Hospital-wide Description of Clinical Indications for Pediatric Anti-infective Use

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ABSTRACT

Purpose: This study is the first description of hospital-wide anti-infective use according to clinical indication for a pediatric hospital. Children's Hospital Colorado (CHCO) is uniquely poised to examine its anti-infective use after the implementation of provider-selected order indications (PSOIs), which are distinct from Diagnosis Related Group classifications in that they are used for clinical treatment as opposed to final diagnosis codes for billing and thus are more granular.

Methods: This study used our institution's mandatory PSOIs to describe overall clinical indications for anti-infective use. For 2016, all anti-infective orders were extracted from the electronic medical record (Epic), including drug name, route, prescribing unit, and PSOI. We calculated the number of times each drug was associated with each indication and the number of times an indication was attributed to each drug, and then analyzed these data in Excel.

Findings: There were 29,258 orders at CHCO in 2016 with at least 1 indication. The most common clinical indication was "prophylaxis—medical/surgical," accounting for 23% of all orders and commonly associated with cefazolin (42% of prophylaxis—medical/surgical orders). This was followed by the indications of "sepsis/bacteremia" and "pneumonia/sinusitis." The most commonly prescribed anti-infectives for nonprophylactic clinical indications were IV vancomycin (14%), ceftriaxone (11%), and ampicillin (6%).

Implications: Knowledge of the clinical reasons for hospital-wide anti-infective use enables hospitals to identify targets for improved use through education and guideline and policy development. This description provides better details than billing codes about the clinical reasons anti-infectives are used and offers a useful template for implementation at other hospitals. (*Clin Ther*. 2019;41:1605—1611) © 2019 Elsevier Inc. All rights reserved.

Keywords: Anti-infectives, Antimicrobial stewardship, Clinical indications, PSOI.

INTRODUCTION

Descriptions of hospital-wide anti-infective use have been published, but these do not include the clinical indications for use.[1—3] Rather, they describe overall use (eg, number of vancomycin days) or use according to specific units or specialties. Diagnostic and billing codes (eg, Diagnosis Related Group classifications) are imprecise, as they are not specific to the anti-infective order and therefore cannot provide a complete image of clinical reasoning for therapeutic treatment. Historically, chart review was the only reliable way to discern the specific clinical reason for the use of an anti-infective, particularly in medically complex situations, but this method is too

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cumbersome to undertake for an entire hospital given the number of anti-infective orders per year. As an example of why diagnostic billing codes are imprecise, consider the case of a medically complex child admitted for bronchiolitis who is prescribed amoxicillin and later cephalexin during his stay. It would be difficult with diagnostic codes and anti-infective use data to discern that the cephalexin was prescribed to treat tracheitis, a complication of the child's intubation for bronchiolitis, and that the amoxicillin was for treatment of a urinary tract infection, a complication of his other medical complexities, particularly if the diagnostic billing codes at discharge did not encompass all of these diagnoses. More specific descriptions of the clinical indications for anti-infective use provide useful data for pharmacists, clinicians, and antimicrobial stewards hoping to encourage more judicious choices. To our knowledge, a study with precise information on the specific clinical indications associated with anti-infective orders has not been published.

Children's Hospital Colorado (CHCO) is uniquely able to harness these data due to the implementation in 2016 of mandatory provider-selected order indications (PSOIs) for all anti-infectives. This provider-selected indication for anti-infective orders is not the same as a diagnostic or billing code and provides more granular detail on therapeutic reasoning. We[4] examined the implementation of PSOIs, including their clinical accuracy and impact on anti-infective dosing and found that PSOIs improve dosing and concluded that PSOIs are largely clinically accurate (inaccurate for 3.8% of orders), although 20% are incomplete (eg, providers select 1 PSOI when they should select 2). Although simplistic in concept, PSOIs provide a unique snapshot of whole-hospital anti-infective use because the clinical indication chosen by the prescribing provider is associated with the anti-infective at the time of order placement; for example, in the aforementioned example, the provider will have chosen "urinary tract infection" for amoxicillin and "tracheitis" for cephalexin. Therefore, clinical indications provide insight into the clinical reasons behind anti-infective use at the patient level, beyond what is gleaned from use by primary diagnosis billing codes or descriptions of hospital-wide anti-infective use.

For the year 2016, we evaluated the frequency of use of anti-infectives according to PSOI and the frequency of PSOIs according to anti-infective.

