Pharmacovigilance of nephrotoxic drugs in neonates: the Pottel method for renal signal detection in ELBW neonates

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Research Article

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Abstract

Background

Extreme low birth weight (ELBW) neonates (birth weight \( \leq 1000 \) grams) are at high-risk to develop drug-induced acute kidney injury (AKI). However, we lack a pragmatic detection tool to capture their time-dependent (patho)physiologic serum creatinine (Scr) patterns. Pottel et al. suggested rescaling Scr by dividing Scr with the mean Scr-value of the age and sex specific reference population. We therefore explored if this Pottel method can detect drug-related nephrotoxic signals in ELBW neonates.

Methods

A previously used dataset on Scr changes in ELBW neonates exposed to ibuprofen, amikacin or vancomycin was updated to calculate Pottel scores for every available Scr value in the first 28 postnatal days. We hereby used already published postnatal age specific 50th centile values in an ELBW population. Linear mixed models were subsequently applied, analyzing Pottel scores as response variable and continuous time (day), drug exposure, and interaction thereof in the explanatory model.

Results

3231 Scr observations in 201 ELBW neonates were collected. A statistically significant rise of Pottel scores was observed with ibuprofen treatment starting from postnatal day 4. In addition, a cumulative effect of treatment with mean Pottel scores on day 0 of 1.020 and on day 3 during treatment of 1.106 (95% CI 1.068–1.145, \( p < 0.001 \)) was observed, when corrected for effect of antibiotics. Antibiotic administrations showed a small but statistical significant difference up to postnatal day 5.

Conclusions

As rescaled Scr biomarker, the Pottel method showed a clear signal in ibuprofen-exposed ELBW neonates, suggesting its applicability as pragmatic bedside tool to assess nephrotoxicity.

INTRODUCTION

Extreme low birth weight (ELBW) neonates (birth weight \( \leq 1000 \) grams) are born during active nephrogenesis. Their disrupted kidney development results in a decreased reserve with evidence showing smaller kidney size and abnormal kidney-related outcomes in childhood compared to healthy controls [1–3]. These patients are also at high-risk to develop acute kidney injury (AKI) due to their immature kidney physiology combined with high-risk events during their neonatal intensive care unit (NICU) stay [4]. Experiencing neonatal AKI further imposes an increased risk of long-term kidney dysfunction, demonstrated by abnormal conventional markers such as estimated glomerular filtration rate (eGFR),
urine protein-to-creatinine ratio or blood pressure during childhood [1, 5]. The development of AKI is multifactorial but several risk factors such as hemodynamic instability, late-onset sepsis (LOS), necrotizing enterocolitis (NEC) or persistent ductus arteriosus (PDA) were reported [4, 6–8].

Interestingly, these risk factors display collinearity with the use of nephrotoxic drugs. As shown in the recent BABY-NINJA trial, identifying neonates at risk for a nephrotoxic-drug induced AKI and implementing guidelines to reduce the rate of high nephrotoxic drug induced AKI and implementing guidelines to reduce the rate of nephrotoxic drug exposure resulted in a significant decrease in AKI prevalence and intensity [7]. As exposure to nephrotoxic drugs is very common (up to 92%) in ELBW neonates, there is potential to reduce or prevent AKI by early and consistent precision pharmacovigilance [8–10]. However, this needs a pragmatic bedside tool for signal detection.

A decade ago, Jetton et al. proposed a neonatal AKI definition as modification of the KDIGO (Kidney disease: improving global outcomes, mKDIGO) definition for adults and children [11]. This neonatal modified definition is based on a grading system, including rises of serum creatinine (Scr) of 0.3 mg/dl or ≥ 50% compared to the previous value for stage 1 [11]. This is currently the most commonly applied definition and has been used in trials such as the AWAKEN study [4, 6]. However, observational studies described the pattern of physiologic Scr changes in ELBW neonates, characterised by an initial progressive Scr increase in the first days, peaking on day 3–4 and a subsequent slow decrease afterwards, with extensive interindividual variability due to maturational and non-maturational factors, like drugs or fluid therapy.

