European Journal of Clinical Microbiology & Infectious Diseases (2019) 38:1915–1923
https://doi.org/10.1007/s10096-019-03626-8

ORIGINAL ARTICLE

Antimicrobial stewardship by academic detailing improves antimicrobial prescribing in solid organ transplant patients

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Received: 4 April 2019 / Accepted: 30 June 2019 / Published online: 19 July 2019

Abstract

We implemented twice-weekly academic detailing rounds in 2015 as an antimicrobial stewardship (AMS) intervention in solid organ transplant (SOT) patients, led by an AMS pharmacist and a transplant infectious diseases physician. They reviewed SOT patients' antimicrobials and made recommendations to prescribers on antimicrobial regimens, diagnostics investigations, and appropriate referrals for transplant infectious diseases consultation. To determine the impact of the intervention, we adjudicated antimicrobials prescriptions using established AMS principles, and compared the proportion of AMS-concordance regimens pre-intervention (2013) with post-intervention (2016) via 4-point-prevalence surveys conducted in each period. All admitted SOT patients who were receiving antimicrobial treatment on survey days were included. Primary outcome was the percentage of antimicrobial regimen adjudicated as AMS concordant. Secondary outcomes were percentage of AMS concordance in patients consulted by transplant infectious diseases; categories of AMS discordance; antimicrobial consumption in defined daily dose/100 patient-days (DDD/100PD); antimicrobial cost in CAD$/PD; and *C. difficile* infections. Balancing measures were length of stay, 30-day readmission, and in-hospital mortality. We compared outcomes using χ^2 test or t-test; significant difference was defined as $p < 0.05$. Pre-intervention surveys included 139 patients, post-intervention, 179 patients, with 62.3% vs. 56.6% receiving antimicrobials, respectively ($p = 0.27$). AMS concordance increased from 69% (60/87) to 83.7% (93/111), $p = 0.01$. Not tailoring antimicrobials was the most common discordance category. AMS concordance under transplant infectious diseases was 82.5% (33/40) pre-intervention vs. 76.6% (36/47) post-intervention, $p = 0.5$. Antimicrobial consumption increased by 15.3% (140.9 vs.162.4 DDD/100PD, $p = 0.001$). Antimicrobial cost, *C. difficile* infection rates and balancing measures remained stable. Academic detailing increased appropriate antimicrobial use in SOT patients without untoward effects.

Keywords Antimicrobial · Stewardship · Organ transplant · Academic detailing

Introduction

Antimicrobial stewardship programs (ASPs) have been advocated to mitigate rapidly rising antimicrobial resistance in health systems globally [1, 2]. Following implementation of ASPs in many jurisdictions, there has been an expansion of literature on the implementation and benefits of antimicrobial stewardship (AMS) [3, 4]. However, literature describing ASPs for solid organ transplant (SOT) recipients remain scarce, precluding our understanding of their potential impact on this population [1, 4, 5]. Indeed, the limited number of new and effective antimicrobial agents, coupled with rising antimicrobial resistance, present unique challenges given SOT patients' vulnerability to infectious complications and frequent exposure to antimicrobials pre- and post-transplantation [6–9]. As organ transplantation increases globally, it is imperative that we safeguard effective antibiotics to ensure the procedure

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10096-019-03626-8) contains supplementary material, which is available to authorized users.

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can be conducted safely and allograft function maintained in the long term [8].

In our academic multi-organ transplant program, over 30% of antimicrobial therapy prescribed for documented or suspected infections were discordant with AMS principles at baseline [5, 10]. We implemented antimicrobial stewardship for SOT patients with academic detailing (also known as prospective audit-and-feedback or post-prescription review) as the main intervention [11–13]. Academic detailing is a behavioral change technique which uses evidence-based education, persuasion, enablement, and modeling to motivate the prescriber to optimize antimicrobial use [1, 14, 15]. The objective of the current study was to determine if this intervention was associated with a change in the proportion of AMS-concordant antimicrobial therapy in SOT patients.