MATERIALS AND METHODS

Setting

CHCO is a freestanding, quaternary care pediatric hospital located in the United States with a robust antimicrobial stewardship program (ASP).[5,6] The main hospital has 444 licensed beds, including 82 beds in the neonatal intensive care unit, 32 in the pediatric intensive care unit, 16 in the cardiac intensive care unit, and a hematology and oncology unit with 48 beds. There are ~97,000 patient-days and 15,000 admissions to the hospital every year. The hospital provides both liquid (eg, bone marrow) and solid (eg, heart/liver/kidney) transplants. The ASP at CHCO, "handshake stewardship," is an expanded form of prospective audit and feedback distinguished by: (1) lack of prior authorization; (2) review of all prescribed anti-infectives at 2 time points (24 and 48−72 h); and (3) a rounding-based, in-person approach to feedback by a pharmacist−physician team.

PSOIs were implemented to aid pharmacists and the ASP in drug dosing assessment and for compliance with regulatory standards.[7] Predetermined PSOIs were developed through a collaboration between the ASP and the pharmacy. The infectious diseases physician and ASP pharmacists developed the PSOI based on national and local guidelines, clinical experience, and local formulary; the document was then vetted by unit liaisons and stakeholders (MDs and clinical PharmDs) and approved by various local committees (pharmacy and therapeutics, electronic medical record [EMR] use, and clinical effectiveness). The indications available for each anti-infective are those considered appropriate for the drug by the ASP and pharmacy; for example, cephalexin will not have "meningitis" as a listed indication because this is not clinically appropriate. A full list of the indications available for each drug is given in the Supplemental Appendix (see the online version at https://doi.org/10.1016/j.clinthera.2019.05.008).

After a successful pilot[4] that used PSOIs for 13 drugs in 2013, our institution selected 71 unique predetermined PSOIs that were extended to 53 anti-infectives in 2016, with no more than 12 PSOIs per anti-infective. Twelve was a limit imposed by the

EMR use committee for prescriber speed and to prevent the need for computer scrolling to enhance usability. Due to EMR build restrictions, the PSOIs are in alphabetical order. Attention was thus given to wording of PSOIs for best presentation; for example, "sepsis/bacteremia" is not called "bacteremia/sepsis" as we wanted this indication to populate later, given it is a less precise diagnosis. When ordering a prescription through the EMR (Epic), providers are required to choose at least 1 of these 12 predetermined PSOIs and/or are given an opportunity to write in a free-text "alternative indication." PSOIs describe the reason the provider is prescribing the anti-infective, which may or may not be related to the reason for hospitalization or the final discharge diagnosis based on *International Classification of Diseases, Tenth Revision,* billing codes.

Study design

This is a descriptive study of a unique dataset harnessed from a novel PSOI design. The study describes inpatient anti-infective use according to its clinical indication chosen by the provider at the time of order placement at CHCO's main academic campus. We measured the number of times a drug is used for each indication and the number of times an indication is attributed to each drug. For 2016, all medical and surgical anti-infective orders were extracted from the EMR (Epic), including drug name, route, prescribing unit, and PSOI. In some patient areas, PSOIs are not implemented, and thus these areas were excluded. These excluded areas include the outpatient clinics (where prescriptions are in the outpatient EMR environment) and the operating rooms and emergency departments (where prescriptions are dispensed through automated drug dispensers [eg, Omnicell, Mountain View, California]); no inpatient units were excluded.

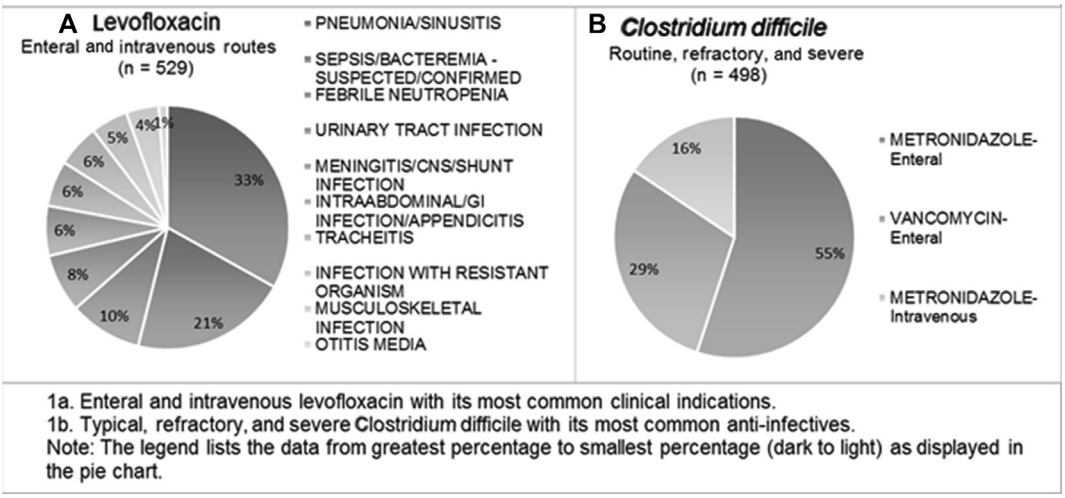
If an order had >1 PSOI, each PSOI was counted separately, and the same drug was attributed to each PSOI. If 2 drugs were used to treat the same indication in a patient, both drugs were attributed to that indication, and the indication will appear twice in the data (once for each drug). These were organized into pivot tables and pie charts for analysis using Excel (Microsoft Corporation, Redmond, Washington; 2016) (Supplemental Appendix in the online version at https://doi.org/10.1016/j.clinthera.2019.05.008).

