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Michael J. Smith

Duke University

Cary Thurm

Children's Hospital Association

Samir S. Shah

University of Cincinnati

Sameer J. Patel

Ann & Robert H. Lurie Children's Hospital

Matthew P. Kronman

University of Washington - Seattle Campus

See next page for additional authors

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Authors

Michael J. Smith, Cary Thurm, Samir S. Shah, Sameer J. Patel, Matthew P. Kronman, Jeffrey S. Gerber, Joshua D. Courter, Brian R. Lee, Jason G. Newland, and Adam L. Hersh

Research Brief

Route of administration for antibiotics with high oral bioavailability

Michael J. Smith MD, MSCE¹, Cary Thurm PhD², Samir S. Shah MD, MSCE³, Sameer J. Patel MD⁴,
Matthew P. Kronman MD, MSCE⁵, Jeffrey S. Gerber MD, PhD⁶, Joshua D. Courter PharmD⁷,
Brian R. Lee MPH, PhD⁸, Jason G. Newland MD, MEd⁹ and Adam L. Hersh MD, PhD¹⁰

¹Division of Pediatric Infectious Diseases, Duke University Medical Center, Durham, North Carolina, ²Children's Hospital Association, Overland Park, Kansas, ³Divisions of Hospital Medicine and Infectious Diseases, Cincinnati Children's Hospital Medical Center and the University of Cincinnati College of Medicine, Cincinnati, Ohio, ⁴Division of Pediatric Infectious Disease, Ann & Robert H. Lurie Children's Hospital, Chicago, Illinois, ⁵Division of Infectious Diseases, Seattle Children's Hospital, University of Washington School of Medicine, Seattle, Washington, ⁶Division of Infectious Diseases, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, ⁷Division of Pharmacy, Cincinnati Children's Hospital Medical, Cincinnati, Ohio, ⁸Division of Infectious Diseases, Children's Mercy Hospital-Kansas City, Kansas City, Missouri, ⁹Division of Pediatric Infectious Diseases, Washington University School of Medicine, St Louis, Missouri and ¹⁰Department of Pediatrics, Division of Pediatric Infectious Diseases, University of Utah, Salt Lake City, Utah

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National stewardship guidelines recommend that hospitals develop interventions to increase use of oral antibiotics.¹ Transition from intravenous to oral route of administration for antibiotics with high oral bioavailability (HOB) is a simple intervention shown to decrease cost and length of hospitalization. We sought to determine the prevalence of use and route of administration of HOB antibiotics at children's hospitals to determine how frequently intravenous to oral switch might be feasible and to quantify potential cost savings of this strategy in hospitalized children.

Methods

We used 2015 data from the Pediatric Health Information System (PHIS), an administrative and clinical database maintained by the Children's Hospital Association.² Patients were included if they were potentially eligible for intravenous to oral switch as defined by (1) receipt of an HOB antibiotic, (2) receipt of ≥ 1 nonantibiotic oral medication on the same day as the antibiotic, and (3) hospital stay > 2 days. The HOB antibiotics included clindamycin, metronidazole, ciprofloxacin, levofloxacin, doxycycline, linezolid and rifampin, all of which have $\geq 80\%$ oral bioavailability.³ Antimicrobials typically used for prophylaxis (azithromycin, trimethoprim-sulfamethoxazole, and azoles) were excluded because they are usually given orally and it is difficult to distinguish treatment from prophylaxis using PHIS data.

Days of therapy (DOT) for each drug were reported overall and stratified by route and hospital. Oral administration of HOB antibiotics was reported using 2 metrics: (1) the percentage of all

HOB antibiotic DOT that were administered orally (% PO DOT) and (2) the percentage of all patients receiving HOB antibiotics who received doses orally, either completely or in combination with intravenous therapy. If children received antibiotic doses via both routes on the same day it was counted as an oral DOT. Specific diagnoses were identified using All Patient Refined Diagnosis Related Groups (APR-DRGs).

Antibiotic costs were estimated using institution-specific cost-to-charge ratios. Maximal cost-savings were estimated using the same institution-specific cost-to-charge ratios under the alternate case of administering all doses of HOB antibiotics orally.

