Monitoring Antibiotic Consumption in Pediatrics. How Close to Reality Are Days of Therapy and Recommended Daily Dose Methods?

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Background: Hospitals are advised to monitor antibiotic use. Several approximation methods do exist to perform this task. Adult cohorts can easily be monitored using the defined daily dose method, or its German adaption recommended daily doses (RDD) method, that seems inapplicable in pediatric cohorts due to body weight variations. Guidelines recommend the days of therapy (DOT) method in pediatrics. Still, there is a need for more detailed analysis regarding the performance of both methods.

Methods: Based on data from 4½ years of our fully computerized patient care data managing system in a combined neonatal and pediatric intensive care unit, we compare the results for DOT and RDD per 100 patient days with exact measurement of antibiotic consumption (individual daily dose per 100 patient days) as internal reference.

Results: The DOT method reflected antibiotic consumption in our cohort on the level of total consumption, subgroups, and agents with almost always high accuracy (correlation with individual daily dose between 0.73 and 1.00). The RDD method showed poor correlation on the level of total consumption (r = 0.21) and fluctuating results on more detailed levels (correlation, 0.01–0.94). A detailed analysis of body weight distribution and ordered packaging sizes of single agents revealed that RDD seems to work well when only one package size of the agent was ordered in our pharmacy.

Conclusion: The DOT method is superior to RDD for monitoring antibiotic drug consumption in pediatric cohorts. RDD seems to work satisfactory well for selected antibiotic agents that are administered with little variation in packaging size.

Key Words: antibiotic, consumption, DOT, monitoring, pediatrics

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More than two decades ago antimicrobial stewardship was introduced in clinical settings to fight misuse and overuse of antimicrobials that lead to antimicrobial resistance, which has been recognized as a global health problem.[1–5] Since that time, antimicrobial stewardship programs (ASP) have broadly been applied in hospitals around the world, and new guidelines have been addressing possible intervention strategies for ASP that aim to minimize inappropriate use of antimicrobials,[6,7] which is a common problem in pediatric patients as well, as demonstrated by the Antibiotic Resistance and Prescribing in European Children (ARPEC) study.[8] To measure the success of interventions, the monitoring of antimicrobial consumption is recommended. There exist 2 different approaches for that monitoring: either counting the length of therapies or counting the administered doses. The latter, the periodical measurement of defined daily doses (DDDs) per 100 or 1000 patient days is the most widely accepted method of consumption monitoring in adult specialties, because the data can easily be requested from the hospital pharmacy and facility level and interfacility benchmarking is possible.[9,10] In contrast, counting the length of therapies is time-consuming, since data can be obtained only by screening all medical records on the patient level. Unfortunately, the DDD method has some disadvantages: apart from subgroups of adult patient that are prone to over- or underestimation of antimicrobial exposure,[11] importantly for those caring for children, the DDD method might be inaccurate since partly used units of antibiotics are frequent due to low body weight for many children. Until today, there is no consensus on the best approximation method to use in Pediatrics: the monitoring of days of therapy (DOT) per 100 or 1000 patient days seems to be suitable, since DOTs are not impacted by dosage adjustments and can be used in both adult and pediatric populations.[6] Other proposed methods include the stratification of children by weight bands[12] or the introduction of specific neonatal DDD.[13] None of the latter have been validated yet.

Based on a large available data set of exactly documented antibiotic prescriptions, we aimed to analyze the performance of the two aggregated approaches DOT and recommended daily doses (RDD) per 100 patient days (German guideline-based adaption of DDD) in depicting antibiotic consumptions in a pediatric unit.

METHODS

Setting

We used data from our 14-bed combined neonatal and pediatric intensive care unit (NPICU) of a tertiary university care hospital including all patients from July 1, 2014, to December 31, 2018, since medical records on our NPICU are fully digital and, therefore, can be analyzed computerized. Patients on our NPICU comprise critically ill children, including those with burns, malignancies, complex congenital heart diseases (not directly after operation), and those requiring bone marrow transplants, as well as all critically ill mature and premature newborns. First antibiotic stewardship elements were introduced in 2017, and a full ASP including prospective audits, point-prevalence analyses, and regular training about topics in infectiology was established at the beginning of 2018. Apart from that, our NPICU has an in-house standard for all antibiotics specifying dose and interval for all age groups that was