The medication orders that included a free-text alternative indication were categorized into groups to improve the PSOI by adding/removing or altering indications in an updated version (as noted in the iterative improvement in the Supplemental Appendix [see the online version at https://doi.org/10.1016/j.clinthera.2019.05.008]). The process for this categorization and implementation of update was through discussion with the ASP team and involved stakeholders; for example, levofloxacin orders were frequently given the free-text indication of "prophylaxis" and thus this was added as a predetermined PSOI after discussion with the oncology liaison and pharmacist.[8] The review was approved by the Organizational Research Risk and Quality Improvement Review Panel at CHCO.

RESULTS

Of the 30,734 orders in 2016 with an indication, 92% (n = 28,213) had at least 1 predetermined PSOI selected (and no free-text alternative indication), 3.4% (n = 1045) had both a predetermined PSOI and a free-text alternative indication (and thus 29,258 included for analysis of predetermined PSOIs), and 4.6% (n = 1476) had only a written free-text alternative indication. Those with only a free-text alternative indication are excluded from further descriptive analysis and were used to update the predetermined indications in the EMR. The Supplemental Appendix (see the online version at https://doi.org/10.1016/j.clinthera.2019.05.008) is an interactive Excel file that is sortable by indication (to view associated anti-infectives) or by anti-infective (to view associated indications) and contains the original predetermined indications for each drug during the time of this study (2016) and the modified version as a result of this evaluation, implemented in 2019. Figure 1 presents 2 samples from the pivot table of the Supplemental Appendix (see the online version at https://doi.org/10.1016/j.clinthera.2019.05.008).

There were 29,258 (95%) orders with at least 1 predetermined PSOI; of these, 26,213 (90%) were antibacterials, 1473 (5%) were antifungals, and 1572 (5%) were antivirals. "Prophylaxis—medical/surgical" was the most commonly selected indication, accounting for 6773 orders (23% of the prescriptions). The most common anti-infective used for prophylaxis—medical/surgical was cefazolin, totaling 2866 orders (42%). To focus on medical



1a. Enteral and intravenous levofloxacin with its most common clinical indications.
1b. Typical, refractory, and severe Clostridium difficile with its most common anti-infectives.
Note: The legend lists the data from greatest percentage to smallest percentage (dark to light) as displayed in the pie chart.

Figure 1. Sample of the pivot table and charts from the Supplemental Appendix (see the online version at https://doi.org/10.1016/j.clinthera.2019.05.008) for (A) an anti-infective and (B) an indication.

uses, however, all orders with the PSOI of prophylaxis—medical/surgical were excluded from the following written analysis, but this indication is still present in the data in the Supplemental Appendix (see the online version at https://doi.org/10.1016/j.clinthera.2019.05.008). Note that some medications have their own specific prophylaxis PSOI; these were still included (eg, acyclovir did not have a prophylaxis—medical/surgical option but did have a "prophylaxis—HSV/VZV" option, which was kept in the subsequent analysis).

Of the remaining 22,485 orders not given for prophylaxis—medical/surgical, the most common indications were sepsis/bacteremia (n = 5305 [24%]), followed by "pneumonia/sinusitis" (n = 3129 [14%]) and "intraabdominal/GI infections/appendicitis" (n = 2246 [10%]). Sepsis/bacteremia was most often treated with IV vancomycin (n = 1500 [28%]), followed by IV ampicillin (n = 791 [15%]) and IV ceftriaxone (n = 702 [13%]). Pneumonia/sinusitis was treated most commonly with enteral amoxicillin-clavulanate (n = 615 [20%]), enteral amoxicillin (n = 602 [19%]), and IV ceftriaxone (n = 500 [16%]), and intraabdominal/GI infections/appendicitis was most commonly treated with IV metronidazole (n = 746 [34%]) and IV ceftriaxone (n = 533 [24%]), followed by IV meropenem (n = 139 [6%]).

