglycosides (J01G) (gentamicin, amikacin)	1	0.86 (0.44–1.7)	1.02 (0.54–1.93)	1.58 (0.85–2.96)	1	2.17 (1.35–3.5)*	2.4 (1.42–4.07)*	0.67 (0.33–1.36)
	Other beta-lactams (J01D) (cefotaxime, meropenem, ceftazidime)	1	0.79 (0.36–1.72)	0.46 (0.21–1)	0.73 (0.35–1.54)	1	0.68 (0.37–1.25)	1.69 (0.92–3.09)	0.49 (0.21–1.14)
	Other antibacterials (J01X) (vancomycin, teicoplanin, metronidazole)	1	0.63 (0.29–1.34)	0.21 (0.09–0.5)*	0.23 (0.1–0.54)*	1	0.66 (0.3–1.47)	2.47 (1.16–5.26)*	0.82 (0.33–2.05)
	Systemic antimycotics (J02A) (fluconazole)	1	0.13 (0.04–0.36)*	0.03 (0.01–0.13)*	0.01 (0–0.05)*	1	0.07 (0.02–0.23)*	0.12 (0.03–0.49)*	0.13 (0.04–0.41)*
Blood and blood-forming organs (B)		1	0.58 (0.33–1.03)	0.26 (0.15–0.46)*	0.2 (0.11–0.35)*	1	0.28 (0.19–0.43)*	0.26 (0.16–0.41)*	0.7 (0.43–1.16)
	Vitamin K and other hemostatics (B02B) (phytomenadione, etamsylate)	1	1.01 (0.38–2.68)	0.5 (0.18–1.39)	2.94 (1.21–7.13)*	1	0.16 (0.09–0.29)*	0.01 (0–0.11)*	0.4 (0.21–0.77)*
	Iron (B03A)	1	1 (0.47–2.11)	0.38 (0.17–0.84)*	0.03 (0.01–0.16)*	1	0.18 (0.08–0.44)*	0.47 (0.2–1.12)	1.24 (0.6–2.55)
	Antithrombotic agents (B01A) (heparin)	1	0.39 (0.18–0.86)*	0.3 (0.13–0.65)*	0.26 (0.11–0.61)*	1	3.32 (1.11–9.94)*	1.83 (0.5–6.67)	6.35 (2.05–20)*

Table 4 (continued)

ATC level 1	ATC level 3 (frequently used active ingredients, arranged by frequency of use)	Gestational age group				Geographic region			
		Extremely preterm (reference) OR (95% CI)	Very preterm OR (95% CI)	Late preterm OR (95% CI)	Term OR (95% CI)	East (reference) OR (95% CI)	North OR (95% CI)	South OR (95% CI)	West OR (95% CI)
Nervous system (N)		1	0.37 (0.21–0.66)*	0.07 (0.04–0.13)*	0.09 (0.05–0.16)*	1	2.64 (1.44–4.83)*	4.17 (2.16–8.07)*	6.67 (3.43–13)*
	Psychostimulants (N06B) (caffeine)	1	0.52 (0.29–0.93)*	0.04 (0.02–0.09)*	0.01 (0–0.03)*	1	10.55 (3.1–36)*	18.75 (5.16–68)*	23.7 (6.7–84)*
	Opioids (N02A) (morphine, fentanyl)	1	0.2 (0.06–0.68)*	0.23 (0.08–0.65)*	0.44 (0.17–1.14)	1	3.97 (0.86–18)	4.99 (1.01–25)*	6.46 (1.31–32)*
Respiratory system (R)		1	1.4 (0.6–3.24)	0.42 (0.17–1.03)	0.15 (0.05–0.42)*	1	0.11 (0.05–0.26)*	0.59 (0.3–1.16)	0.23 (0.1–0.53)*
	Other systemic drugs for obstructive airway disease (R03D) (aminophylline)	1	1.75 (0.63–4.87)	0.48 (0.16–1.39)	0 (0–Inf)	1	0.02 (0–0.09)*	0.41 (0.19–0.88)*	0.1 (0.03–0.28)*
Cardiovascular system (C)		1	0.33 (0.13–0.86)*	0.18 (0.06–0.51)*	0.48 (0.2–1.11)	1	1.91 (0.76–4.76)	0.98 (0.3–3.18)	1.78 (0.61–5.21)
	Cardiac stimulants (C01C) (dopamine, dobutamine)	1	0.06 (0.01–0.47)*	0.17 (0.05–0.58)*	0.2 (0.06–0.66)*	1	1.78 (0.45–6.95)	1.23 (0.24–6.36)	0.64 (0.1–4.24)