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introduced in 2011. Doses and intervals for mature and premature newborns are based on recommendations of the Neofax Manual 2007.[14] Doses and intervals for infants and children are based on the German Pediatric Infectious Disease Society handbook.[15]

Data Collection

On our NPICU, we use a fully computerized integrated care data managing system (Draeger, Lübeck, Germany), which is updated regularly to its newest version. Data collection of each patient was performed by pseudonymization after approval of the local ethics committee (registration number 2018-58) and included the following: age in days on admission, gestational age (if newborn), sex, length of stay, listing of single administrations of an antibiotic given orally or intravenously (including dose and interval for courses), weight on admission, and all weight measurements during the stay. Altogether more than 30,000 intravenous or oral administrations of antibiotics were documented. The data query of the integrated care data managing system database produced one excel file per patient named with a running number.

Data regarding consumption of antibiotics were provided by our university pharmacy quarterly and yearly including the following for each agent: brand name, generic name, number of units delivered, amount per unit (package size).

For calculation of antibiotic use density, patient days per quarter and per year were provided by the central controlling of our hospital. Day of admission and day of discharge were counted half a patient day each.

Antibiotics were grouped on the basis of the ATC/DDD index provided by the World Health Organization.[16] Some minor adjustments were done to merge antibiotics that were administered in small amounts (Table 1). Folate antagonists include sulfamethoxazole-trimethoprim and trimethoprim alone. The group "other antibacterials" included metronidazole, colistin, fosfomycin, linezolid, and tigecyclin.

Data Management and Verification

Before combining all data into a single database for further analyses and introducing a new precise internal reference, the following steps were conducted: (1) check for completeness of documentation of each administration: correct spelling of drug, dose errors, interval, instant of time, route of administration; (2) correction of formatting (eg, intravenously must be always abbreviated iv, not i.v.), to guarantee correct operation of the computer search algorithms if necessary; (3) exclusion of test patients (dummies) that were regularly created for integrated care data managing system training; (4) exclusion of data sets if weight was not documented (0.015%, exclusively children older than 28 days).

Methods of Calculating Antibiotic Consumption Density

Since DDD does not necessarily reflect the RDD in our country, the German antibiotic use surveillance provides RDD information for all antibiotics[17] that is reasonably comparable with prescribed daily doses in adults.[18,19] In addition, RDD are used for national surveillance and annual interhospital comparison of antimicrobial consumption.[20]

RDD per 100 patient days was calculated quarterly and yearly based on annually updated RDD information according to the consumption data of our ward delivered by our pharmacy.

DOT per 100 patient days was calculated quarterly and yearly. Every calendar day on which the patient received an administration of a defined antibiotic was counted as one day of treatment.

To compare the accuracy of DOT and RDD in a pediatric setting, we had to introduce a method for calculating accurate consumption density that assigned every single administration with a precise value. These precisely calculated values were denominated individual daily doses (IDDs) per 100 patient days. To understand this manuscript, it is critical to recognize that IDD is not an approximated value but represents the exact body weight–adjusted antibiotic consumption on our NPICU and is individually calculated for every single administration. IDD was calculated quarterly and yearly as follows: (1) based on our in-house standard, all antibiotics being used during the observation period were allocated to specific dosage recommendations dependent on age and gestational age at the moment of administration in milligram (mg) per kilogram (kg) body weight per day (Table, Supplemental Digital Content 1, http://links.lww.com/INF/E625); (2) doses of an administered drug were normalized on mg per kg body weight using the closest weight measurement to the administration of the drug. Hereby, we could easily check for dose errors as well. Within the first 14 days of life of a newborn, the birth weight was used to minimize bias of physiologic fluid loss or excessive weight gain in that period. For children older than 1 year with a length of stay shorter than 14 days, the body weight on admission was used. (3) Finally, an IDD value was calculated for every normalized dose according to the point in time (current age and current gestational age at administration). Example:

Table 1. Overview of Administered Doses During Observation Period (Third Quarter 2014–2018)

	Number of Doses		
Substance group	Orally	Intravenously	Sum
Penicillins with narrow spectrum	72	129	201
Penicillins with extended spectrum	9	6109	6118
Penicillins + β-lactamase inhibitor	156	1416	1572
First- and second-generation cephalosporins	407	1062	1469
Third- and fourth-generation cephalosporins	5	4188	4193
Aminoglycosides	0	798	798
Carbapenemes (meropenem only)	0	7021	7021
Glycopeptides	0	6088	6088
Macrolides and lincosamides	1118	739	1857
Folate antagonists	102	181	283
Quinolones	31	125	156
Other antibacterials	165	588	753
Overall use	2065	28,444	30,509

Other antibacterials include 558 doses of metronidazole; the remaining doses include colistin, fosfomycin, linezolid, and tigecyclin.

