Assessment of Intravenous versus Oral Antimicrobials in a Large Regional Health Authority

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ABSTRACT

Background: Many antimicrobials given by the intravenous (IV) route have oral (PO) formulations with high oral bioavailability. The advantages of using the PO rather than the IV formulation include lower risk of adverse reactions, shorter length of hospital stay, and lower health care costs.

Objectives: The primary objective was to determine the proportions of patients who received the IV and PO formulations of antimicrobials with high oral bioavailability. The secondary objectives were to determine the proportion of patients who were eligible to receive PO antimicrobials from the start of treatment, the proportion who qualified for IV-to-PO step-down, and areas of improvement to increase use of PO antimicrobials.

Methods: A retrospective chart review was conducted in hospitals in the Fraser Health Authority, British Columbia, between October 18, 2019, and March 5, 2020. Two hundred charts were randomly selected for patients who had received either azithromycin, ciprofloxacin, clindamycin, fluconazole, levofloxacin, linezolid, moxifloxacin, metronidazole, sulfamethoxazole–trimethoprim, or voriconazole.

Results: Of the 200 patients, 124 (62.0%) received the PO formulations, while 76 (38.0%) received the IV formulations. Of the 76 patients receiving IV antimicrobials, 39 (51.3%; 95% confidence interval 44.7%–57.9%) were eligible to receive PO antimicrobials from the start of treatment or could have been stepped down from IV to PO administration.

Conclusions: More than half of patients who received IV therapy were eligible to receive the PO formulation of antimicrobials known to have high oral bioavailability; relative to earlier studies, this proportion has not improved over time. This finding highlights the need for continued vigilance in encouraging the use of PO rather than IV formulations for hospitalized patients.

Keywords: antimicrobials, intravenous therapy, oral therapy, intravenous-to-oral step-down

RÉSUMÉ

Contexte : De nombreux antimicrobiens administrés par voie intraveineuse (IV) ont des formulations orales (PO) avec une biodisponibilité orale élevée. Les avantages de l'utilisation de cette formulation plutôt que de la formulation IV comprennent un risque moins élevé d'effets indésirables, une durée d'hospitalisation plus courte et des coûts de soins de santé inférieurs.

Objectifs : L'objectif principal visait à déterminer les proportions de patients ayant reçu les formulations IV et PO d'antimicrobiens à haute biodisponibilité orale. Les objectifs secondaires consistaient, quant à eux, à déterminer la proportion de patients pouvant recevoir des antimicrobiens par voie orale dès le début du traitement, la proportion de patients qualifiés pour passer de l'administration IV à l'administration par voie orale et les domaines d'amélioration pour augmenter l'utilisation des antimicrobiens par voie orale.

Méthodes : Un examen rétrospectif des dossiers a été effectué dans les hôpitaux de la Fraser Health Authority, en Colombie-Britannique, entre le 18 octobre 2019 et le 5 mars 2020. Deux cents dossiers ont été sélectionnés au hasard pour les patients qui avaient reçu soit de l'azithromycine, de la ciprofloxacine, de la clindamycine, du fluconazole, de la lévofloxacine, du linézolide, de la moxifloxacine, du métronidazole, de la sulfaméthoxazole-triméthoprime ou du voriconazole.

Résultats : Sur les 200 patients, 124 (62,0 %) ont reçu les formulations PO, tandis que 76 (38,0 %) ont reçu les formulations IV. Sur les 76 patients recevant des antimicrobiens par voie intraveineuse, 39 (51,3 %; intervalle de confiance à 95 % 44,7 % à 57,9 %) étaient admissibles pour recevoir des antimicrobiens par voie orale dès le début du traitement ou auraient pu passer de l'administration IV à l'administration par voie orale.

Conclusions : Plus de la moitié des patients ayant reçu une thérapie IV étaient admissibles pour recevoir la formulation PO d'antimicrobiens connus pour avoir une biodisponibilité orale élevée; par rapport aux études antérieures, cette proportion ne s'est pas améliorée avec le temps. Cette découverte souligne la nécessité d'une vigilance continue pour encourager l'utilisation de formulations PO plutôt que IV pour les patients hospitalisés.