Materials and methods

Study setting

University Health Network (UHN) in Toronto, Ontario, Canada, is an academic teaching hospital affiliated with the University of Toronto. UHN houses Canada's largest multi-organ transplant program, which has a 70-bed capacity. Over 630 transplantations were performed in 2017, involving the heart, lung, liver, pancreas, and kidney. Patients are admitted to their respective primary organ transplant team, composed of staff physicians, surgeons, medical and surgical trainees, nurse practitioners, physician assistants, and pharmacists. Under UHN's medical directives, nurse practitioners and physician assistants have prescribing privileges to initiate and adjust medications (including antimicrobials) and to order routine tests and diagnostic imaging studies. A transplant infectious diseases (TID) service operates with four rotating attending physicians and TID fellows. They consult on patients upon request from the primary team.

The Sinai Health System-University Health Network Antimicrobial Stewardship Program (SHS-UHN ASP) was established in 2009. It has implemented AMS interventions in a wide range of acute care settings, such as critical care, hematologic malignancies, stem cell transplantation, and general medicine [16, 17]. The AMS team for SOT consists of TID physicians (SH) and a pharmacist (MS) specialized in immunocompromised hosts.

Study design

We used serial point-prevalence surveys to evaluate the effectiveness of academic detailing. We compared the proportion of AMS-concordant antimicrobial prescriptions before and after implementing the intervention of regular academic detailing rounds with prescribers caring for SOT patients. Pre-intervention data were 4 historical point-prevalence surveys in 2013, and post-intervention data from 4 surveys in 2016, with academic detailing intervention implemented on November 23, 2015 (Fig. 1) [5]. We included all patients admitted to SOT, irrespective of transplant status, reasons for admission, or consultation by TID. Donors were excluded. All active antimicrobial treatments on survey day were assessed. Routine post-transplant prophylaxis, such as co-trimoxazole prophylaxis against *Pneumocystis jirovecii*, was exempted from adjudication in the point-prevalence surveys.

Antimicrobial stewardship intervention: academic detailing

Academic detailing requires trained clinicians to provide clinically relevant, critically evaluated, accessible, and evidence-informed recommendations to prescribers [11, 12]. For our intervention, academic detailing was led by the immunocompromised host AMS team (MS and SH), who met with prescribers caring for SOT recipients every Monday and Wednesday. Participants were nurse practitioners, a physician assistant, a TID team member, and a transplant pharmacist. The AMS team's recommendations were founded on established AMS principles, literature, and published guidelines pertinent to SOT [10, 18–22]. The recommendations accounted for patient's clinical status, history of infection and colonization, prior antimicrobial exposure, donor cultures, microbiological investigations, source control attainment, and local susceptibility patterns [10, 18]. Common recommendations included a selection of empiric therapy; tailoring (escalation or de-escalation) regimen based on investigation results; defining duration of treatment; referral to TID consultation; modifying route of administration, dose or frequency; and therapeutic drug monitoring [10]. Per SHS-UHN ASP's practice, prescribers were encouraged but not mandated to implement AMS recommendations, an approach described as non-coercive or "handshake stewardship" [17, 23, 24]. Our recommendations were not entered in patients' health records, but only communicated verbally. We revoked all antimicrobial restriction policies in 2011. Prescribers can order any antimicrobial on hospital formulary without pre-approval, irrespective of spectrum of activity. Instead of restriction, we foster knowledge translation to improve prescribing behaviors through collaboration and dialogues, such as academic detailing, local guidelines, and education.

Evaluative method of the intervention: serial point-prevalence surveys

The AMS pharmacist (MS) and clinical trainees on antimicrobial stewardship rotations conducted the point-prevalence surveys. Pre-intervention, the trainee was a Doctor of Pharmacy