The odds (OR) of neonates receiving commonly used ATC groups

Adjusted for GA and geographic region

*Significant at $\alpha = 0.05$

(5/100 and 4/100, respectively) and rare among late preterm and term neonates.

In multivariate analysis, significant GA-related variations were observed in all six commonly used ATC level 1 groups (Table 4). After adjusting for region, GA significantly affected the prescription rates of the following ATC level 1 categories: in comparison to extremely preterms anti-infectives and cardiovascular agents were less frequently used in very and late preterms; medicines for blood and blood-forming organs in late preterms and term neonates; respiratory and alimentary medicines in term neonates and nervous system agents in all other GA groups. Based on ATC level 3 other antibacterials (J01X) and iron were less frequently used in late preterm and term babies; opioids in very and late preterms; and psychostimulants, systemic antimycotics, cardiac stimulants and antithrombotic agents in all other GA groups compared to extremely preterms while phytomenadione was used more frequently in term babies.

Medicine use and region

The West region stood out with a significantly higher prescription rate (423/100) compared to other regions. Prescriptions rates in other regions were similar to each other (270/100 North, 272/100 East, 283/100 South) (Fig. 3, Table 5).

The list of most frequently used medicines varied between region**s.** While in the North, South and West multivitamins dominated, phytomenadione was the most commonly used in the East (Table 3). Although multivitamins were the most commonly used medicines in three regions, we observed high variability in composition of multivitamin products used between countries and hospitals.

In multivariate analysis when adjusting for GA, the region was significant in all the most commonly used ATC groups except cardiovascular medicines (Table 4). Based on ATC level 3 in comparison to the East psychostimulants (caffeine) were more commonly used in all other regions, penicillins in the North, aminoglycosides in the North and South, other antibacterials (e.g. vancomycin) in the South, antithrombotic agents in the North and West and opioids in the South and West regions. The use of iron supplements was lower in the North and the use of systemic antimycotics, phytomenadione and other systemic medicines for obstructive airway disease were lower in all regions compared to the East (Table 4).

Discussion

To the best of our knowledge this is the largest international survey of medicine use covering neonatal units across Europe and neonates of all GA groups.

Key findings

We have made the following observations: first, the most commonly used medicines in European neonatal units were multivitamins but the composition of these products was highly variable. Second, there is a significant variation in medicine use depending on GA as expected but also unexpectedly depending on geographical region. While GA-based variations could be explained by different underlying conditions, geographic variations likely refer to the lack of standardized evidence-based guidelines. Variations in anti-infectives' use may reflect different patterns of infections or resistance as described elsewhere [16]. Third, although neonates receive many medicines during hospitalization, almost no specific medicines are available for treatment or prevention of conditions affecting especially neonates and directly related to their mortality like respiratory distress syndrome, intraventricular haemorrhage (IVH), perinatal asphyxia and/or necrotizing enterocolitis (NEC) [17]. This suggests the urgent need to understand the underlying mechanisms of these conditions followed by the development of new treatment options (including medicines).

Variations in most commonly used medicines

We demonstrated that medicines for alimentary tract were by far the most commonly used mainly because of high prescription rate of vitamins and probiotics similarly shown in previous studies [1]. High variability in multivitamin products composition could be explained by the lack of international guidelines despite the availability of national recommendations suggesting multivitamins for babies born at GA < 34 weeks. However, there is limited evidence of required vitamin quantities [18, 19].