Mots-clés : antimicrobiens, thérapie intraveineuse, thérapie orale, passage voie intraveineuse voie orale

INTRODUCTION

Hospitalized patients are often given intravenous (IV) formulations of antimicrobials that also have oral (PO) formulations with excellent bioavailability.[1] Use of PO rather than IV antimicrobials offers advantages such as lower costs, shorter length of hospital stay, and lower risk of adverse events.[2] A previous evaluation in the Fraser Health Authority found suboptimal use of PO antimicrobials.[3] This evaluation was undertaken to investigate the current state of antimicrobial prescribing in the same health authority to determine if the rate of prescribing of PO antimicrobials had increased relative to prescribing of IV formulations.

The primary objective was to determine the proportion of patients who received IV or PO formulations from a prespecified list of antimicrobials known to have high oral bioavailability. The secondary objectives were to determine the proportion of patients who could have received PO antimicrobials upon treatment initiation and the proportion of patients eligible for step-down from IV to PO administration, and to identify areas of improvement to increase PO antimicrobial usage.

METHODS

Data collection for this retrospective chart review did not include patient identifiers. The information collected was available only to the investigators and remained confidential. The Fraser Health Research and Ethics Board provided an exemption from ethics approval for this study.

Antimicrobial Selection

Fraser Health formulary antimicrobials with high oral bioavailability were selected for analysis. The institution's existing IV-to-PO step-down protocols, as well as those of Northern Health, Vancouver Coastal Health, Alberta Health Services, and the Nebraska Medical Center, were examined to determine whether they listed the selected antimicrobials.[1,4-6] Ciprofloxacin, clindamycin, fluconazole, linezolid, moxifloxacin, metronidazole, sulfamethoxazole–trimethoprim, and voriconazole were common to all lists.[1,4-6] Some lists also included azithromycin or levofloxacin, and both of these medications were included in the review.

Setting and Participants

An evaluation of electronic medical records was conducted in Fraser Health hospitals between October 18, 2019, and March 5, 2020; this period was chosen because of the historically higher rates of respiratory infections and antimicrobial use during winter. Fraser Health is a large health authority with a spectrum of facilities, ranging from small rural community hospitals to large urban tertiary teaching centres. The following hospitals were included in the study: Abbotsford Regional Hospital and Cancer Centre, Burnaby Hospital, Chilliwack General Hospital, Delta Hospital, Eagle Ridge Hospital, Fraser Canyon Hospital, Langley Memorial Hospital, Mission Memorial Hospital, Peace Arch Hospital, Queen's Park Care Centre, Ridge Meadows Hospital, Royal Columbian Hospital, and Surrey Memorial Hospital.

Patients older than 17 years of age who were admitted to any of these facilities and received 1 of the 10 prespecified antimicrobials during the study period were eligible for inclusion.

Sample Size

A MEDITECH report for any of the prespecified antimicrobials (IV or PO formulation) yielded a total of 19 343 orders. From this list, 200 charts were selected using systematic, random sampling with proportional representation from sites. This sample achieved a confidence interval of 95% and 6.6% margin of error for the primary outcome (proportions of patients who received IV and PO antimicrobials). The sample size was based on the assumption that 37% of all orders for IV antimicrobials could have been for PO formulations, based on an unpublished scoping review of previously published IV-to-PO evaluations identified through searches in Google Scholar, PubMed, and Ovid MEDLINE.[2,3,7,8]

Data Extraction

A student investigator (M.D.) used a pilot-tested data extraction form to collect data from the health region's pharmacy information software system (MEDITECH, Medical Information Technology Inc). Data extraction from the first 5% of charts was also conducted by the 2 other investigators (T.S., A.M.T.) to confirm accuracy. Another audit was done midway through the data collection process to confirm continued accuracy.

According to a draft document entitled *Sequential Antimicrobial Therapy in Adults – Best Practice Recommendations,* prepared in 2020 by the BC Health Authorities Pharmacy & Therapeutics Committee, the criteria for initiating or converting to PO administration are defined as the absence of nausea, vomiting, dysphagia, gastrointestinal (GI) bleeding, loss of consciousness without a nasogastric or orogastric tube present, poorly functioning GI tract (ileus, GI obstruction, short GI transit time, malabsorption, gastrectomy, short bowel syndrome), or any significant drug interactions between a fluoroquinolone and enteral formula. Additionally, patients had to be able to tolerate other oral medications and a solid or liquid diet. Those in shock and receiving vasopressors, as well as those with conditions that could only be treated with IV antimicrobials (e.g., meningitis), were considered ineligible for PO therapy. Only descriptive statistics were used.

