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Optimized Antimicrobial Dosing Strategies: A Survey of Pediatric Hospitals

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Abstract:

Background

Extended-interval aminoglycoside (EIAG) and extended- and continuous-infusion β-lactam (EIBL and CIBL) dosing strategies are increasingly used in adults, but pediatric literature is limited.

Objective

The objective of this study was to describe the use of EIAG, EIBL, and CIBL dosing in pediatric hospitals in the USA.

Study Design, Setting, and Participants

A national survey of children's hospitals was conducted. A single practitioner from each target hospital was identified through the Children's Hospital Association. Practice-based survey questions identified whether hospitals utilize EIAG, EIBL, and CIBL dosing.

Main Outcome Measure

The main outcome measure was the percentage utilization of the dosing strategies, with secondary outcomes being the reasons for not using these dosing strategies.

Results

Seventy-seven of 215 identified practitioners (36 %) participated in the survey. EIAG, EIBL, and CIBL dosing were utilized in 63 %, 24 %, and 13 % of responding hospitals, respectively. The most common reasons for not using EIAG were concern regarding lack of efficacy data (56 %) and concern regarding the duration of the drug-free period (41 %). Respondents who did not utilize EIBL cited concern due to lack of pediatric EIBL efficacy data (54 %), the need for more intravenous access (54 %), intravenous medication compatibility issues (39 %), and the time during which the patient is attached to an intravenous infusion (31 %).

Conclusion

This survey of children's hospitals indicates that EIAG is used in over 50 % of hospitals, but there is some lag in adoption of EIBL and CIBL dosing, both of which are used in fewer than 25 % of hospitals. Additional studies may provide much-needed evidence to increase the utilization of these strategies.

1 Introduction

Judicious and optimal antimicrobial use in children has become increasingly important in light of emerging bacterial resistance and its association with poor patient outcomes [1, 2]. Optimal antimicrobial utilization includes employing dosing strategies designed to enhance the drugs' pharmacokinetic and pharmacodynamic properties for the most effective dosing regimen [3]. Dosing strategies such as extended-interval aminoglycoside (EIAG) and extended- and continuous-infusion β-lactam (EIBL and CIBL) have been well described in adults [4–7]. A complete review of experience with these dosing strategies in adults is beyond the scope of this report. While adoption of these dosing strategies has become increasingly common in the adult population, there remain limited data in children regarding efficacy, safety, and prevalence [8–14].

Pediatric EIAG use has been well described, but definitive safety and efficacy data, in comparison with conventional aminoglycoside dosing, are not widely available. The prevalence of EIAG in practice is not widely known. Prescott found that once-daily aminoglycoside dosing is used in nearly 85 % of programs caring for patients with cystic fibrosis exacerbations [15]. In a survey of 500 acute care hospitals, Chuck and colleagues found that EIAG dosing specifically for pediatrics was used in 23 % of responding hospitals [16]. Extended-infusion piperacillin–tazobactam (EIPT) has been described in one pediatric cohort, which demonstrated the feasibility of the dosing strategy [10]. Courter and colleagues demonstrated with Monte Carlo simulation the enhanced probability of target attainment with EIPT and extended-infusion cefepime (EIC) [13]. A 2014 study, utilizing pediatric serum concentration data, also demonstrated increased probability of target attainment using EIPT strategies [14]. Despite this, there are very few data describing EIBL in children. The prevalence of use of these optimized dosing strategies in children remains largely unknown.

Continual assessment and quality improvement of institutional antimicrobial utilization is an important component of an antimicrobial stewardship program (ASP). The goal of assessing the current use of EIAG, EIBL, and CIBL dosing in the USA is to identify and promote safe and optimal utilization of these antimicrobials. The objective of this study was to determine the prevalence of use of EIAG, EIBL, and CIBL dosing in pediatric hospitals in the USA, and to determine barriers to using the strategies in practice.