A term newborn, 5 days of age, with birth weight of 3890 g received 200 mg cefotaxime twice a day. The recommended dosage according to our in-house standard is 50 mg/kg twice a day, so 1 IDD represents 389 g consumption of cefotaxime for that individual. Since the patient was administered 400 g per day, the consumption per day was calculated with 1.03 IDD.

To keep abbreviations simple, further use of DOT, RDD, and IDD in this article are always measurements of aggregate use per 100 patient days.

Software and Statistical Analysis

All analyses for RDD, DOT, and IDD were performed with SAS software, version 9.4 (SAS Institute, Cary, NC, USA). We used differencing (eg, $RDD' = RDD_t - RDD_{t-1}$) to transform the time series to account for possible trends. Moving average calculation of 4 consecutive quarters [$mav4 = 1/4\ (q_{t-3} + q_{t-2} + q_{t-1} + q_t)$] was performed to smoothen possible seasonal impacts in the time series. The Shapiro-Wilk test was performed for testing all samples for normality. For samples that did not show normality of the distribution and single quarterly values were zero, we calculated Spearman's correlation (ρ) of the changes between 2 consecutive quarters in RDD or DOT with changes in IDD. For samples that showed a Gaussian distribution, Pearson´s correlation (r) was calculated. If the data set of one method did not show normality of distribution, Spearman´s was used to compare all 3 methods of that sample. This correlation measures how closely RDD or DOT follow IDD.

RESULTS

Patient Cohort

Altogether 2299 patients with cumulative 18,767 patient days were analyzed. 49.5% patients were older than 28 days on admission, 50.5% were newborns. Fifty-five percent of the newborns were premature born babies. The ratio between children older than 28 days and newborns, as well as the number of patient days per quarter, varied only marginally during the observation period. From 2014 to 2018, cohort characteristics did not change significantly. A slight tendency of higher body weight and preterm newborns with higher gestational age and birth weight was observed. Additional information is shown in Table 2.

Antibiotic Drug Consumption

Thirty thousand five hundred nine administrations of an oral or intravenous antibiotic drug passed the checks of completeness of documentation. 93.3% were administered intravenously and 6.7% orally. The listing of prescribed antibiotic subgroups including the number of administered doses is outlined in Table 1. During the observation period, there was a decline of total antibiotic consumption when comparing 2015 (IDD = 93.14) with 2018 (IDD = 72.40; Fig. 1A). Table, Supplemental Digital Content 2, http://links.lww.com/INF/E626 comprises the quarterly data of total antibiotic consumption and of antibiotic subgroups. The introduction of antibiotic stewardship during that period might be a reason for that decline but was not the topic of that paper.

Comparison of the Performance of DOT and RDD

For the total antibiotic consumption, we found a much higher agreement between DOT and IDD than for RDD and IDD. Correlation of quarterly changes was 0.79 (CI, 0.51–0.92) versus 0.21 (CI, −0.32 to 0.62; Fig. 1A). Implementing moving average calculation showed a better performance for DOT (r = 0.98; CI, 0.93–0.99), while the agreement of RDD with IDD remained low (0.11; CI, −0.42 to 0.59; Fig. 1B). Also, when analyzing antibiotic consumption density on the more detailed level of antibiotic subgroups (Fig. 2), we found a good or very good agreement between DOT and IDD (range, 0.73–1.00, data of all subgroups; Table, Supplemental Digital Content 3, http://links.lww.com/INF/E627). RDD showed very fluctuating results on the subgroup level and, in comparison with DOT, RDD changes showed weaker correlation with IDD changes (range, 0.01–0.93). Next, we compared DOT and RDD on the level of antibiotic substances for all subgroups and its agents that were administered regularly during the observation period (Fig. 2). Again, DOT performed better for almost every antibiotic (range, 0.73–1.00) than RDD (range, 0.36–0.94) except for ampicillin-sulbactam (DOT, ρ = 0.88; RDD, ρ = 0.94) and vancomycin (DOT, r = 0.84; RDD, r = 0.93), but RDD showed strong correlations for some agents as well. Finally, a subgroup analysis of newborns and patients older than 28 days on admission demonstrated strong correlations between DOT and IDD in both groups (Figure, Supplemental Digital Content 4, http://links.lww.com/INF/E628). It was not possible to perform this analysis for RDD, since drugs are ordered in case of low stockpile at our pharmacy but not because of daily individual prescriptions. Therefore, it is not possible to stratify these orders afterward.