Consistent with other studies, systemic anti-infectives were commonly used with four antibiotics (gentamicin, ampicillin, benzylpenicillin, vancomycin) belonging to the 15 most common APIs [7, 20]. This is not surprising as many neonates in neonatal units have either risk factors for getting infections or confirmed bacterial infections [21]. High use of penicillins, aminoglycosides and other beta-lactams in neonatal units has also been shown in previous studies [22]. In multivariate analysis anti-infectives were less

commonly given to very and late preterms than to extremely preterm and term neonates. We suggest that reasons for that are high rate of infection in extremely preterm neonates. In addition, infections are likely one of the most frequent cause of hospitalization of term neonates.

Gestational age-based variations

Similarly to previous studies we demonstrate a negative correlation between GA and number of medicines per patient [1, 7, 23, 24]. We found that extremely preterms received medicines for alimentary tract and metabolism (e.g. multivitamins, vitamin D, amino acids) given likely as supplementation recommended by learned societies to support growth and development significantly more commonly compared to term neonates [25, 26].

Regional variations

In contrast to our hypothesis, we observed significant regional differences in medicine use in multivariate analysis adjusted GA. We believe that geographical differences in use of anti-infectives' are partly explained by differences in microbial resistance rate—the microorganisms causing infection in the South are generally more resistant compared to those in other regions [27]. Similar to ARPEC study we showed higher penicillins' use in the North, higher aminoglycosides' use in the South and North, and higher use of other antibacterials' (e.g. vancomycin) in the South [28].

All other differences are likely explained by the customs and variability of medical practices. For example regional variations in use of systemic antimycotics' with higher prescription rate in the East compared to other regions are likely driven by the discrepancies between the local guidelines as shown in a pan-European study [29].

Less frequent use of caffeine or more frequent use of phytomenadione and aminophylline in the East, lower use of iron in the North compared to other regions or more frequent use of heparin in the North and West than in the East and South or greater use of opioids in the South and West compared to the East and North are likely driven by the lack international commonly accepted guidelines. While studies have shown beneficial effect of caffeine in reducing bronchopulmonary dysplasia in preterms with apnoea the data on using bronchodilators (e.g. aminophylline) are less convincing according to the published literature [30, 31]. Although opioids are routinely used in neonatal units for analgesia and sedation, their possible long-term negative impact is unclear due to conflicting results concerning neurodevelopmental outcome [32, 33]. We believe that these regional differences are partly explained by the lack of reliable studies (e.g. bronchodilators) or failure to implement results of randomized controlled trials (RCTs) into clinical practice (e.g. caffeine) suggesting that further efforts should be focused to both directions.

Limitations

Some limitations need to be noted. We were not able to perform the cluster randomised approach to sample size calculations as we intended at the outset of PPS [11], because no country had a full list of neonatal units. The voluntary participation prevented including the data from whole Europe proportionally and led to missing data from some large countries (e.g. Germany). Due to inability to randomly select participants, some small countries (e.g. Estonia) were covered almost completely, while large countries were represented with a few areas. As most participants were from teaching hospitals and level III neonatal units, it was impossible to detect the impact of teaching status and departments' level on the prescription pattern.

As GA and body weight are inter-related, we have decided to use GA as co-variate in this analysis but acknowledge that this could be debatable. Neonates were not divided equally between GA groups and regions which could also impact the effect of analysed factors. In this study moderately preterm neonates (32–34 weeks) were considered "late preterms" (32–36 weeks), which could affect some results as these newborns may behave as very preterm infants or as late preterms. Also, postnatal age which was not taken into account could affect results of some medicines' administration (e.g. phytomenadione).

The selection of study methodology can affect the results of this study—for medicines that are commonly used (e.g. antibiotics like ampicillin, gentamycin or phytomenadione) one day PPS will describe their consumption sufficiently, however, for agents that are rarely used longer study period will capture more APIs.