Consultation with the antimicrobial stewardship (AMS) group concluded that IV antimicrobials were appropriate for patients with blood culture results pending. For those with positive results on blood culture, IV therapy was deemed appropriate, whereas negative results meant that step-down to PO therapy should occur.

Concurrent antimicrobials were noted but were not assessed for appropriateness of route of therapy, given that for each patient included in the study, the sole focus was the antimicrobial identified in the MEDITECH report.

RESULTS

Of the 200 charts initially selected for review, using site-based, proportional, systematic random sampling, 13 documented an order for an antimicrobial that was not administered; data were not collected for those patients, and in each case the next randomized chart from the same hospital was selected. Of the final sample of 200 patients, 124 (62.0%) received PO antimicrobials, while the remaining 76 (38.0%) received IV medications (Table 1, Figure 1).

Of the 76 patients receiving IV therapy, 5 were considered eligible to receive IV antimicrobials because they had positive results on blood culture. Thirty-nine patients (51.3%, 95% confidence interval 44.7%–57.9%) could have been initiated on or stepped down to PO therapy. More specifically, 18 (23.7%) of the 76 patients should have been initiated on PO therapy, and 21 (27.6%) should have been converted to PO therapy (Figure 1). The remaining 32 patients (42.1%) had a legitimate reason to receive IV antimicrobials (i.e., ineligible to receive PO antimicrobials; see Table 1).

The following areas were identified as possible targets for future interventions: therapy for respiratory infections; use of azithromycin, ciprofloxacin, or moxifloxacin; and therapy for patients whose blood culture results are negative. IV antimicrobials were most commonly used to treat respiratory infections (Table 1); further investigation is required to determine why this was the case. Furthermore, it is unknown why azithromycin, ciprofloxacin, and moxifloxacin were disproportionately administered by the IV route (Table 1). Finally, patients may require IV antimicrobials while waiting for the results of blood culture; however, once a negative result is determined, patients should be assessed and switched to PO therapy as soon as possible.

For the 76 patients who received IV antimicrobial therapy, the total number of days of IV therapy was 218. The number of days of IV therapy that could have been saved with appropriate use of PO therapy was calculated post hoc. For the 18 patients who could have been initiated on PO therapy, 44 days of IV therapy might have been saved. For the 21 patients with negative blood culture results, 26 days of IV therapy could have been saved. Therefore, in total, 70 (32.1%) of the 218 days of IV therapy could have been saved with use of PO antimicrobials.

DISCUSSION

More than half of the patients in this study were eligible to receive PO antimicrobials either from initiation of therapy or through IV-to-PO conversion during treatment. This

TABLE 1. Patient Characteristics

Characteristic	No. (%) of Patients[a] (*n* = 200)	
All patients		
Age (years) (median and range)	68.4	(21–103)
Sex, male	101	(50.5)
Hospital site		
Abbotsford Regional Hospital and Cancer Centre	34	(17.0)
Burnaby Hospital	9	(4.5)
Chilliwack General Hospital	21	(10.5)
Delta Hospital	4	(2.0)
Eagle Ridge Hospital	7	(3.5)
Fraser Canyon Hospital	5	(2.5)
Langley Memorial Hospital	9	(4.5)
Mission Memorial Hospital	8	(4.0)
Peace Arch Hospital	9	(4.5)
Queen's Park Care Centre	1	(0.5)
Ridge Meadows Hospital	7	(3.5)
Royal Columbian Hospital	28	(14.0)
Surrey Memorial Hospital	58	(29.0)
Duration of stay (days) (mean and range)	4.4	(1–102)
Indication for antimicrobials		
Respiratory infection	85	(42.5)
Urinary tract infection	13	(6.5)
Gastrointestinal infection	13	(6.5)
Sepsis or bacteremia	11	(5.5)
Fungal infection	8	(4.0)
Abscess	6	(3.0)
Cellulitis	6	(3.0)
Colitis	3	(1.5)
Other	55	(27.5)
Patients receiving IV antimicrobials	***n* = 76**	
Indication		
Respiratory infection	49	(64.5)
Sepsis or bacteremia	7	(9.2)
Gastrointestinal infection	3	(3.9)
Cellulitis	2	(2.6)
Pancreatitis	2	(2.6)
Shock	2	(2.6)
Other	11	(14.5)
IV antimicrobial received		
Azithromycin	41	(53.9)
Ciprofloxacin	15	(19.7)
Moxifloxacin	12	(15.8)
Fluconazole	3	(3.9)
Linezolid	3	(3.9)
Metronidazole	2	(2.6)
Patients ineligible for PO antimicrobials	***n* = 32**	
Nausea or vomiting	13	(40.6)
Dysphagia	7	(21.9)
NPO order	5	(15.6)
Loss of consciousness without NG/OG tube	3	(9.4)
Shock	2	(6.3)
Interaction or non-adherence	2	(6.3)