Analysis of Body Weight Distribution and Utilized Package Sizes

Since RDD performed very inconsistently even on the level of antibacterial substances, further analyses of selected agents were conducted to find out whether body weight distribution of all

Table 2. Description of the Study Sample

Year		2014	2015	2016	2017	2018
Patients (n)	All	228	474	469	574	554
	Ped.	114	229	232	277	287
	Mat.	43	98	109	140	130
	Premat.	71	147	128	157	137
Median age in years (Q1–Q3)	Ped.	2.50 (0.50–8.71)	3.25 (0.6–10.75)	2.95 (0.40–11.29)	3.69 (0.53–11.42)	4.64 (1.48–11.62)
Median GA in days (Q1–Q3)	Mat.	267 (262–273)	273 (266–280)	274 (266–283)	277 (269–283)	274 (269–282)
Median GA in days (Q1–Q3)	Premat.	225 (199–240)	231 (200–245)	228 (202–240)	229 (216–245)	230 (209–244)
Median body weight on admission in kilogram (Q1–Q3)	Ped.	11.75 (4.15–22.00)	13.00 (4.68–30.00)	12.50 (4.92–31.50)	13.85 (5.25–36.00)	16.00 (9.90–36.00)
	Mat.	3.06 (2.72–3.52)	3.37 (3.00–3.64)	3.37 (2.90–3.77)	3.47 (3.12–3.78)	3.44 (3.04–3.79)
	Premat.	1.65 (0.92–2.11)	1.71 (1.12–2.31)	1.67 (1.24–2.28)	1.87 (1.40–2.25)	1.82 (1.25–2.33)
Median length of stay in days (Q1–Q3)	All	2 (1–6)	2 (1–8)	3 (1–9)	3 (1–8)	2 (1–7)
	Ped.	1 (1–3)	1 (1–3)	1 (1–5)	1 (1–4)	1 (1–3)
	Mat.	2 (1–6)	2 (1–4)	3 (1–7)	2 (1–6)	3 (1–6)
	Premat.	5 (2–14)	8 (4–31)	10 (4–21)	8 (3–16)	9 (5–18)

Data are presented as medians and interquartile range.

GA indicates gestational age; Mat., mature newborns; N, total cohort per year; Ped., pediatric patients older than 28 days on admission; Premat., premature newborns.