Although vitamin D was among 3 most commonly used medicines in Europe, we did not add it into regional analysis as hospitalized neonates could receive it from different sources e.g. multivitamin compositions or breast milk fortifiers. The data about last-mentioned products was not collected according to the ESNEE study protocol and multivitamin compositions were not viewed separately, which makes it impossible to compare the vitamin D prescription in different regions precisely. Nevertheless, we believe that

none of these factors prevented us drawing adequate conclusions in describing medicine use across Europe and analysing regional differences.

No data regarding the treatment outcomes or adverse events was collected at the ESNEE Point Prevalence Survey, however, we agree that this is an important topic for future studies.

Despite all limitations we believe that the collected data gives good coverage of European neonatal population. This study indicates the need to prioritize research to the areas where there is the most urgent need to develop new medicines. It also suggests areas where clinical trials are needed to promote appropriate use of available medicines and to prevent potentially unnecessary prescriptions in a vulnerable population of neonates.

Conclusion

This study highlights the influence of geographic region and GA on medicine prescriptions in European neonatal units. While the impact of GA is explained by differences in maturation, requirements of regular nutritional supplementation and individualized care of preterm neonates, geographical differences with the exception of antimicrobials most likely indicate the lack of reliable RCTs and/or evidence-based guidelines for treatment of many important neonatal conditions. The presented data calls for greater collaboration between academia, basic scientists, practitioners, pharmaceutical industry and regulators in developing new medicines and support pan-European cooperation in facilitating neonatal medicine development to improve the health and well-being of neonates.

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Conflicts of interest The authors declare that they have no conflicts of interest.

Appendix

Ethics committees that approved the European Study of Neonatal Exposure to Excipients point prevalence study

Universitair Ziekenhuis Gent, Comissie voor Mediche Ethiek, Belgium.

Scientific Committee of each participating hospital in Greece.

Research Ethics Committee of the University of Tartu, Estonia.

Ethics Committee of the Semmelweis University Clinic, Hungary.

Ethics Committee of the National Maternity Hospital, Dublin Ireland.

Comitato di Bioetica della Provincia Romana del FBF, Italy.

Kauno Regioninis Biomedicininiu Tyrimu Etikos Komitetas, Lithuania.

University of Malta Research Ethics Committee—UREC, Malta.

Institutional Review Board of the Erasmus MC, the Netherlands.

Komisija Republike Slovenije Medicinsko Etiko, Slovenia.

Comite Etico de Investigacion Clinica de EUSCADI (CEIC-E), Spain.

Kantonale Ethikkomission Zürich, Switzerland.

NRES Committee East of England—Cambridge Central, National Ethics Service, UK; NHS/HSC.

Ethics Committee approval was not required in Austria, France, Portugal, Latvia, Serbia and Bulgaria.

See Tables 5, 6, 7.

Table 5 Distribution of registered prescriptions

	Gestational age group					Geographic region					Total
	Extremely preterm	Very preterm	Late preterm	Term neonates	*p* value[b]	East	North	South	West	*p* value[b]	
Total number of prescriptions (rate[a])	394 (469)	603 (372)	612 (265)	564 (227)	< 0.001	503 (272)	741 (270)	404 (283)	525 (423)	< 0.001	2173 (299)
No of prescriptions per neonate, median (IQR)	4 (3–6)	3 (2–5)	2 (1–3)	2 (1–3)		2 (1–4)	2 (2–3)	2 (1–4)	4 (2–6)		2 (1–4)
Distribution of prescriptions based on ATC level 1, No (rate[a])											
Alimentary tract and metabolism	109 (130)	199 (123)	240 (104)	128 (51)	< 0.001	148 (80)	235 (86)	100 (70)	193 (156)	< 0.001	676 (93)
Anti-infectives	82 (98)	128 (79)	153 (66)	209 (84)	NS	134 (72)	223 (81)	147 (103)	68 (55)	0.001	572 (79)
Blood and blood-forming organs	98 (117)	159 (98)	144 (62)	117 (47)	< 0.001	152 (82)	140 (51)	65 (45)	161 (130)	< 0.001	518 (71)
Nervous system	70 (83)	75 (46)	37 (16)	48 (19)	< 0.001	20 (11)	87 (32)	51 (36)	72 (58)	< 0.001	230 (32)
Respiratory system	9 (11)	31 (19)	19 (8)	15 (6)	0.006	29 (16)	14 (5)	21 (15)	10 (8)	0.006	74 (10)
Cardiovascular system	17 (20)	9 (6)	7 (3)	23 (9)	0.003	9 (5)	30 (11)	6 (4)	11 (9)	NS	56 (8)
Other groups	9 (11)	2 (1)	12 (5)	24 (10)	< 0.001	11 (6)	12 (4)	14 (10)	10 (8)	NS	47 (6)