This time-dependent pattern is most pronounced in the most immature cases like ELBW cases, showing a higher peak and more delayed normalization [12, 13]. Consequently the mKDIGO has limitations as it e.g. fails to detect the absence of appropriate, expected decline of Scr in the second part of the first week of life and beyond. Furthermore, its use needs consecutive Scr measurements. This brought up to the idea to explore the use of assay-specific mean and centile Scr values to describe postnatal renal function trends, facilitating AKI recognition [14].

In 2013 Pottel et al. suggested to normalize Scr by dividing Scr by the mean Scr-value of the appropriate age (from 2 years and onwards) and sex specific healthy population, rescaling it to a renal biomarker with a normal distribution around the mean of 1 [15].

In previous work on Scr patterns in ELBW neonates, a modest decrease of creatinine clearance and a shift of Scr of about 1 standard deviation (SD) in ibuprofen-exposed neonates was documented, as well as a minor increase of Scr when treated with amikacin and/or vancomycin [14, 16, 17]. In the present study, we investigated whether the Pottel method also enables detection of a drug-related nephrotoxic signal in the same dataset, as this approach would make detection more feasible bedside, as e.g. based on a single observation.

**METHODS**

**Study population and clinical characteristics**
A previously reported dataset, initially used to define Scr trends and drug-toxicity signals in ELBW neonates admitted to the NICU of the University Hospitals Leuven in the two periods of July 2007 to August 2011 and June 2015 to March 2017, was re-used for this analysis [13, 16, 17]. This dataset contains retrospectively collected data on demographics, relevant clinical data (e.g. mode of delivery), and documented days of treatment with ibuprofen, amikacin, vancomycin, or exposure to inotropics, and the available Scr for the first 42 days of life [13]. The Leuven NICU uses ibuprofen for the pharmacological closure of a PDA, whereas the combination of amikacin and vancomycin is the established regiment for suspected LOS. Amikacin is also used as co-treatment with amoxicillin for early-onset sepsis, and with piperacillin-tazobactam in the treatment of necrotizing enterocolitis.

Serum creatinine was analyzed enzymatically by Roche (Roche Diagnostics, Mannheim, Germany) during the study period, and all measurements were isotope dilution mass spectrometry (IDMS) traceable [13].

We restricted the dataset to observations obtained in the first 28 days after birth. After review of the available data, 30 patients were excluded due to insufficient baseline data, early neonatal death (< 7 days) or late referral (≥ postnatal age (PNA) day 15), or duplication. This resulted in 3231 Scr observations in 201 patients (Fig. 1). Pottel scores for every available Scr were calculated based on available 50th centile values per postnatal day in ELBW neonates [14]. Ethics approval was provided (S63405, Ethics Committee Research UZ Leuven).

**Statistical methods**

Population characteristics were described by mean and SD or median and range (Table 1). Descriptive summary statistics of the Pottel score were calculated, including mean and SD, based on values collected from days without influence of ibuprofen or antibiotics (i.e. no administration of any of these drugs the day before Scr measurement was performed). A histogram was plotted combined with a normal density curve, based on the observed mean and hypothesized mean of 1 of the Pottel score.
Table 1

Demographic data presented as mean [standard deviation] or as number (%); obs, observations. Data on mode of delivery and antibiotic exposure are calculated on 199 and 200 patients respectively, due to missing data

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ELBW neonates (obs)</td>
<td>201 (3231)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>27 [2]</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
<td>808 [135]</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>107 (53,2%)</td>
</tr>
<tr>
<td>Male</td>
<td>94 (46,8%)</td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>63 (31,7%)</td>
</tr>
<tr>
<td>Caesarian</td>
<td>136 (68,3%)</td>
</tr>
<tr>
<td>Lung maturation (yes)</td>
<td>171 (86,8%)</td>
</tr>
<tr>
<td>Neonatal death (yes)</td>
<td>17 (8,5%)</td>
</tr>
<tr>
<td>Ibuprofen exposure (yes)</td>
<td>124 (61,7%)</td>
</tr>
<tr>
<td>Amikacin exposure (yes)</td>
<td>151 (75,5%)</td>
</tr>
<tr>
<td>Vancomycin exposure (yes)</td>
<td>152 (76%)</td>
</tr>
<tr>
<td>Amikacin exposure without vancomycin exposure (yes)</td>
<td>10 (5,0%)</td>
</tr>
<tr>
<td>Vancomycin exposure without amikacin exposure (yes)</td>
<td>11 (5,5%)</td>
</tr>
<tr>
<td>Amikacin and vancomycin exposure (yes)</td>
<td>141 (70,5%)</td>
</tr>
<tr>
<td>No ibuprofen or antibiotic exposure</td>
<td>26 (12,9%)</td>
</tr>
</tbody>
</table>