2 Methods

This was a national survey of hospitals providing acute care for children, and was approved by the Butler University Institutional Review Board. Target hospitals were chosen by identification of members of the Children's Hospital Association (CHA). A single practitioner from each hospital was identified as the survey contact through a search of the American College of Clinical Pharmacy Practice and Research Networks for Pediatrics and Infectious Diseases, the American Society of Health System Pharmacists Online Residency Directory, the CHA Directors of Quality

list, a contact list provided at the 4th Annual International Pediatric Antimicrobial Stewardship Conference in Kansas City (MO, USA), or from information provided by the hospital via telephone in response to direct requests by the researchers. The practitioner contact's e-mail address was obtained through this search and utilized for survey distribution.

The survey questions focused on demographics, antimicrobial stewardship practices, aminoglycoside dosing practices, and β-lactam dosing practices. Conditional logic was incorporated, and respondents could answer a maximum of 25 questions. Demographic and antimicrobial stewardship questions assessed the presence of an ASP, pharmacokinetic consult services, antimicrobial order guidance, hospital size, and geographic location. Practice-based survey questions identified whether hospitals are utilizing EIAG, EIBL, and CIBL dosing strategies, as well as reasons cited for not using these dosing strategies. Open-ended text boxes were utilized to capture additional reasons for not utilizing a particular dosing strategy.

The survey was conducted through SurveyMonkey (Palo Alto, CA, USA). A survey link was e-mailed, along with a cover letter invitation and survey description, to the identified practitioners at each hospital on January 15, 2014. Practitioners received follow-up e-mail reminders to complete the survey at weeks 2 and 4, and the survey remained open for a total of 6 weeks.

2.1 Data Analysis

Descriptive statistics were utilized to characterize respondent demographics. Analysis of the nonparametric correlations between demographic characteristics and the use of EIAG, EIBL, and CIBL was performed using χ^2 analysis and Spearman's rank order correlation. *P* values of less than 0.05 were considered to be statistically significant. Statistical analyses were conducted using Statistical Package for Social Sciences version 19.0 (SPSS, Inc., Chicago, IL, USA).

3 Results

A total of 236 hospitals were identified through the CHA. Practitioners with e-mail contact information were identified for 221 of these. The initial survey e-mail was undeliverable for five of these contacts, and one practitioner was subsequently identified as being unaffiliated with a pediatric hospital, yielding a final sample of 215 hospitals. Seventy-seven practitioners completed the survey, for a 36 % response rate.

Survey respondents were primarily clinical pharmacists (79.2 %) and prescribers (13 %). Hospitals were described primarily as non-profit (84.4 %) and teaching hospitals (93.5 %). The majority of hospitals were free-standing children's hospitals (46.8 %) or a children's hospital within an adult hospital (48.1 %), and 51.9 % (40/77) contained 100–200 beds. Hospitals were equally distributed across geographic regions. ASPs were present in 72.5 % of hospitals (56/77), and 57 % of those programs had at least one full-time employee (FTE) dedicated to the program. Pharmacokinetic consult services and written antimicrobial order guidance were available in 74 % of hospitals (57/77) and in 80.5 % of hospitals (62/77), respectively. Demographic responses are summarized in Table 1.

Table 1

Demographic characteristics

Characteristic [*N* = 77]	***n* (%)**
Position of survey respondent	
Clinical pharmacist	61 (79.2)
Physician: infectious diseases specialist	6 (7.8)
Other pharmacist	6 (7.8)
Medical doctor	2 (2.6)
Nurse practitioner	2 (2.6)
Hospital description	
Free-standing children's hospital	36 (46.8)
Children's hospital within an adult hospital	37 (48.1)
Children's ward within an adult hospital	3 (3.9)
Adult hospital that cares for children [no specific children's unit]	1 (1.3)
Hospital size	
<100 beds	7 (9.1)
100–200 beds	13 (16.9)
201–500 beds	40 (51.9)
501–800 beds	11 (14.3)
>800 beds	6 (7.8)
Geographic region	
Northeast	18 (23.4)
Southeast	18 (23.4)
Midwest	19 (24.6)
West	12 (15.6)
Southwest	10 (13.0)