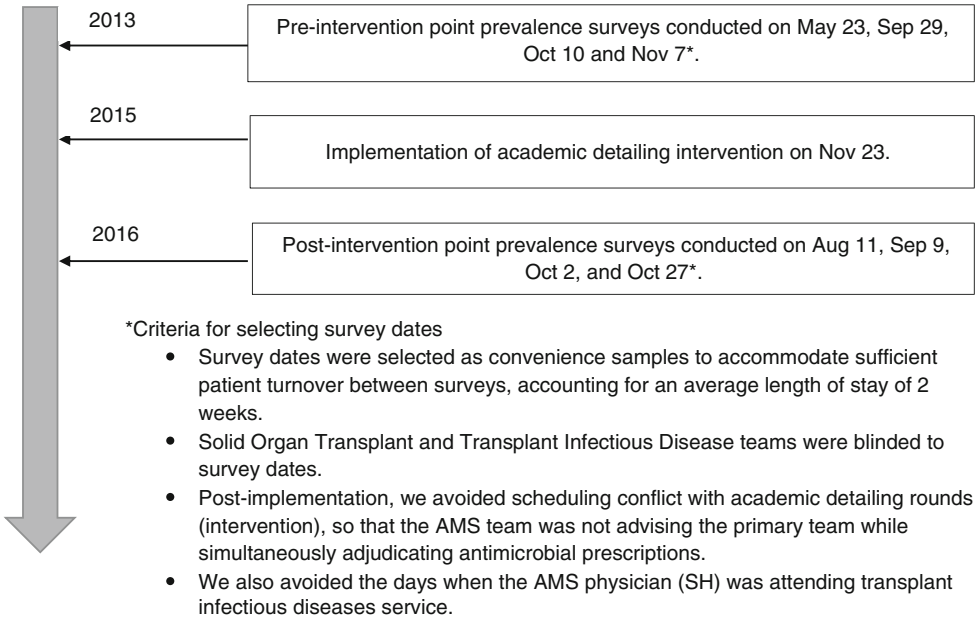

Fig. 1 Timeline of point-prevalence surveys

student [5]. Post-intervention, 3 transplant infectious diseases fellows (post-graduate year 5) and a pharmacy resident (post-graduate year 1) conducted the surveys. The AMS pharmacist provided training on the survey form and materials for adjudicating antimicrobial prescriptions. We identified patients by unit census and collected the following information from electronic health records in the standardized survey form: demographics; antimicrobial allergy history; details of active antimicrobial prescriptions on day of survey; pertinent microbiological investigations; diagnostic imaging results; sign-over notes from the primary and consulting teams; transplant status; procedures history; and relevant past medical history.

We applied the following AMS principles in the adjudication: timely management of antimicrobials (initiated when indicated or discontinued when not needed); selection of antimicrobial with appropriate spectrum of activity to treat the suspected or confirmed infectious syndrome based on most likely causative pathogens; appropriate administration (route, dose, frequency, duration); appropriate tailoring, escalation or de-escalation based on investigations; and use of expertise at point of care, including TID consultation [10]. We also referred to current literature and published guidelines pertinent to SOT patients [10, 18–21]. Antimicrobials were adjudicated as "concordant" or "discordant" with AMS principles, and multiple regimens concurrently active in a patient were evaluated as a single adjudication. Reasons of AMS discordance include empiric regimen being too broad or narrow for the intended indication; lack of tailoring of therapy following results from investigations without justification; duration too long or short for the intended indication; inappropriate regimen (dose, route or frequency) based on pharmacology, pharmacokinetics, and pharmacodynamics; lack of timeliness in initiating necessary antimicrobial regimen, defined as > 24 h after availability of investigation results; and non-infection indications, with the exception of azithromycin for bronchiolitis obliterans pneumonia post-lung transplant.

For quality assurance and determination of inter-rater agreement, two adjudicators (SH and MS) independently but concurrently reviewed the antimicrobial prescriptions of 16 randomly selected patients in 2013 [5]. In 2016, 10 patients were randomly selected for independent adjudication by a different AMS pharmacist (SN) from another institution who was not involved in the care of SOT patients.

Outcome measures

The primary outcome was the percentage of AMS-concordant antimicrobial prescriptions. Secondary outcomes were percentage of AMS-concordant prescriptions in patients consulted by TID, and frequency of each category of AMS discordance. Additional secondary outcomes were antimicrobial consumption in defined daily dose per 100 patient-days (DDD/100 PD) and antimicrobial cost per patient day (C$/PD) during the periods when the two study cohorts were admitted, as well as hospital-acquired *C. difficile* infections per 1000 patient-days (CDI/1000 PD). Balancing measures were average hospital length of stay, unplanned readmission within 30 days, and in-hospital mortality within 30 days. Antimicrobial consumption, costs, and *C. difficile* rates were routinely reported by SHS-UHN ASP to all stakeholders. Length of stay, readmission, and mortality were supplied by the Department of Decision Support. *C. difficile* rates were provided by the Infection Prevention and Control Program at UHN.