To evaluate the effect of ibuprofen and antibiotics (amikacin and/or vancomycin) on the Pottel score and to determine whether the score showed a significant signal, linear mixed models were used, with the Pottel score as response variable and continuous time (PNA, expressed in days), pharmacotherapy (ibuprofen, amikacin and/or vancomycin, yes/no, and consecutive days), and the interaction thereof in the explanatory model. Random intercept and slope in time were modelled to account for the longitudinal data structure.

As the effect of pharmacotherapy is expected to be seen with a one-day delay (‘lag’ time), treatment was modelled as a binary variable, with value 1 if the respective treatment was administered on the day before outcome evaluation, and value 0 if otherwise. Log-transformation was applied to the time variable to deal
with non-linear trends over time, as this resulted in a better model fit (lower Akaike information criterion or AIC) compared to cubic splines models.

Results are presented graphically, presenting calculated Pottel score over time with 95% confidence bands in presence or absence of drug exposure.

To evaluate the cumulative time effect of ibuprofen or antibiotic administration on the Pottel score, we used similar linear models for data-analysis, modelling the Pottel score as an effect of the number of consecutive days of drug administration. In addition, the combined effects of ibuprofen and antibiotics were used in multivariable models to explore possible cumulative exposure effects by estimating the effect of ibuprofen corrected for antibiotics, and vice versa.

Analyses were performed using SAS software (version 9.4 of the SAS System for Windows). A p-value of < 0.05 was considered statistically significant.

RESULTS

Study population

Data from 201 ELBW neonates with a mean BW of 808 (370–1000) grams and a mean gestational age (GA) of 27 (23–34) weeks were available. 171 neonates (86.8%) received prenatal lung maturation (maternal steroids) and 136 neonates (68.3%) were born following caesarean delivery. Late neonatal death (PNA day ≥ 7) occurred in 17 patients (8.5%) (Table 1).

At some point in time during neonatal life (PNA day 1–28), 124 neonates (61.7%) received ibuprofen, 151 (75.5%) received amikacin and 152 (76%) received vancomycin. Ibuprofen was administered for a mean of 4.3 days, amikacin for a mean of 6 days, and vancomycin for 7 days. Twenty-six (12,9%) patients never received any of the above described nephrotoxic drugs (Table 1). There were missing data on respectively 4 patients concerning use prenatal steroids, 2 patients concerning mode of delivery and 1 patient concerning administration of any antibiotic, which were excluded for their respective analyses.

Pottel scores

To explore Pottel score distribution in our cohort without impact of drug exposure, scores collected on days without drug administration on the previous days were used to plot a histogram and to obtain summary statistics. This analysis revealed a normal distribution with a mean of 1.01 (SD 0.257).

Signal detection after drug administration over postnatal age (Supplementary table 1)

Ibuprofen

Pottel scores, calculated in function of ibuprofen exposure on the previous day, showed statistically significant differences starting from PNA day 4 with higher Pottel scores after exposure compared to no exposure (on PNA day 4 mean difference in Pottel score 0.040 [0.017;0.063], p = 0.0005). Magnitude of
differences increased with PNA, with larger confidence intervals reflecting more dropout cases, resulting in a sample size effect. Results of ibuprofen corrected for administration of antibiotics were comparable (Fig. 2).

**Antibiotics**

Effects for amikacin alone, vancomycin alone, and a combination of both antibiotics were calculated, with comparable results for these 3 analyses. Antibiotic administration resulted in a small but statistically significant difference in Pottel scores up to PNA day 5 (on PNA day 5 for amikacin mean difference 0.070 [0.035;0.106] with \( p = 0.0001 \), for vancomycin mean difference 0.080 [0.045;0.114] with \( p \leq 0.0001 \), for antibiotics combined mean difference 0.069 [0.036;0.102] with \( p \leq 0.0001 \)). In contrast, starting from PNA day 25 we observed a statistically significant difference resulting in a lower Pottel score with amikacin or vancomycin administration alone, but not with both antibiotics combined (on PNA day 25 for amikacin mean difference \(-0.030 [-0.054;-0.006] \) with \( p = 0.0159 \), for vancomycin mean difference \(-0.034 [-0.058; -0.010] \) with \( p = 0.0057 \), for antibiotics combined mean difference \(-0.022 [-0.044;0.001] \) with \( p = 0.0610 \)). When correcting for the use of ibuprofen again similar results were obtained, with statistical significant differences up to PNA day 5 (Fig. 3).