3.1 Extended-Interval Aminoglycoside Dosing

Forty-seven of 75 responding practitioners (62.7 %) stated that EIAG dosing was used within their hospital, with 57.4 % of those respondents (27/47) indicating use all or most of the time for aminoglycoside dosing. There were no significant relationships observed between EIAG and presence of an ASP ($r_s = 0.158$), ASP FTE ≥1 ($r_s = 0.026$), teaching hospital ($r_s = -0.096$), region ($r_s = -0.184$), or free-standing children's hospital ($r_s = -0.107$). A fair positive and significant relationship was observed between total bed number and EIAG utilization ($r_s = 0.304$, $P = 0.008$). EIAG dosing was utilized in 45, 61.5, 81.8, and 100 % of hospitals with <100, 100–200, 501–800, and >800 beds, respectively.

Twenty-seven of the 28 practitioners who stated that their hospitals did not use EIAG provided a rationale for why EIAG was not utilized. Nearly 60 % of hospitals stated that a lack of data supporting the efficacy of EIAG in children was the reason for not utilizing the dosing strategy. Other reasons cited by at least 15 % of hospitals were concern regarding the duration of the drug-free period (40.7 %), concern regarding the possibility of increased ototoxicity (18.5 %), concern regarding the possibility of poorer clinical outcomes (14.8 %), and lack of overall safety data (14.8 %). Aminoglycoside dosing practices and reasons for not using EIAG are summarized in Table 2.

Table 2

Extended-interval aminoglycoside (EIAG) dosing

	***n* (%)**
Dosing description	
Initial tobramycin and gentamicin therapy [*n* = 41]	
<3 mg/kg/dose	3 (7.3)
3–5 mg/kg/dose	2 (4.9)
>5 mg/kg/dose	25 (61)
Other	11 (26.8)
Target tobramycin and gentamicin peak concentration [*n* = 42]	
≤10 μg/mL	8 (19)
11–14 μg/mL	6 (14.3)
15–19 μg/mL	6 (14.3)
≥20 μg/mL	22 (52.4)
Reasons cited for not utilizing EIAG [*n* = 27]	

	***n* (%)**
Lack of data supporting efficacy of EIAG dosing	15 (55.6)
Concern about duration of drug-free period	11 (40.7)
Concern about possibility of increased ototoxicity	5 (18.5)
Concern about possibility of poorer clinical outcomes	4 (14.8)
Lack of overall safety data	4 (14.8)
Lack of data regarding incidence of ototoxicity	3 (11.1)
Concern about therapeutic drug monitoring	3 (11.1)
Lack of data regarding incidence of nephrotoxicity	2 (7.4)
Concern about possibility of increased nephrotoxicity	2 (7.4)
Lack of drug resistance within hospital	1 (3.7)

3.2 Extended- and Continuous-Infusion β-Lactam Dosing

Sixty-seven practitioners (87 %) responded when asked if EIBL dosing was utilized in their hospitals. Of these, 16 (23.9 %) stated that EIBL was used in their hospitals, with EIPT being most common at 93.8 % utilization, followed by extended-infusion meropenem (68.8 %) and cefepime (31.3 %). EIBL dosing was reported as being used in most and in some patients in 18.8 and 81.2 % of hospitals, respectively. There was a fair positive relationship between EIBL and ASP FTE ≥ 1 ($r_s = 0.228$). Hospitals in the Eastern US regions use EIBL significantly more frequently than those in the Midwest/West (40 versus 10.8 %, $P = 0.009$). No other associations were observed. The most common reasons for not utilizing EIBL were a lack of efficacy data in pediatrics and concern about requiring more intravenous access, both of which were cited by 54.5 % of practitioners. Other reasons can be found in Table 3.