NS not significant at $\alpha = 0.05$

[a]Rate—number of prescriptions per 100 admissions

[b]*p* values from Quasi-Poisson model

Table 6 Odd ratios (OR) of receiving commonly used ATC level 1 drug groups, based on univariate logistic regression analysis

	Gestational age group				Geographic region			
	Extremely preterm	Very preterm	Late preterm	Term neonates	East	North	South	West
Alimentary tract and metabolism (A)	1	0.86 (0.46–1.62)	0.55 (0.3–0.98)*	0.14 (0.08–0.25)*	1	1.39 (0.95–2.02)	0.95 (0.61–1.47)	5.14 (2.94–8.99)*
Anti-infectives (J)	1	0.59 (0.35–1.01)	0.55 (0.33–0.91)*	0.85 (0.52–1.39)	1	1.01 (0.7–1.48)	1.57 (1.01–2.43)*	0.66 (0.41–1.06)
Blood and blood-forming organs (B)	1	0.6 (0.35–1.06)	0.29 (0.17–0.5)*	0.26 (0.15–0.45)*	1	0.4 (0.27–0.58)*	0.31 (0.19–0.48)*	1.06 (0.66–1.68)
Nervous system (N)	1	0.35 (0.2–0.61)*	0.07 (0.04–0.12)*	0.07 (0.04–0.12)*	1	3.66 (2.08–6.44)*	3.97 (2.14–7.36)*	9.26 (5.03–17.06)*
Respiratory system (R)	1	1.74 (0.78–3.88)	0.66 (0.28–1.55)	0.31 (0.12–0.82)*	1	0.19 (0.09–0.41)*	0.76 (0.4–1.44)	0.44 (0.2–0.97)*
Cardiovascular system (C)	1	0.31 (0.12–0.8)*	0.16 (0.06–0.44)*	0.38 (0.17–0.86)*	1	2 (0.83–4.84)	0.92 (0.29–2.97)	1.99 (0.72–5.49)

*Significant at $\alpha = 0.05$

Table 7 Medicines most commonly used in neonatal units

Rank	Medicine	Prescription rate
1	Multivitamins	33
2	Vitamin D	19
3	Caffeine	19
4	Gentamicin	18
5	Amino acids for parenteral nutrition	18
6	Phytomenadione	13
7	Ampicillin (/+sulbactam)	12
8	Benzylpenicillin	12
9	Fat emulsion for parenteral nutrition	11
10	Probiotics	8
11	Iron	8
12	Heparin	7
13	Folic acid	7
14	Aminophylline	6
15	Vancomycin	5
16	Amikacin	5
17	Cefotaxime	4
18	Fluconazole	4
19	Calcium gluconate	4
20	Pyridoxine	3
21	Phenobarbital	3
22	Nystatin	3
23	Domperidone	3
24	Paracetamol	3
25	Meropenem	3
26	Solution for parenteral nutrition (combinations)[a]	3
27	Morphine	3
28	Ceftazidime	3
29	Amoxicillin/(+clavulanic acid)	2
30	Tocopherol	2
31	Dopamine	2
32	Etamsylate	2
33	Levocarnitine	2
34	Calcium gluconate + Calcium levulinate	2
35	Furosemide	2
36	Fentanyl	2
37	Teicoplanin	2
38	Ranitidine	2
39	Tobramycin	2
40	Dobutamine	2

[a]Solution for parenteral nutrition (combinations)—ATC code B05BA10

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