IV = intravenous, NG = nasogastric, NPO = nothing by mouth, OG = orogastric, PO = oral.
[a]Except where indicated otherwise.

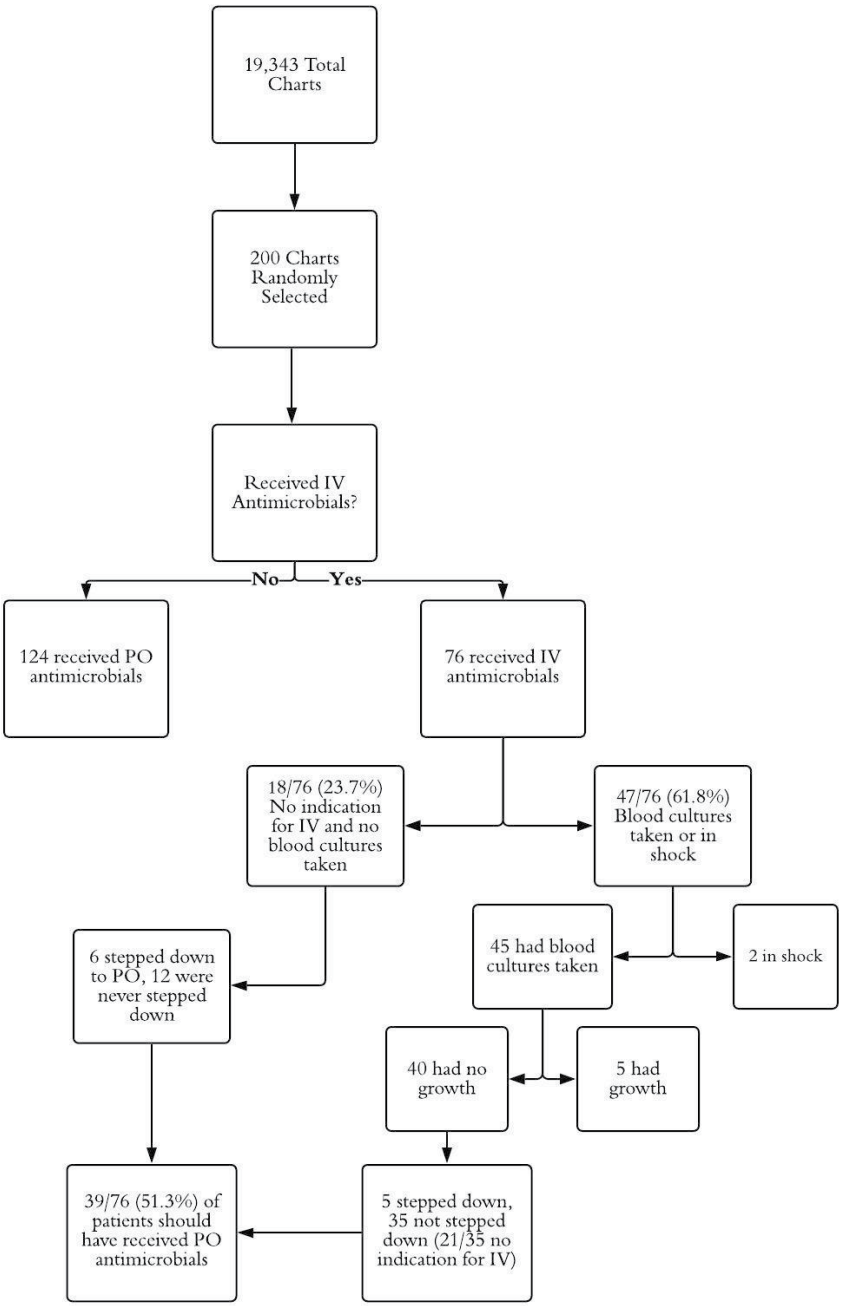

FIGURE 1. Flow chart for analysis of therapy for patients receiving intravenous (IV) or oral (PO) antimicrobials. Those receiving IV antimicrobials were further categorized according to whether IV administration was or was not warranted. Among the 76 patients who received IV antimicrobials, the figure shows 18 patients with no indication and no blood culture and 47 patients with blood culture or shock; in addition, there were 11 patients without blood culture for whom IV therapy was warranted because they were ineligible for PO therapy (e.g., because of dysphagia, shock, nausea and vomiting).

proportion is likely an underestimate, as we did not assess concurrent antimicrobials for appropriateness for IV-to-PO step-down. For example, if the MEDITECH system identified a patient receiving metronidazole PO for whom ceftriaxone IV was also prescribed, only the metronidazole therapy was evaluated for this study; the potential for use of oral ceftriaxone was not assessed.

An additional evaluation showed that 70 days of IV therapy could have been saved if patients had been started on PO therapy or stepped down to PO therapy once appropriate. This result represents an additional area of potential improvement and cost savings in the future.

A previous Fraser Health study investigated patients eligible for conversion to PO therapy and determined that

34.7% (95% confidence interval 29.7%–39.7%) were eligible for IV-to-PO conversion.[3] The current evaluation suggests continued suboptimal use of oral antimicrobials in Fraser Health hospitals (with 27.6% of patients being eligible for step-down), despite focused AMS efforts (e.g., clinical pharmacy assessment of most antimicrobial orders, standardized order sets suggesting PO antibiotics, and recent development of internal clinical practice guidelines for sequential antimicrobial therapy). This situation highlights the need for continued vigilance and periodic re-evaluation. Our results may not directly apply to other jurisdictions, but they serve as a call to action. Whether or not particular organizations have done similar evaluations in the past, and even for those organizations that have had success in reducing unnecessary IV antimicrobial use, we suggest performing or repeating evaluations to determine current status and to identify areas for improvement. In our case, areas for potential improvement include increasing the use of PO therapy for respiratory infections and as the initial route of administration, as well as determining why IV is more frequently prescribed than PO therapy for azithromycin, ciprofloxacin, and moxifloxacin.