Table 3

Stated rationales for not utilizing extended-interval β-lactam (EIBL) and continuous-infusion β-lactam (CIBL)

	***n* (%)**
Reasons cited for not utilizing EIBL [*n* = 67]	
Lack of efficacy data in pediatric patients	36 (53.7)

	***n* (%)**
Concern about requiring more intravenous access sites	36 (53.7)
Concern about compatibility with other administered drugs	26 (38.8)
Concern about prolonged use of intravenous access	21 (31.3)
Lack of drug resistance within hospital	17 (25.4)
Lack of safety data in pediatric patients	12 (17.9)
Concern about possibility of inappropriate dosing when switching to extended-interval dosing	7 (10.4)
Concern about drug stability	6 (9)
Reasons cited for not utilizing CIBL [*n* = 64]	
Concern about requiring more intravenous access sites	23 (35.9)
Concern about prolonged use of intravenous access	35 (54.7)
Concern about compatibility with other administered drugs	8 (12.5)
Lack of efficacy data in pediatric patients	11 (17.2)
Lack of drug resistance within hospital	13 (20.3)
Lack of safety data in pediatric patients	9 (14.1)
Concern about drug stability	26 (40.6)
Concern about possibility of inappropriate dosing when switching to extended-interval dosing	13 (20.3)

Sixty-three responding practitioners provided information about using CIBL, and eight of these (12.7 %) reported CIBL being used in their hospitals. Of the respondents who indicated CIBL use,

all utilize continuous-infusion (CI) nafcillin, 62.5 % (5/8) utilize CI penicillin, and 12.5 % (1/8) utilize CI oxacillin. The reasons provided for not using CIBL are summarized in Table 3, with the most common being concern about requiring more intravenous access sites, at 54.7 %. No significant relationships between utilizing CIBL and any other variables were observed.

4 Discussion

With the increasing prevalence of bacterial resistance, and the associated negative outcomes, antimicrobial dosing strategies incorporating fundamental pharmacokinetic–pharmacodynamic principles that aim to optimize the drugs' efficacy should be considered [1, 2, 17]. This is especially important in children where, because of clinical research limitations, there may be fewer novel antimicrobials available for pediatric use than for adult use. Dose optimization also remains an important strategy in both adult and pediatric ASP [18, 19]. Pharmacokinetics develop across the age spectrum of pediatrics and can make extrapolation of adult literature difficult [20].

Age, however, does not alter antimicrobial-specific pharmacodynamic properties. In pediatrics and adults, aminoglycosides are concentration dependent, relying on high peak concentrations relative to the organism MIC for maximal bacterial killing, and β-lactam antibiotics are time dependent, relying on the length of time for which the free antibiotic concentrations remain above the MIC for optimal killing [21, 22]. With pharmacodynamics in mind, careful investigation of pharmacokinetic development is imperative to fully optimize antimicrobial dosing. With increasing bacterial MICs to aminoglycosides, conventional doses may not attain a desired peak concentration to optimize the peak:MIC ratio [21, 23]. Given the short half-lives of β-lactam antimicrobials in children, traditional infusion times (those of 30 min or less) may have a lower probability of target attainment in infections due to bacteria with elevated MICs [13, 14].

EIAG, EIBL, and CIBL dosing strategies utilize fundamental pharmacokinetic–pharmacodynamic principles and can optimize drug therapy in adults and children [3, 24]. Despite growing reports on these strategies in adults, general use in pediatrics is widely unknown. Our findings demonstrate that, according to the practitioners' responses to the survey, nearly two-thirds of US hospitals caring for children are utilizing the optimized dosing approach of EIAG, but less than one-quarter utilize EIBL or CIBL.