Statistical analysis

Baseline characteristics were reported with descriptive statistics. Outcome measures were compared using chi-square test for categorical variables, and *t* test for continuous variables (STATA MP15 Houston, TX, USA). A significant difference was defined by $p < 0.05$. To avoid repeatedly surveying the same patients with prolonged hospitalization, only the first encounter of the patient if he/she was receiving antimicrobial treatment on survey days was included to minimize bias.

Results

The pre-intervention cohort included 139 patients; post-intervention cohort had 179 patients (Table 1). The two cohorts were similar in age (median 57 vs. 57.5 years), age of allograft (median 68.5 vs. 66 days), types of organ transplantation (the lung, kidney, and liver being the most common), and predictive mortality from Charlson comorbidity index [25].

Primary outcome

The number of patients receiving active antimicrobial treatment on survey day in the pre-intervention and post-intervention cohorts were similar, 62.3% vs. 56.6%, $p = 0.27$ (Table 2). The proportion of adjudications classified as antimicrobial stewardship concordant increased from 69% (60/87) pre-intervention to 83.7% (93/111) post-intervention, $p = 0.01$. The most common category of discordance was lack of tailoring of antimicrobial therapy for both cohorts, accounting for 29.6% (8/27) of adjudications pre-intervention, and 44.4% (8/18) post-intervention, $p = 0.31$ (Fig. 2). Details of antimicrobial stewardship-discordant cases in post-intervention cohort are available in Electronic Supplementary Material eTable 1.

Secondary outcomes

Proportion of patients under TID consultation was similar in both cohorts (46% vs. 42.3%, $p = 0.61$). Concordance with antimicrobial stewardship principles under TID was 82.5% (33/40) vs.

Table 1 Baseline characteristics of patients in the pre- and post-intervention cohorts

Baseline characteristics	Pre-intervention	Post-intervention	*P* value
Number of patients	139	196	–
Median age (years) (IQR)	57 (19.5)	57.5 (18.3)	–
Mean age (years) (SD)	53.7 (13.8)	55.3 (13.9)	0.31
Male (%, number of patients)	57.6% (80/139)	61.2% (120/196)	0.46
Charlson comorbidity index			
0–1	84.8%	85.3%	0.73
2–3	10.6%	9.7%	0.49
4–5	3.1%	3%	0.93
≥ 6	1.5%	2%	0.44
Organ received (%, number of patients)			
Lung	30.9% (43/139)	27% (53/196)	0.44
Kidney	22.3% (31/139)	30.1% (59/196)	0.11
Liver	23.7% (33/139)	23% (45/196)	0.87
Kidney-Pancreas	7.2% (10/139)	4.6% (9/196)	0.31
Heart	5% (7/139)	6.1% (12/196)	0.67
Miscellaneous[¶]	4.3% (6/139)	3.1% (6/196)	0.54
Patients awaiting an organ and have never received transplantation (%, number of patients)	6.5% (9/139)	6.1% (12/196)	0.90
Age of allograft (days), median (IQR)	68.5 (1146.8)	66 (867.5)	–
Age ≤ 7 days (%, number of patients with allograft)	15.4% (20/130)	20.7% (38/184)	0.24
Age 8–30 days (%, number of patients with allograft)	23.1% (30/130)	16.3% (30/184)	0.13
Age 31–90 days (%, number of patients with allograft)	14.6% (19/130)	16.8% (31/184)	0.59
Age > 90 days (%, number of patients with allograft)	46.9% (61/130)	46.2% (85/184)	0.90
Received at least one transplantation before current transplantation (%, number of patients)	9.2% (12/130)	10.7% (21/184)	0.54
Currently re-listed, awaiting another transplantation (%, number of patients)	2.3% (3/130)	1% (2/184)	0.65

[¶] Includes heart-lung, kidney-liver, liver-pancreas, pancreas-alone, pancreas-after-kidney, and small bowel transplantations