The most commonly prescribed anti-infectives for our medical orders were IV vancomycin (n = 3119 [14%]), IV ceftriaxone (n = 2466 [11%]), and IV ampicillin (n = 1261 [6%]). IV vancomycin was most commonly prescribed with an indication of sepsis-bacteremia (n = 1500 [48%]), "meningitis/CNS/shunt infection" (n = 496 [16%]), and pneumonia/sinusitis (n = 305 [10%]). IV ceftriaxone was most commonly prescribed with an indication of sepsis/bacteremia (n = 702 [28%]), intraabdominal/GI infections/appendicitis (n = 533 [22%]), and pneumonia/sinusitis (n = 500 [20%]). IV ampicillin was most commonly prescribed with an indication for sepsis/bacteremia (n = 764 [70%]), pneumonia/sinusitis (n = 156 [12%]), and meningitis/CNS/shunt infection (n = 127 [10%]).

Due to the high percentage of antivirals and antifungals that are used for medical/surgical prophylaxis, we calculated the following with the additon of the 6773 "Prophylaxis-medical/surgical" orders to appropriately capture the full use of antivirals and antifungals. The most common antivirals were enteral acyclovir (n = 493 [407 of which were for the indication of HSV/VZV prophylaxis]), representing 1.7% of all anti-infective orders (n = 29,258); IV acyclovir (n = 409 [1.4%], 178 of which were for "neonatal HSV" and 137 of which were for HSV/VZV prophylaxis); and enteral

valganciclovir (n = 260 [0.09%], 175 of which were for CMV/EBV prophylaxis). The most common antifungals were IV micafungin (n = 504 [1.7%], 304 of which were for medical/surgical prophylaxis and 104 of which were for invasive mold infection), IV fluconazole (n = 301 [1.0%], 145 of which were for medical/surgical prophylaxis), and enteral fluconazole (n = 309 [1.0%], 165 of which were for prophylaxis). Details are provided in the Supplemental Appendix (see the online version at https://doi.org/10.1016/j.clinthera.2019.05.008).

Categorization of the free-text alternative indications was done to improve the predetermined indications. The categories can be summarized as either: (1) another term for a PSOI that is already in the list (eg, "asplenia" instead of prophylaxis—medical/surgical); (2) a more in-depth description of the patient's unique presentation (eg, "aspiration" instead of pneumonia/sinusitis); (3) an indication that was added to the available PSOI list during quality improvement revision (eg, "cystic fibrosis exacerbation"); (4) an indication that the ASP team does not want to add to the available PSOIs to discourage the use of a drug for that indication (eg, "urinary tract infection" for azithromycin); or (5) an elaboration of the selected predetermined PSOI (eg, "infection with enterococcus and enterobacter"). The Excel file in the Supplemental Appendix (see the online version at https://doi.org/10.1016/j.clinthera.2019.05.008) contains a full list of the predetermined indications for each anti-infective, the written-in PSOIs, and the revised version of the predetermined indications resulting from this study.

DISCUSSION

The aim of the current study was to describe the clinical reasons for anti-infective use in a freestanding, quaternary care children's hospital; to our knowledge, this study is the first of its kind in the inpatient setting. PSOIs have been proven accurate in their application to diagnoses and effective in decreasing the number of inappropriate prescriptions.[4] It is also likely, although very difficult to prove, that the list of appropriate indications for each drug causes providers to think more thoroughly about their drug choice if they are prescribing a drug for a reason that does not appear on the PSOI list of the order; this theory is supported by the associated decrease in percentage of children ever receiving anti-infectives (decreasing by 10%) and the overall drop in anti-infective use.[9] Indeed, in the outpatient setting, a declaration of the clinical indication for anti-infective use decreased prescribing in one study.[10] Analysis of these PSOIs allow the ASPs to understand anti-infective use at a hospital in more granular detail than general descriptions of anti-infective use and diagnostic codes, which are uncoupled from their clinical indication for use.