**Cumulative effect during treatment over consecutive days (Supplementary table 2)**

**Ibuprofen**

A clear cumulative effect of ibuprofen on the Pottel score was observed, with significant differences starting from day 1 after administration (mean Pottel score on day 0 1.018 [0.994;1.042], on day 1 of administration 1.048 [1.012;1.085] with \( p = 0.0393 \)). A significant further rise of scores in the following days of exposure was seen, with a subsequent flattening of the mean scores (mean Pottel score on day 3 1.101 [1.063;1.140] with \( p \leq 0.0001 \) and on day \( \geq 5 \) 1.132 [1.079;1.185] with \( p \leq 0.0001 \)). When corrected for antibiotics there is a similar trend (mean Pottel score on day 0 1.020 [0.995;1.044], on day 3 1.106 [1.068;1.145] with \( p \leq 0.0001 \) and on day \( \geq 5 \) 1.135 [1.082;1.187] with \( p \leq 0.0001 \)) (Fig. 4).

**Antibiotics**

A small statistically significant difference was observed only on \( \geq 5 \) days of treatment (mean Pottel score on day 0 1.027 [1.002;1.052], on day 3 of administration 1.034 [0.997;1.071] with \( p = 0.6399 \) and on day \( \geq 5 \) of administration 1.055 [1.022; 1.088] with \( p = 0.0194 \)), with similar results when corrected for ibuprofen (mean Pottel score on day 0 1.024 [0.999;1.048] and on day \( \geq 5 \) of administration 1.060 [1.027;1.093] with \( p = 0.0021 \)) (Fig. 5).

**DISCUSSION**

In this retrospective study the applicability of the Pottel method - obtaining a rescaled Scr marker by dividing Scr with the mean Scr value of the age and sex specific healthy population (Qcrea) - to detect
nephrotoxicity following exposure to nephrotoxic agents was assessed in a cohort of 201 ELBW neonates. An existing cohort was updated, previously used to elucidate Scr patterns in ELBW neonates during the use of ibuprofen, amikacin or vancomycin [16, 17]. A statistically significant increase in Pottel scores during ibuprofen treatment was demonstrated starting from PNA day 4, possibly explained by the fact that this drug is rarely administered during the first days of life in the Leuven unit. Furthermore, there is a progressive increase of the Pottel score with consecutive days of ibuprofen exposure. These findings align with our earlier findings demonstrating substantial increases in Scr and concurrent absolute reductions in creatinine clearance during ibuprofen treatment, manifesting as shifts of approximately 1 SD in ibuprofen-exposed ELBW neonates [14, 16]. In contrast, a significant signal when evaluating the Pottel score during the use of amikacin and/or vancomycin was not identified. The quantification of an AKI threshold such as the previously reported value of 1.33 in older populations was not possible, as well as defining grades of AKI, as we rather wanted to illustrate the feasibility [15].

AKI is a common morbidity in neonates, strongly correlated with lower GA or BW, with reported incidences of 28–48% in extremely premature neonates (GA < 28 weeks) and up to 60% in ELBW neonates [4, 18–20]. Accurate detection of AKI remains challenging. Several definitions are available, such as the current predominantly used mKDIGO as well as pRIFLE (pediatric risk, injury, failure, loss, end-stage renal disease) and AKIN (Acute Kidney Injury Network), showing similar AKI incidences in ELBW neonates [20]. These definitions all rely on defined changes in urine output (UOP) or Scr assuming a steady-state situation and needing at least 2 observations. Their use is therefore limited in preterm neonates due to their time-dependent Scr physiology as well as challenges in accurately measuring UOP [11, 14, 21]. ELBW neonates exhibit a postnatal Scr rise from the day of birth (day 1) to approximately day 3 with a subsequent decline, more delayed with increasing immaturity [12]. This physiological rise over the first days often already is in line with the definition of AKI stage 1 (0.3 mg/dl changes) and the absence of an expected decline afterwards is not captured by current definitions [14].