One limitation of our study relates to blood culture: we assumed that a negative blood culture result made sepsis or bacteremia unlikely and IV antibiotics unnecessary (according to the appropriateness criteria of our local AMS group). However, it is possible that, despite a negative blood culture result, there may have been valid reasons for a patient to remain on IV antibiotics (e.g., abscess, joint sepsis, intermittent bacteremia). A post hoc assessment suggested that 9 patients may have been in this situation; for these patients, the indications were abscess, gangrene, or "other". If it is assumed that all of these patients received IV antibiotics appropriately, then our original estimate of the proportion who should have received PO therapy upon initiation would be reduced from 27.6% (21/76) to 15.8% (12/76). In our opinion, this more conservative estimate still represents an important problem.

Another limitation was lack of consideration of the impact of clinical practice guidelines on prescribing behaviour. Most notably, some guidelines recommend initial IV antibiotic therapy for patients admitted to hospital for respiratory infections, with switching to PO therapy when the fever abates.[9] Although we may not agree with all aspects of these guidelines, these points could be considered in future analyses.

CONCLUSION

In a randomly selected sample of hospitalized patients receiving antimicrobial therapy, approximately 50% could have been started on or stepped down to PO versions of their medication. This proportion is larger than reported from previous evaluations and supports continued efforts to evaluate and optimize PO antimicrobial use.

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Competing interests: For activities not directly related to this study, Aaron Tejani has received honoraria for presentations from the BC Ministry of Health Research Rounds, Divisions of Family Practice in British Columbia; payments for provision of expert opinion to law firms for cases related to drug harm; and honoraria for participation on the Guidelines, Protocols and Advisory Committee of Doctors of BC. No other competing interests were declared.

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