PSOIs may not only aid with prescribing review,[4,11] but they also provide insight into prescribing habits and potential targets for local stewardship interventions. Guideline development and improvement provide the most obvious target. For example, our results reveal that a large portion of our orders are associated with prophylaxis—medical/surgical, which gives our stewardship team cause to review these orders to determine the appropriateness of surgical prophylactic treatment in our hospital, a study that we are currently conducting.[12] In addition, the practice of treating hospitalized patients for otitis media (n = 412, in patients hospitalized for other reasons) is being evaluated because, in some months, it contributes up to 50 days of anti-infective therapy per 1000 patient-days on our medical wards, even though it is a diagnosis often amenable to a wait-and-watch approach, perhaps even in those <2 years of age in the hospitalized setting. Some commonly chosen indications, such as "skin/soft tissue infection" (n = 1420), "febrile neutropenia" (n = 1176), and "meningitis/shunt infection" (n = 1153), do not yet have local inpatient guidelines and will be prioritized for guideline development. It is also notable that much of the antifungal and antiviral use is related to medical prophylaxis; this may need an alternate stewardship approach to those traditionally described. In addition to local hypothesis generation that can be harnessed into quality improvement, institutions that adopt PSOIs can use these comparative datasets to pinpoint variability and open avenues for change.

The use of PSOIs presents certain limitations. First, although PSOIs are likely more accurate than diagnostic billing codes, they are still flawed. In our previous study, of 604 orders evaluated, 120 were only partially correct (eg, patient with PSOI of sepsis/bacteremia should also have had a PSOI of pneumonia/sinusitis), and another 23 were incorrect (PSOI did not reflect clinical diagnosis determined on

chart review)[4]; thus, up to 3.8% of the indications in this article may be inaccurate. Sepsis/bacteremia was the most common PSOI to be only partially correct. A second limitation is the restriction on the number of PSOIs allowed per drug to 12; this approach necessitated combining certain indications (eg, sepsis/bacteremia, pneumonia/sinusitis) that would be more clinically helpful and descriptive if separated. For example, the PSOI of pneumonia/sinusitis does not distinguish ventilator-associated pneumonia from community-acquired pneumonia. However, our stakeholder and leadership input strongly indicated that our list should be optimized for speed and lack of computer screen scrolling for prescriber usability. Third, PSOIs are not changed with a change in diagnosis. For example, if an anti-infective is prescribed for sepsis/bacteremia and later the child is diagnosed with pneumonia/sinusitis, the PSOI is not altered unless a new order is written. Fourth, this study was conducted at a center with a robust stewardship program (ie, Handshake Stewardship), which likely influences overall prescribing choices and clinical pharmacist vigilance. A benefit of this program may be that its presence likely prevents "gaming"; that is, filling in an inaccurate PSOI in an effort to make prescribing appear compliant, as all anti-infective orders are reviewed by the ASP team with in-person feedback to prescribers. Because of the unique design of the stewardship program, results may not be similar in other institutions. These limitations add caveats to the interpretability and applicability of these data, although they still represent the most accurate available without chart review linking anti-infective order to a specific clinical indication for use.

CONCLUSIONS

This study offers a model that other institutions can replicate to monitor hospital-wide anti-infective use for their own clinical use and stewardship interventions in more granular detail than previously available. The strength of this description is best shown in the interactive online materials (see the Supplemental Appendix in the online version at https://doi.org/10.1016/j.clinthera.2019.05.008).

Although we have presented data for the most common anti-infectives and clinical indications, we encourage readers to explore other indications and anti-infectives in the Supplemental Appendix (see the online version at https://doi.org/10.1016/j.clinthera.2019.05.008) for a more comprehensive view of anti-infective use at a freestanding, acute-care pediatric hospital. If use of PSOIs was widespread, in both the inpatient and outpatient settings, it would facilitate a greater understanding of anti-infective use and help drive the national conversation about prescribing.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinthera.2019.05.008.

Ms. Williams was responsible for the formal analysis; writing of the original draft, and review and editing of the manuscript; and visualization. Ms. Obermeier contributed to writing of the original draft and formal analysis, and visualization. Dr. Hurst contributed to conceptualization, methodology, investigation, review and editing of the manuscript, and funding acquisition. Dr. Saporta-Keating was responsible for writing of the original draft of the manuscript and formal analysis. Ms. Pearce was responsible for data curation. Dr. MacBrayne was responsible for investigation, formal analysis, and review and editing of the manuscript. Dr. Child was responsible for conceptualization, methodology, investigation, review and editing of the manuscript, and funding acquisition. Dr. Parker was responsible for conceptualization, methodology, investigation, review and editing of the manuscript, supervision, project administration, and funding acquisition.

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