Traditional aminoglycoside dosing (e.g., tobramycin 2.5 mg/kg given every 8 h) typically fails to take advantage of aminoglycosides' concentration-dependent bactericidal activity and postantibiotic effect (PAE) [3, 9]. Extended-interval dosing can optimize the pharmacokinetic–pharmacodynamic principles but requires larger cumulative doses at an interval of once daily or longer (e.g., 4.5–7.5 mg/kg given every 24 h) [3, 9]. In 1993 and 1998, national surveys of 500 acute care hospitals in the USA were conducted to evaluate the adoption of EIAG. Although only 19 % of hospitals surveyed had adopted this dosing strategy in adult patients in 1993, 75 % of the responding facilities were using EIAG in the adult population by 1998 [16, 25]. Despite this rapid increase in EIAG usage in adults, in 1998 only 23 % of respondents used EIAG for pediatric patients [16]. Over the 16 years since Chuck and colleagues performed their survey, EIAG use has grown modestly, from 23 to 63 %, and there still appear to be hospitals caring for children that do not use EIAG.

Though this survey cannot determine all barriers to adoption of EIAG, some barrier themes can be investigated. Previously published concerns regarding EIAG in pediatric patients include limited available data, increased aminoglycoside clearance in children, determination of the most appropriate dose, and the overall safety and efficacy of this dosing strategy [3, 9]. The most common reason cited for not using EIAG in this survey was a lack of supporting efficacy data, which was identified by nearly 60 % of hospitals. Reviews and meta-analyses have summarized neonatal and pediatric EIAG efficacy data [8, 9, 26, 27]. Given the available efficacy data, the high percentage of respondents describing the lack of supporting efficacy data as a barrier is surprising. Perhaps the more important barrier is the lack of direct comparative efficacy relative to traditionally dosed aminoglycosides. However, well-designed and adequately powered studies directly comparing EIAG with traditionally dosed aminoglycosides are not likely to be feasible, because of cost and subject recruitment considerations.

Another common concern was related to the duration of the drug-free period, which was a concern stated by 40.7 % of hospitals. This is a similar concern to those discussed in other reports, but one of interest relating to the term “drug-free” [9]. This likely has more to do with the unknown duration of the PAE, which can be impacted by factors such as the infecting bacteria and the initial serum concentration, and the potential for bacterial regrowth following the end of the PAE [9, 28, 29]. Clinically, the precise duration of the aminoglycoside PAE may not be known, but it is unlikely that an aminoglycoside would be used as monotherapy. The available EIAG efficacy data in children suggest, despite the unknown PAE duration, that EIAG is an effective dosing strategy. This could be more of a perceived barrier than an actual barrier and is related, to some degree, to the concern about efficacy data. This barrier could be overcome by focused efforts with education on the available EIAG efficacy data.

There were fewer safety-related reasons for not adopting EIAG. Reasons related to ototoxicity and nephrotoxicity were cited in fewer hospitals than efficacy concerns, with 30 and 15 % of hospitals, respectively, reporting these concerns. The challenge for pediatric practitioners is balancing those concerns with the potential benefits of providing an optimized aminoglycoside dose. A solution would be to increase hospital education efforts, which, along with dose optimization, is a supplemental ASP strategy to increase awareness of the existing literature and fundamental drug knowledge among practitioners using aminoglycosides [18, 19]. This might be especially important in smaller hospitals, where there appears to be a negative relationship with EIAG use.

Fewer than 25 % of hospitals utilized EIBL or CIBL. With both of these dosing strategies, concerns related to intravenous access or need for additional intravenous access were most common and were reported by at least 40 % of hospitals. These are valid concerns, given the challenge of obtaining and maintaining intravenous access in pediatrics. Nichols and colleagues [10] demonstrated the feasibility of using EIPT in a pediatric cohort without the need for additional intravenous access. The presence of these feasibility data could be one explanation for why most hospitals in our survey utilize EIPT over meropenem or cefepime with respect to the concern about intravenous access. It is possible that these reasons may present more of a perceived barrier to the use of these dosing strategies, rather than an actual barrier. If each patient were evaluated as an

individual case, considering other medications to be administered and the state of the patient's intravenous access, it might be possible to implement these dosing strategies more frequently.