Consequently, strategies to optimize the bedside use of Scr in ELBW neonates are indicated to improve AKI diagnosis and treatment. Of interest is the Pottel method with a multicohort study in a population > 2 years of age demonstrating a distribution of Scr/Qcrea around 1, with the 2.5th and 97.5th percentile at 0.67 and 1.33 respectively, showing specificity and sensitivity for impaired kidney function close to 90% over all age groups [15, 22]. Previously defined p50 values per PNA day in an ELBW cohort enabled us to calculate Pottel scores for every available Scr value, adjusting for the postnatal time-dependent Scr changes [14].

Medication stewardship during nephrotoxic drug exposure, frequent in ELBW neonates, was shown to significantly reduce the AKI rates in NICUs by improving medication adjustments, altering nephrotoxic medication pharmacologic monitoring or discontinuation where appropriate. [7, 8, 21]. Furthermore, in preterm neonates exposure was also associated with elevated markers of kidney dysfunction at a median age of 5 years, irrespective of the development of AKI according to the classical definitions, and thus suggesting subclinical kidney damage [23]. We hypothesized that the Pottel method could be useful for pharmacovigilance in ELBW neonates, exploring drug-related nephrotoxicity signals.
In ibuprofen-exposed neonates a clear signal was observed, with the difference in scores increasing with advancing age, suggesting a more robust nephrotoxic AKI signal during later neonatal life. However for amikacin and vancomycin, two of the more frequently used antibiotics in our unit, a significant signal in Pottel scores beyond PNA day 5 could not be shown, suggesting either a less pronounced nephrotoxic effect of these antibiotics within our study population or a suboptimal timing for capturing their effects [8]. Notably in our prior analysis there was already a more modest change in Scr dynamics during amikacin and vancomycin treatment compared to ibuprofen, with Scr increases typically remaining below the 0.3 mg/dL threshold for mKDIGO criteria [17]. Exploring the cumulative effect during treatment with ibuprofen revealed a rising Pottel score until day 3 of exposure followed by a relatively stable value thereafter. This emphasizes the importance of well-timed assessments during drug treatment before drawing definitive conclusions about potential kidney damage as early measurements might not fully capture the complete nephrotoxic effect.

Scr reflects impaired kidney function due to decreased filtration, where urinary and serum biomarkers reflect kidney damage due to an aberrant expression in response to kidney injury. Several biomarkers have been explored in the pediatric and adult literature, but data on the premature neonatal population are limited. In preterm neonates serum cystatin C demonstrates high diagnostic accuracy surpassing Scr but urinary levels yield conflicting results [24–27]. Neutrophil gelatinase-associated lipocalin (NGAL) shows promise in preterm neonates for both serum and urine concentrations but the specificity appears to be limited by strong associations with inflammatory parameters [24, 26, 28]. A scala of other potential biomarkers, such as urinary kidney injury molecule-1 (uKIM-1) have been investigated in limited studies in premature neonates [24, 26, 29, 30]. Recently various urinary biomarkers were found to be statistically significantly elevated in extremely premature neonates treated with or without nephrotoxic drugs, without a significant difference in AKI diagnosis showing their potential to detect subclinical kidney (tubular) damage [31]. However most urinary biomarkers also show variation with GA, in part determined by the degree of prematurity at birth, emphasizing the need to establish GA-and PNA-adjusted reference values [32, 33]. Despite the promising potential, also due to their non-invasive way of diagnosing and reducing iatrogenic anaemia, the current lack of comprehensive data in premature neonates indicates that they are not yet ready for integration into clinical practice.