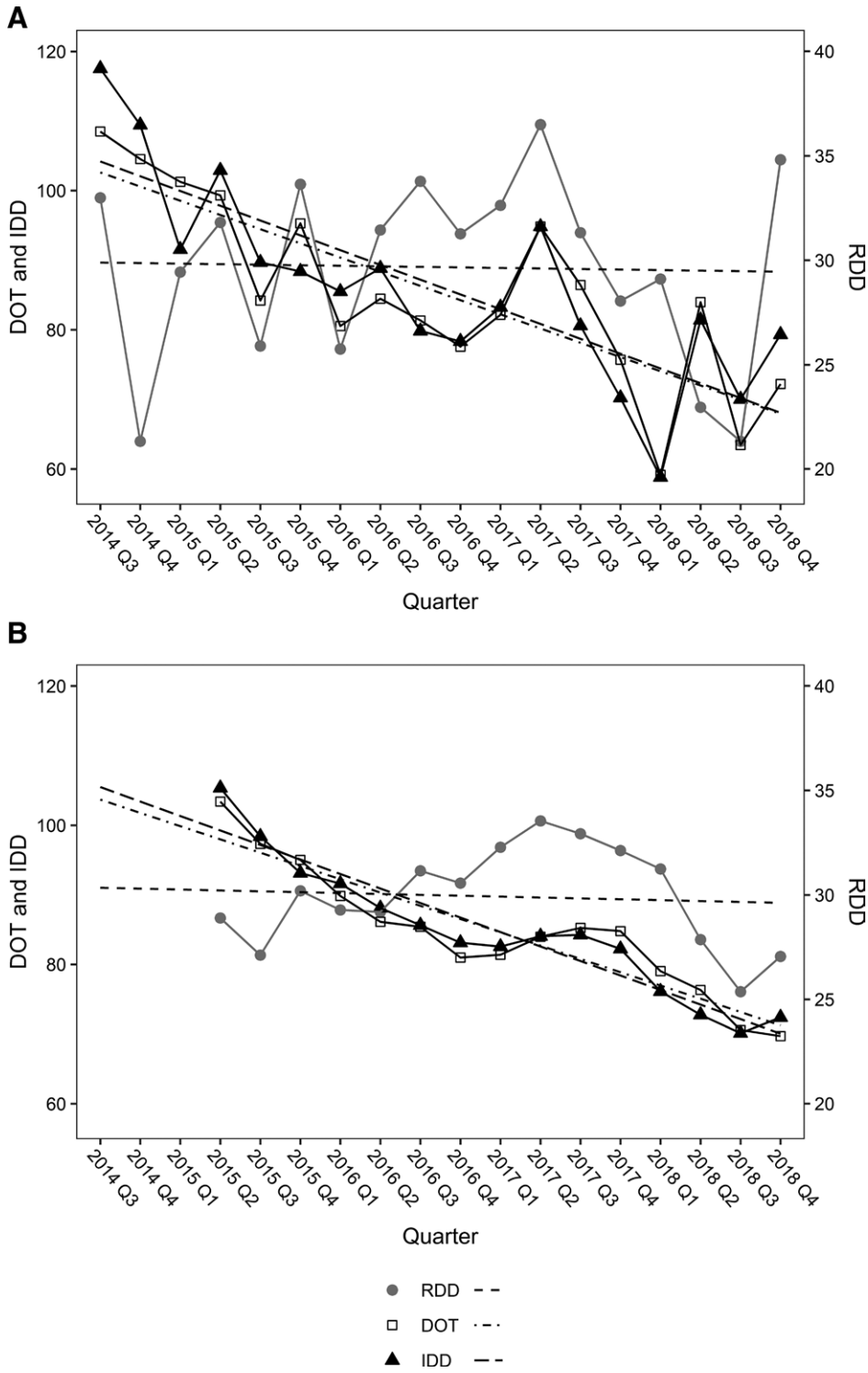

FIGURE 1. Total consumption of antimicrobial substances from the third quarter of 2014 to fourth quarter of 2018 in our neonatal and pediatric intensive care unit. Quarterly values are depicted by symbols with corresponding regression lines. **A,** Variation in DOT, RDD, and IDD. **B,** Variations in DOT, RDD, and IDD using moving average calculation (average of last 4 quarters to smoothen the time series).

patients receiving a specific agent or variations in ordered package sizes during the observation period are responsible for this picture. We have chosen ampicillin, cefotaxime, gentamicin, meropenem, piperacillin-tazobactam, teicoplanin, and vancomycin for further analysis because these agents were used most often on our NPICU and were administered exclusively intravenously. As exemplarily