Table 2 Outcome measures in the pre-intervention and post-intervention cohorts

Outcomes	Pre-intervention	Post-intervention	*p* value
Patients with ≥ 1 antimicrobial treatment	62.3%(87/139)	56.6% (111/196)	0.27
Adjudications concordant with antimicrobial stewardship principles	69% (60/87)	83.7% (93/111)	*0.01*
Patients with transplant infectious diseases (TID) consultation	46% (40/87)	42.3% (47/111)	0.61
Patients with TID consultation and received antimicrobial(s) concordant with antimicrobial stewardship principles	82.5% (33/40)	76.6% (36/47)	0.50
Antimicrobial consumption (DDD/100 patient-days)	140.9	162.4	*0.001*
Antibiotics consumption (DDD/100 patient-day)	97.3	114.2	*0.007*
Antifungals consumption (DDD/100 patient-day)	43.5	48.2	*0.01*
Antimicrobial cost ($CAD/patient-day)	$37.88	$33.80	0.52
Antibiotic cost ($CAD/patient-days)	$15.74	$16.30	0.67
Antifungal cost ($CAD/patient-day)	$22.13	$17.51	0.41
Hospital-acquired *C. difficile* infections (cases/1000 patient-day)	0.69	0.69	–
Average hospital length of stay (days), SD	13.4 (1.8)	13.3 (2.1)	0.93
Unplanned readmissions ≤ 30 days (% of total discharges)	2.9% (48/1666)	1.9% (45/2258)	0.1
In-hospital mortality (% total discharges)	1.4%	1.5%	0.8

Significant values are shown in italics

76.6% (36/47), $p = 0.5$ (Table 2). Length of stay, in-hospital mortality, and hospital-acquired *C. difficile* rates were similar in the two cohorts. Unplanned readmission at 30 days was 2.9% (48/1666) pre-intervention, and 1.9% (45/2258) post-intervention ($p = 0.1$). Indications of antimicrobial therapy are available in Table 3. The most common syndrome requiring treatment was respiratory tract infection, followed by intra-abdominal infections. Overall antimicrobial consumption