Several limitations of our study warrant acknowledgment. The p50 values used for calculating the Pottel scores were derived from the same cohort as this study, influencing statistical outcomes. However our main intention was to introduce the concept rather than conducting a comprehensive analysis. A next obvious step would be to determine p50 values for Scr for a diversity of subpopulations commonly admitted in neonatal intensive care units, to validate the approach used. Our limited sample size could have impacted the statistical power in detecting antibiotic-related signals, possibly requiring a larger population to detect significant differences. The current study is single-centre and focuses solely on ELBW neonates, while still displaying considerable heterogeneity in terms of BW (500-1000g) and GA (23–34 weeks), resulting in substantial variability regarding disease severity and limiting possible generalization of the results. The relationship between Scr and GFR in ELBW neonates remains unclarified resulting in uncertainty to what degree the Pottel score accurately predicts kidney damage. We
did not account for prolonged medication effects after cessation of treatment nor did we study the impact of piperacillin-tazobactam as well as other nephrotoxic drugs, often co-administered alongside amikacin in NEC. The impact on the Pottel score could be different based on the type and duration of drug exposure. For instance, the signal for ibuprofen becomes pronounced after 1–3 days of treatment where a milder nephrotoxic effect with antibiotics could occur after a longer duration of treatment. However, our main aim was to illustrate the utility of a bedside applicable tool to diagnose and quantify AKI.

In summary and taking these limitations into account, our findings underscore the potential value of the Pottel method in Scr-based bedside pharmacovigilance for ELBW neonates. In addition, it also provides a way to standardize AKI definitions in clinical trials, improving the comparability in this population. While other prospective biomarkers display promising results, their integration into clinical practice necessitates rigorous further investigation. Scr remains a widely recognized and measured biomarker, and the application of the Pottel method moderates certain inherent limitations linked to its use in this population. It’s important to note that the established upper limit of 1.33, validated as a dependable threshold in other populations, does not seem to be applicable in ELBW neonates. Our initial findings hint towards a considerably lower threshold. Comprehensive observational large-scale multicentre studies are necessary to validate and effectively develop this tool as well as ascertain solid p50 values and the appropriate cutoff values in this unique and vulnerable patient population.

**Conclusion**

The Pottel method as rescaled Scr biomarker showed a clear signal in ibuprofen-exposed ELBW neonates, suggesting its applicability as pragmatic bedside tool to detect AKI. However, we did not observe a significant signal in Pottel scores for amikacin and vancomycin, warranting further investigation with larger sample sizes. The need of well-timed assessments with a minimal waiting time of 48 hours during drug exposure before drawing conclusions about the complete nephrotoxic effects was demonstrated by the increasing Pottel scores during ibuprofen treatment.

**Declarations**

**Ethics approval**

Previously provided ethical approval covered the current analysis and no additional data search in patients was needed (S63405, Ethics Committee Research UZ Leuven).

**Consent to participate/publish**

Due to the nature of this study, no additional consent was needed.

**Funding**
No funding was received for conducting this study.

**Competing interest**

The authors have no competing interests to declare that are relevant to the content of this article.

**Data and/or Code availability**

The corresponding author can be contacted. Data availability will be considered, if based on a reasonable study proposal.

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**Author contributions**

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by M. Dumoulin, K. Allegaert and A. Laenen. The first draft of the manuscript was written by M. Dumoulin and K. Allegaert. All authors commented on previous versions of the manuscript. All authors read and approved the final version of the manuscript.

**References**


Figures

Figure 1

Selection of study population with respective exclusions. Nephrotoxic drugs include ibuprofen, amikacin and vancomycin. ELBW: extreme low birth weight.
Figure 2

Mean Pottel score per postnatal day in function of administration of ibuprofen the day before or not, corrected for administration of antibiotics. The estimated curves are presented within the range of observations: days on which (almost) no influence of ibuprofen was present (as there was (almost) no administration on the day before) are not shown. Estimated means are presented with 95% confidence intervals.
Figure 3

Both antibiotics were combined for this analysis. Mean Pottel score per day (postnatal) in function of administration of antibiotics the day before or not, corrected for administration of ibuprofen. The estimated curves are presented within the range of observations: days on which (almost) no influence of antibiotics was present (as there was (almost) no administration on the day before) are not shown. Estimated means are presented with 95% confidence intervals.
Figure 4

Cumulative impact of consecutive days of administration of ibuprofen, corrected for antibiotics, on the Pottel score. Estimated means are presented with 95% confidence intervals.
Figure 5

Cumulative impact of consecutive days of administration of antibiotics, corrected for ibuprofen. Estimated means are presented with 95% confidence intervals.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- GraphicalabstractDumoulin2023.pptx
- Supplementarytables.pdf