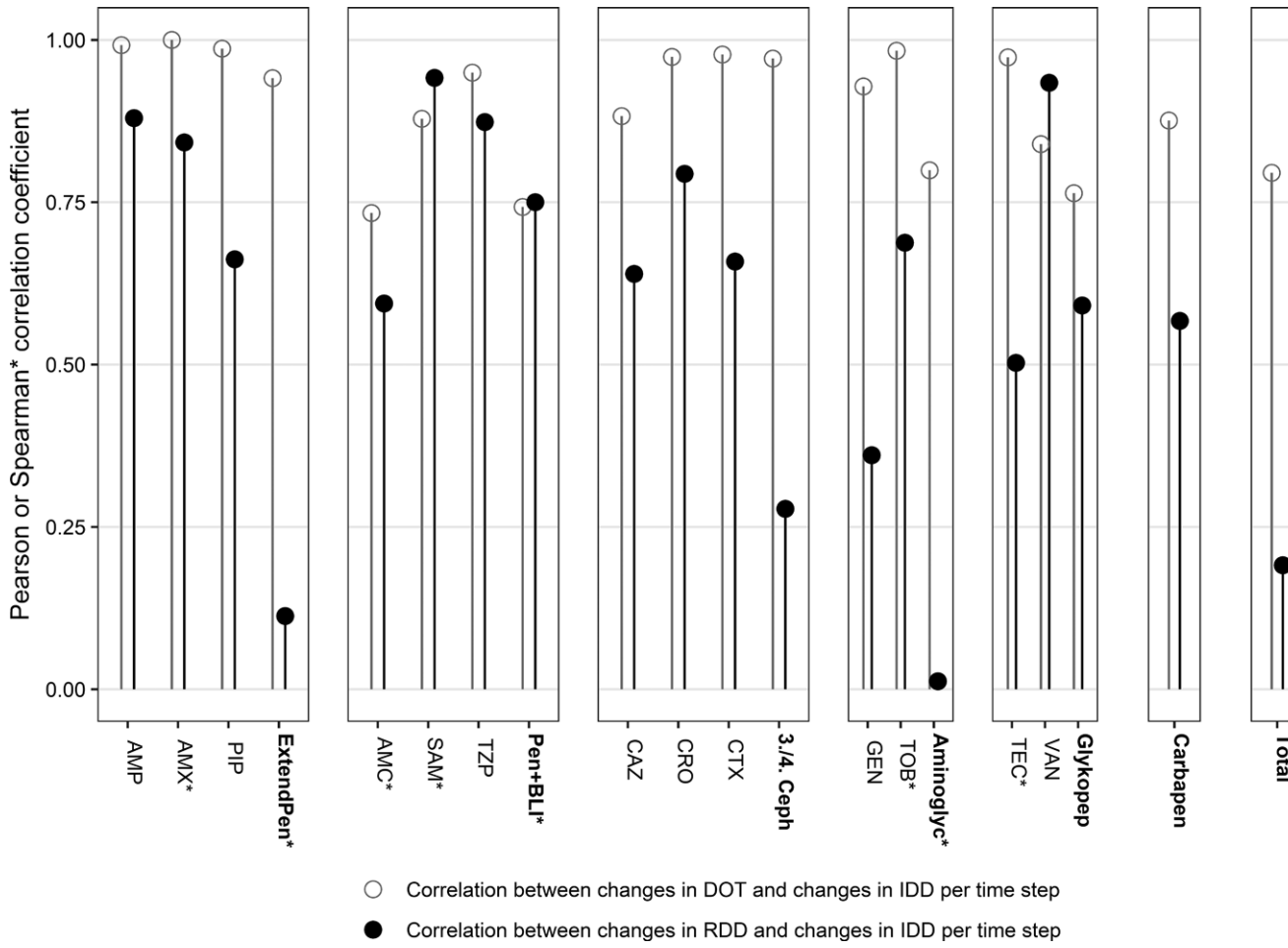

FIGURE 2. Performance of DOT and RDD when compared with the exactly calculated IDD for subgroups of antibiotics and its substances (correlations are based on changes in measure from one quarter to the other). Detailed information for each data point is provided in Table, Supplemental Digital Content 3, http://links.lww.com/INF/E627. 3./4. Ceph indicates third- and fourth-generation cephalosporins; AMC, amoxicillin + clavulanic acid; Aminoglyc, aminoglycosides; AMP, ampicillin; AMX, amoxicillin; Carbapen, carbapenems (meropenem only); CAZ, ceftazidime; CRO, ceftriaxone; CTX, cefotaxime; ExtendPen, penicillins with extended spectrum; GEN, gentamicin; Glycopep, glycopeptides; Pen+BLI, penicillins + β-lactamase inhibitor; PIP, piperacillin; SAM, ampicillin + sulbactam; TEC, teicoplanin; TOB, tobramycin; TZP, piperacillin-tazobactam; VAN, vancomycin.

depicted in Fig. 3 for vancomycin and gentamicin, ordering various package sizes of an agent was always associated with weak correlation between RDD and IDD, whereas drugs only being available in one size showed good correlations. Analyses of variations of body weight distribution for these 7 drugs showed inconsistent results. Figure, Supplemental Digital Content 5, http://links.lww.com/INF/E628 illustrates the data for all analyzed drugs.