Results

Data from 48 freestanding children's hospitals were included: 38,933 children received 221,535 DOT of HOB antibiotics and at least 1 nonantibiotic oral medication, accounting for $\sim 17\%$ of all PHIS antibiotic use. Overall, 35.8% of all HOB DOT were administered orally, ranging from 21.3% to 63.8% across institutions. Clindamycin was the most commonly prescribed HOB antibiotic, accounting for nearly half of all HOB DOT (Table 1). However, it had the lowest percentage of oral DOT (21.7%) and the highest percentage (63.0%) of intravenous-only receipt. Cellulitis was the most common diagnosis associated with clindamycin use, for which 27.6% of DOT were oral. Other common diagnoses included pneumonia (26% oral DOT) and musculoskeletal infections (16% oral DOT).

The HOB antibiotics most likely to be prescribed orally were rifampin (80.5% of all DOT) and doxycycline (70.8% of all DOT). Fluoroquinolones were administered orally for only half of all DOT. However, there was significant variation in the proportion of oral fluoroquinolone use across institutions, ranging from 27.0% to 98.3% for ciprofloxacin and from 0 to 100% for levofloxacin. Similarly, less than one-third of linezolid DOT were administered orally, ranging from 0 to 100% across institutions.

Author for correspondence: Michael J. Smith, MD, MSCE, Pediatric Infectious Diseases, Box 3499 Duke University Medical Center, Durham, North Carolina, 27710. E-mail: michael.j.smith@duke.edu

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Table 1. Prevalence of High Oral Bioavailability Antibiotic Use and Proportion of Oral Administration

Drug	DOT	% PO DOT Overall	Min %	Max %	No. of Patients	Route of Antibiotic Administration, % Patients		
						PO Only	IV Only	Both
Clindamycin	102,628	21.7	4.7	65.7	21,956	9.1	63.0	27.9
Metronidazole	52,478	38.4	12.3	71.7	10,270	32.1	53.0	15.0
Ciprofloxacin	26,125	55.1	27.0	98.3	5,480	53.9	29.8	16.3
Levofloxacin	14,341	50.4	0.0	100.0	2,496	48.6	34.6	16.8
Linezolid	9,820	30.8	0.0	100.0	1,644	32.3	54.3	13.4
Doxycycline	8,189	70.8	29.6	98.3	1,522	61.2	20.8	17.9
Rifampin	7,954	80.5	0.0	100.0	998	75.3	12.8	11.9
Overall	221,535	35.8	21.3	63.8	38,993	22.9	50.8	26.3

Note. PO, per oral; DOT, days of therapy; Min %, % PO DOT at hospital with lowest % PO DOT for each drug; Max %, % PO DOT at hospital with highest % PO DOT for each drug; IV, intravenous.

The total hospital cost for all HOB antibiotics administered during the study period was \$11,662,963. The estimated cost had all doses been administered orally was \$5,891,137.

Discussion

Only 36% of HOB antibiotic DOT were administered orally in this cohort of children receiving other oral medications. These data suggest that intravenous to oral switch programs should be prioritized in children's hospitals. Clindamycin should be a priority target for such programs because it is both commonly used and often administered intravenously. It is well-documented that intravenous to oral switch is safe and effective for children with osteomyelitis^{4,5} and complicated pneumonia,⁶ 2 common indications for clindamycin. However, in this cohort, children with these diagnoses were more likely to be treated with intravenous clindamycin.

Intravenous to oral switch programs would be cost saving in pediatrics. We estimated a nearly 50% decrease in drug cost alone. Although this represents the maximum potential savings in direct drug costs, it does not account for additional cost savings due to drug administration, shorter hospital stays, avoidance of outpatient parenteral antibiotic therapy and catheter-associated infections.

The reasons for underutilization of oral administration are uncertain. Some clinicians and parents may have the perception that intravenous antibiotics are more effective⁷ or that insurance companies mandate intravenous therapy for reimbursement of hospitalization. Future studies should focus on differences in clinical outcomes between children who received HOB antibiotics via oral as compared to intravenous routes.

This analysis has several limitations. We utilized administrative data to identify children eligible for oral conversion. Although this approach has been used in other studies,⁸ we could not account for patient factors such as severity of illness or intolerance of oral antibiotics, though inclusion in this cohort required receipt of another oral medication. We did not exclude diagnoses that mandate intravenous therapy such as endovascular or central nervous system infections. However, it is unlikely that differences in the prevalence of these infections would explain more than a minority of the variation in use of oral antibiotic across hospitals. Finally, because PHIS only includes data from freestanding children's hospitals, most of which have

formal ASPs,⁹ these results may not be generalizable to other settings.

In conclusion, we observed frequent intravenous administration of HOB antibiotics at children's hospitals. Intravenous to oral conversion programs, with a focus on clindamycin and fluoroquinolones, are potential high-impact targets for antimicrobial stewardship.

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