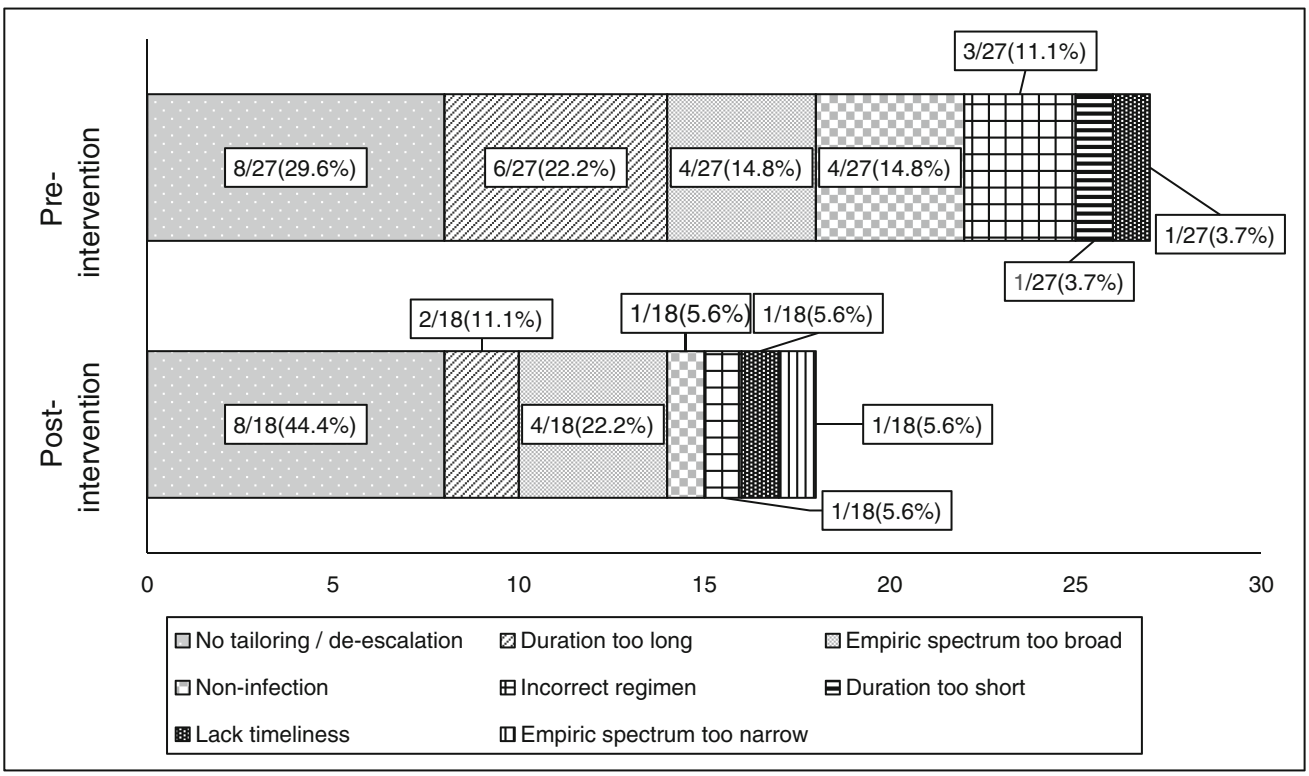

Fig. 2 Categories and frequency of antimicrobial prescriptions adjudicated as stewardship-discordant pre- and post-academic detailing

Table 3 Indications for antimicrobial therapy

Indications (%, frequency of total number of syndromes)	Pre-intervention	Post-intervention
Total number of infectious syndromes*	95	141
Total bloodstream infections (BSI)	15.8% (15/95)	13.5% (19/141)
With suspected or confirmed endovascular infection	13.3% (2/15)	10.5% (2/19)
Total respiratory tract infections (RTI)	32.6% (31/95)	34% (48/141)
Donor-derived RTI	16.1% (5/31)	10.4% (5/48)
Esophageal candidiasis	1.1% (1/95)	0
Intra-abdominal infections (IAI) total, excluding *Clostridium difficile* infection	17.9%% (17/95)	14.2% (20/141)
Total urinary tract infections (UTI)	10.5% (10/95)	14.2% (20/141)
Donor-derived UTI	0	10% (2/20)
Skin and soft tissue infections	7.4% (7/95)	7.1% (10/141)
Bone and joint infections	0	2.1% (3/141)
Clostridium difficile infections	3.2% (3/95)	7.1% (10/141)
Viral syndromes (HSV, VZV, CMV)	10.5% (10/95)	4.3% (6/141)
Febrile neutropenia	0	0.7% (1/41)
Sepsis of unknown origin	0	0.7% (1/141)
Donor-derived VDRL positivity	0	1.4% (2/141)
Prostatitis	0	0.7% (1/141)
Central nervous system infection	1.1% (1/95)	0

HSV, herpes simplex virus; *VZV*, varicella zoster virus; *CMV*, cytomegalovirus

*Patients may be treated for more than one syndrome currently

increased by 15.3% ($p = 0.001$): antibiotics by 17.4%, antifungals by 10.6%. Antimicrobial cost remained stable at $37.88/PD pre-intervention, and $33.88/PD post-intervention ($p = 0.52$). Antimicrobial consumption and cost by drug class are available in eTable 2 in Electronic Supplementary Material.

Inter-rater agreement

Pre-intervention surveys' inter-rater agreement was 87.5% (14/16) [5]. Post-intervention, inter-rater agreement was 50% (5/10). The five disagreed adjudications centered around the following reasons: the role of combination therapy, uncertainty on the specific infectious syndromes being treated, and the associated spectrum of antimicrobial activity required. Specifically, two adjudications involved *C. difficile* infections. Both patients received oral vancomycin in combination with IV metronidazole for severe infections. One of the patients was a new lung transplant recipient (post-operative day 3) and was transferred to intensive care. Both patients' *C. difficile* treatments were adjudicated as AMS-concordant by the survey team, but discordant by the non-SOT AMS pharmacist. Her rationale was that in the absence of documented ileus or septic shock, both of which were criteria of severity in UHN's *C. difficile* infection treatment algorithm, meant that intravenous metronidazole was not warranted.

Discussion

In the current study, academic detailing provided to clinicians caring for solid organ transplant patients by an antimicrobial stewardship team specialized in immunocompromised hosts was associated with increased concordance with antimicrobial stewardship principles in prescribing practices. We did not observe any negative impact on length of stay, unplanned readmission, or mortality. *C. difficile* rates also remained stable. However, antimicrobial consumption increased in the post-intervention cohort compared with baseline.