DISCUSSION

Using a precise database of medical prescriptions from a tertiary care pediatric center, this study demonstrated that the DOT method reflects the actual use of antimicrobials quite accurately and much better than RDD in pediatric care. Also, we showed the impact of different packaging sizes as a source of errors in depicting antibiotic use when using the RDD method. The results deliver a valuable contribution to the ongoing discussion which method is more appropriate, since monitoring antibiotic consumption as an instrument to evaluate the success of ASPs has remained a controversy that is represented by several national guidelines either favoring the DOT or RDD (DDD) method.[6,7,21–25]

Theoretically, IDD is the best approach to monitor the real antibiotic consumption in a pediatric cohort, since it is not an approximation procedure but an exact representation of consumption. Furthermore, it can be used for monitoring dose accuracy as well. Unfortunately, that method needs accurate digitalized documentation of each antibiotic administration. Even with this documentation, the analysis of such data is extremely time-consuming and, therefore, in our opinion currently only actionable in research context. Because of a normalization step, it could be used for interfacility benchmarking, although our IDD method is based on an in-house standard dosage list that makes its calculation unique for every institution. Nevertheless, we believe that further progress of digitalization and improvement of database analysis algorithms might favor methods like IDD in the future. Fortunately, DOT displayed a high agreement with IDD on all 3 levels of analysis (total, antibiotic subgroup, agent) as well as in cohort subgroups and seems to be particularly responsive to changes over time. Thus

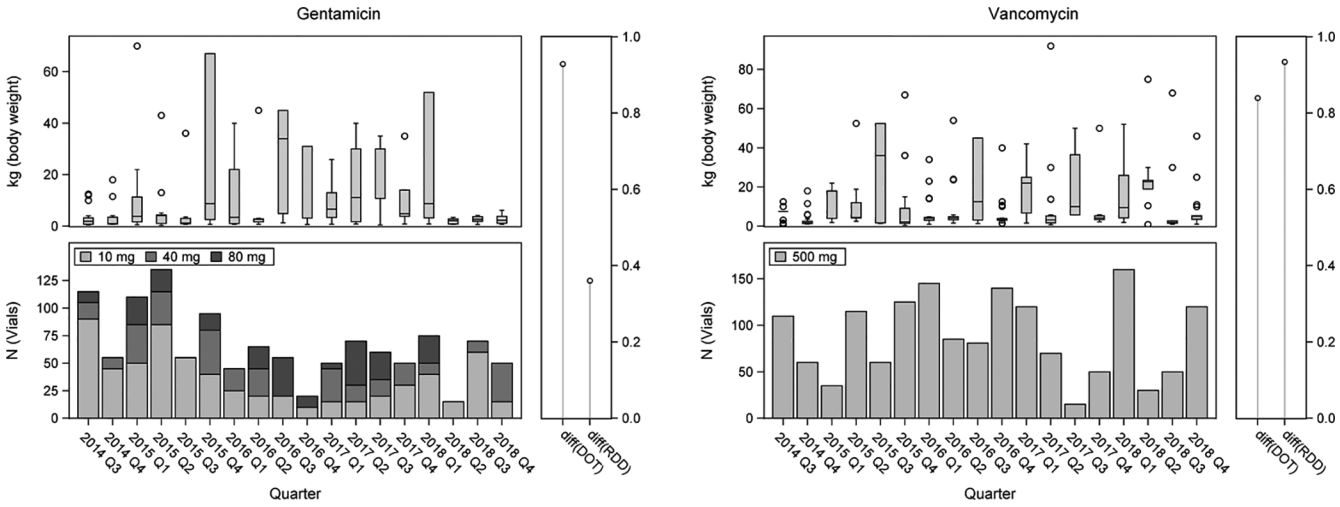

FIGURE 3. Analyses of body weight distribution (upper left box) and ordered packaging sizes (lower left box) for gentamicin and vancomycin (further drugs are shown in the Figure, Supplemental Digital Content 5, http://links.lww.com/INF/E628). Various package sizes are associated with weak correlation between RDD and IDD (right box).