Efficacy concerns about EIBL were also cited (53.7 %) as reasons why this dosing strategy is not utilized. While adult data have demonstrated efficacy and positive patient outcomes with EIPT, similar pediatric data are lacking [4–6]. Courter and Cies [13, 14] both demonstrated higher probability of target attainment with EIBL regimens, but did not report patient outcomes data. Tamma and colleagues [17] demonstrated a nearly 25 % 30-day mortality rate in children with bacteremia due to *Pseudomonas aerugonisa* isolates with elevated piperacillin MICs. Bacteremia due to *Pseudomonas aerugonisa* isolates with a piperacillin MIC ≥32 μg/mL was associated with increased mortality compared with bacteremia due to more susceptible isolates. Courter and Cies [13, 14] each demonstrated less than 20 % probability of target attainment when using commonly recommended piperacillin doses administered over a 30-min infusion for *Pseudomonas aerugonisa* isolates with MICs ≥32 μg/mL. Considering this along with Tamma's data [17], it is reasonable to posit that EIBL regimens could positively benefit patient outcomes. Despite the lack of similar data summarizing the impact of elevated cefepime and carbapenem MICs on pediatric clinical outcomes, it is also reasonable to suspect similar negative clinical outcomes with respect to those antimicrobials. Because the time from obtaining a specimen for culture until availability of susceptibility data can be days, it is critical to optimize β-lactam dosing at therapy initiation. Delaying this optimization potentially increases the risk of poor clinical outcomes and, in some cases, waiting may just create too much delay. This observation underscores the global need for additional research to document the efficacy of these dosing strategies in pediatric patients. For both EIBL and CIBL, concerns regarding inappropriate dosing when switching to one of these regimens were reported by at least 10 % of hospitals. Development of order guidance forms, specifically with EIBL and CIBL dosing regimens included, would be one solution for addressing this concern.

The limitations of our survey and the generalizability of its findings include a lower response rate, which introduces the potential for non-response bias. A small sample of respondents could limit the interpretation of any significant relationships between tested parameters and dosing strategies. Our survey used all CHA hospitals as the target population. Considering the comparable distribution of hospital sizes, types, and US locations of the hospitals responding to our survey, a sampling of 36 %, which was our survey response rate, does appear to be a representative sample of the target population. In order to develop a survey that practitioners would be able to complete in a timely manner, the survey was able to query only basic information regarding the use of these dosing strategies at the target hospitals. How the dosing strategies are being used in institutions, such as whether they are used only in cystic fibrosis exacerbations or for organisms with elevated MICs, was not examined, which may limit some of the generalizability of the findings. More detailed information could be obtained from a larger survey, but that could further decrease the response rate. Lastly, our findings are based on the response from a single representative from the hospital. It is reasonable to think that there could be some variability in response if multiple practitioners from the hospital completed the survey.

Our survey indicates that EIAG dosing strategies have become increasingly adopted in pediatric patients but are still only utilized in just over 60 % of hospitals caring for children. There remains room for improvement in both the utilization of, and education on, existing pediatric data. Dosing strategies to optimize the pharmacokinetic–pharmacodynamic principles of β-lactam antimicrobials, including EIBL and CIBL, are used with much lesser frequency in 25 % of hospitals. Further study into EIBL and CIBL will provide valuable data that can be used to support increased adoption of these dosing strategies in children. Focused education efforts, along with ongoing ASP strategies, where present, remain important in the pursuit of optimizing pediatric antimicrobial dosing.

Conflicts of interest

C.A. Knoderer, K.R. Nichols, and E.G. Fox have no potential conflicts of interest to disclose.

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