The most effective way to implement antimicrobial stewardship in SOT patients is unclear [5, 7, 26]. In a survey of US transplant centers, 87% (62/71) of the respondents reported to have an institutional ASP at their site, but the comprehensiveness and types of interventions offered varied widely [26]. A sizable proportion (26%) did not utilize academic detailing (in the format of prospective audit-and-feedback or post-prescription review) although this intervention is recommended by the Infectious Diseases Society of America and the US Centers for Disease Control to optimize antimicrobial use [1, 26]. To our knowledge, the current study was the first to evaluate the effect of this intervention specifically in SOT patients. In this setting, we used academic detailing rounds as a forum to engage SOT and TID clinicians in discussing antimicrobial decisions systematically at the patient level [12]. In turn, our primary outcome of concordance with antimicrobial

stewardship principles in prescribing practices improved. Since stewardship concordance in TID-consulted patients remained stable in both cohorts, we postulate that the significant improvement in overall stewardship concordance may be attributed to academic detailing intervention with SOT clinicians.

Antimicrobial consumption in SOT increased post-intervention, which contrasted with our experience with another immunocompromised patient population locally. At UHN's Princess Margaret Cancer Centre, academic detailing in leukemia units was associated with a significant decrease in antimicrobial consumption and cost [16]. Such diverging outcomes may be explained by a major difference between the two patient populations, even though both are considered immunocompromised. Infections in patients with leukemia are homogenously and primarily related to chemotherapy-induced neutropenia [27, 28]. Following neutrophil recovery, risks of infections subside substantially [27]. In SOT recipients, root causes of infections are heterogenous and not easily modifiable [22]. As we examined the antimicrobial stewardship-discordant prescriptions (available in eTable 1), the emerging themes in causes of infections and antimicrobial therapy are consistent with current literature: technical challenges with source control attainment; donor-derived infections; colonization or infections from multidrug-resistant organisms; and surgical site infections [7, 18, 22, 26]. Concurrent rejection issues impacting graft function, the required level of immunosuppression, and the interaction between infections and rejection further complicate the clinical picture [22]. Despite the ambiguity of diagnosis and uncertainty in treatment endpoints, when clinicians perceived the consequence of missing a treatable infection to be significant, they may have a low threshold to initiate and continue antimicrobial treatment [7, 26]. Therefore, a decrease in antimicrobial consumption may not be the most applicable "low hanging fruit" target for ASPs in SOT patients. Furthermore, we found unclarified self-reported penicillin allergies to be a hindrance to tailoring therapy, leading to prolonged use of carbapenem and other penicillin-alternatives. "De-labeling" patient self-reported penicillin allergy has been identified as an opportunity for antimicrobial stewardship in patients with hematological malignancies [29]. However, the magnitude of the issue and the most optimal way to address it in SOT patients remain to be explored.

Within SOT recipients, there is also heterogeneity regarding different requirements for immunosuppression and propensities for particular clinical syndromes, leading to varying risks and severity of infections [22]. The implications are two-fold. First, there is no universally applicable scoring system to classify morbidity and mortality risks in all SOT recipients. The Model for End-Stage Liver Disease and Lung Allocation Scores are organ-specific, and not prognostic markers post-transplantation. We chose the Charlson comorbidity index, which is based on administrative data and has been validated in SOT recipients as our comorbidity measure [30]. It is possible that we were unable to detect important clinical differences between the two cohorts that may explain the increase in antimicrobial consumption. Second, since 2015, the SOT units have observed increased nosocomial vancomycin-resistant enterococci infections causing significant morbidity and mortality, especially in liver and lung recipients [31, 32]. Furthermore, Amp-C and extended spectrum beta-lactamases-production (e.g., CTX-M) in Gram-negative bacteria was 55.3% in 2013 and 63.6% in 2016 at our institution (local data, eTable 3). Perceptions of a high prevalence of multidrug-resistant pathogens may have prompted prescribers to select broad-spectrum antimicrobials for surgical prophylaxis and empiric therapy to ensure adequate coverage [33, 34]. Duration of treatment may be prolonged for infections such as liver abscesses or empyema if source control was not attained.