for the purpose of internal comparisons over time, DOT can be an alternative to IDD. A big advantage of the DOT method is its applicability for benchmarking between pediatric facilities as demonstrated by a recent multicenter study.[26] In contrast, the RDD method showed a low agreement with IDD in our cohort for monitoring total antibiotic consumption and several subgroups. Interestingly, on the level of therapeutic agents, the RDD method showed variable results and in comparison with the subgroup or total analysis a trend to better correlations. Thus, the RDD method monitored consumptions of some antibiotics, for example, vancomycin, ampicillin, and piperacillin-tazobactam, as good as the DOT method, whereas it failed for other substances. Further analysis of antibiotics being used in large amounts in our cohort could not verify the findings of recent work that varying body weight might be a reason for weak RDD correlation.[27] On the other hand, there might be a simplier answer: although our patients who received vancomycin and piperacillin-tazobactam varied extremely in body weight, the RDD method showed strong correlation with IDD. Both drugs are only available at one size in our pharmacy. In contrast, patients receiving teicoplanin (200 or 400 mg vials) showed only little variation in body weight, but the correlation between RDD and IDD was still worse compared with vancomycin. In our setting, variation in packaging sizes was more important as variation in body weight in explaining disagreements between RDD and IDD. These results are consistent with the findings of Mostaghim et al[28] who demonstrated by a different approach that in pediatric cohorts the number of vial sizes and percentage of waste influence the accuracy of DDD. In agreement with Liem et al,[13] we found that the RDD method reflected real consumption well, when there was little variance of body weight as well as ordered packaging sizes. This was the case for, for example, ampicillin in our study. Recent work using weight-adjusted DDD[29] or introducing weight-specific subgroups before DDD calculation[12,30] are addressing the same problem in pediatric cohorts and show similar conclusions. Relating to our results, we presume that the abovementioned packaging size problem is the reason that RDD correlations of total consumption or subgroups are always worse than correlations for single agents, since the percentage of waste differs between drugs when used for a patient with little weight.

The strength of our study is the completeness of our database that allowed us to calculate an exact age- and weight-dependent dose equivalent for each administered antibiotic and thus development of the IDD as an internal reference. To our knowledge, this is the first study that analyzes pediatric antibiotic consumption with such accuracy and obtained quarterly data that do not represent an approximation but a precise value. Since data entry and query of the database is fully computerized, there is no bias because of missing data sets, misinterpretation of medical prescription because of scratchy handwriting, etc. In addition, a specific point of time and most current weight was assigned to each administration, which allowed us to rule out variations of doses per kilogram due to weight gain. Finally, our sample consists of patients covering the whole range of weight—the smallest child weighted 0.34 kg; the heaviest, 92 kg—and except organ transplant and extracorporal membrane oxygenation reflects the whole spectrum of critically ill children.

Our study has some limitations: to confirm our findings statistically, further analyses of independent cohorts are necessary since our data do not allow to make conclusions about the performance of these methods in comparing different hospitals. Furthermore a multicohort data set is needed to verify statistically by time series analysis our visual impression in Fig. 1 that DOT is highly responsive to changes over time. As mentioned above, it is not possible to transfer the IDD method to other institutions without adaption because it relies on unique dosage recommendations. Furthermore, it was not possible to analyze the RDD method on a cohort subgroup level (eg, neonate, non-neonate), since ordered drugs at the pharmacy could not be assigned to individuals after distribution. In this context, it is important to mention that there is potential for selection bias since the body weights of our cohort were not normally distributed (>55% with patients of 5 kg or less). Taken together, it remains unclear in our study whether the RDD method works better on the level of monitoring total consumption or subgroups of antibiotics in selected cohorts such as neonates who have minor variances of body weight than pediatric cohorts including patients from birth till adolescence.

In conclusion, the DOT method is superior to RDD for monitoring antibiotic drug consumption in pediatric cohorts. DOT displayed high correlation at all levels of monitoring—total consumption, subgroup, agent—in comparison with our internal reference IDD. However, it is a time-consuming and labor-intensive method if it cannot be performed by computational search algorithms since data have to be gathered by analyzing individual patient files and, therefore, might not

be feasible in every hospital.[25,31] Of course, the IDD method is closer to reality, and DOT does not provide information about dosage accuracy but neither does RDD.

Recommendation for praxis: currently, DOT is the preferred method for monitoring antibiotic consumption density in a pediatric cohort. If time or personnel resources are short at hand, based on our results in accordance to literature, we especially encourage institutions caring for newborns to use the RDD method for monitoring antibiotic consumption density in ASP. Although we have to wait for further verification, in agreement with prior work, the RDD method (or similar methods like DDD) can be used under the following conditions and limitations: (1) it can be used on the agent level in cohorts with little variance of body weight, if only one packaging size is distributed by the pharmacy. (2) A comparison of RDD between agents to compare the amount of consumption between, for example, meropenem and ampicillin is not possible in pediatric cohorts, since dose per kg body weight and packaging size does not represent the same RDD equivalent. For example, in our study, DOT of 20 days of ampicillin was equal to 1 RDD; in contrast, a DOT of 20 days of meropenem was equal to 5.5 RDD.

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