Sikkens et al. used a similar evaluative method of serial point-prevalence survey in a tertiary setting to assess the impact of their AMS interventions [35]. The authors reported a 13.5% increase in appropriateness of antimicrobial use at 12-month follow-up, without reduction in antimicrobial consumption [35]. The authors postulated that prescribers may have opted for narrower spectrum agents more often, but did not refrain from initiating or stopping therapy [35]. We did not observe this pattern in our data regarding changes in spectrum of activity (eTable 2). At a tertiary center's antifungal stewardship program in Spain, Valerio et al. described a similar AMS intervention and evaluative method to adjudicate antifungal use, with over 50% of patients categorized as being immunocompromised [24]. Comparable with our findings, the authors reported increase in optimal antifungal use, but no statistically significant changes in consumption or cost post-intervention [24]. Since the primary objective of an antimicrobial stewardship program is to optimize antimicrobial therapy, concordance with AMS principles remained our primary outcome measure for quality of prescribing.

Inter-rater agreement was lower in the post-intervention cohort, compared with pre-intervention. The change in the independent adjudication process for quality assurance by an external AMS pharmacist without expertise in SOT may explain the decrease, and highlights the need for AMS personnel to understand the unique challenges in SOT patients. We advocate that in addition to AMS knowledge and skills, antimicrobial stewards for SOT should be equipped with expertise in transplant infectious diseases to strengthen the validity of their recommendations. Conversely, we cannot exclude biases in the survey team. However, the adjudication was conducted using standardized criteria to minimize this effect.

Our study has several strengths. First, we used a consistent evaluative method of serial, point-prevalence survey to capture prescribing patterns. Repeated point-prevalence surveys have increasingly been used to assess antimicrobial prescribing, and our data were more robust with longitudinal measures [24, 36,

37]. Second, our approach reflects assessment of real-world decision-making by the prescriber, as opposed to retrospective evaluations. Third, our results are more comprehensive with the inclusion of antimicrobial consumption, costs, *C. difficile* infection rates, and balancing measures such as LOS, readmission, and mortality. We did not identify any unintended consequences following the academic detailing intervention to optimize antimicrobial prescribing. Fourth, for transparency, we provided case details of AMS-discordant adjudications (eTable 1) and involved a non-SOT AMS pharmacist for quality assurance to improve the robustness of our process.

Our study has limitations. First, although we reviewed all available information in real-time in the adjudication, we did not have access to the full insight into the entire thought process of the prescribers. But through the surveys, we created opportunities in the future to facilitate consensus on defining appropriate antimicrobial use in SOT. Second, at the time of conducting the study, we did not have a locally developed guideline to serve as benchmark. We have since created and implemented a local guideline in 2017, which will be our best practice standard against which future point-prevalence surveys are adjudicated [38]. Third, we reported aggregate data for secondary outcomes, such as defined daily dose. Prescriber-specific and patient-level data, such as days of therapy may better reflect the impact of our intervention. We are standardizing a process to provide prescriber-specific feedback. Lastly, both academic detailing and point-prevalence surveys are resource-intensive, and may not be easily implemented in smaller transplant centers.

Our evaluation found that academic detailing is an effective and safe AMS intervention to improve the quality of antimicrobial use in SOT patients. Serial point-prevalence survey is a feasible method to capture the effect of antimicrobial stewardship interventions. As next steps, we aim to study the cumulative impact of a locally developed guideline, academic detailing, and prescriber-specific point-prevalence surveys.

Acknowledgments We are grateful for the collaboration of clinicians in the Multi-Organ Transplant Program, Transplant Infectious Disease Team, and the MOT Pharmacy Team at the University Health Network. We would like to acknowledge the contribution from Claire Aguilar, MD, Mohammed AlAbdulla, MD, Yamama Aljishi, MD, Daisy Yang, PharmD, and Jam Bravo, PharmD.

Compliance with ethical standards

Ethics Statement The study was approved by the Research Ethics Board at UHN (CAPCR ID 17-5742).

Conflict of interest Miranda So, Andrew Morris, Chaim Bell, and Sandra Nelson have no disclosures. Shahid Husain has the following disclosures: grants from Pfizer, Merck, Astellas, Cidara.

Abbreviations ASP, antimicrobial stewardship programs; AMS, antimicrobial stewardship; SOT, solid organ transplant; UHN, University Health Network; TID, transplant infectious diseases; SHS-UHN ASP, Sinai Health System-University Health Network Antimicrobial Stewardship Program; AD, academic detailing; DDD/100 PD, defined daily dose per 100 patient-days; C$/PD, cost in Canadian dollar per patient-day; CDI/1000 PD, *Clostridium difficile* infection per 1000 patient-days

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