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TRANSPLANT INFECTIOUS DISEASE

BRIEF COMMUNICATION

Bridging the gap: An approach to reporting antimicrobial stewardship metrics specific to solid organ transplant recipients

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Abstract

Background: This study seeks to describe inpatient antimicrobial use (AU) utilizing the National Healthcare Safety Network-AU (NHSN-AU) framework among solid organ transplant recipients (SOTr) within 12 months after transplant.

Methods: This cross-sectional study included SOTr ≥ 18 years of age who underwent transplantation from January 2015 to December 2016 at a Midwestern US transplant center. Inpatient AU was followed for 12 months post-transplant. Hospital days present up to 12 months post-transplant, AU variables, and *Clostridioides difficile* infection (CDI) occurrences were analyzed.

Results: The cohort of 530 SOTr included 225 kidney (42.5%), 171 liver (32.3%), 45 lung (8.5%), 40 heart (7.5%), 39 multivisceral (7.4%), seven small bowel (1.3%), and three pancreas (0.6%) transplants. Total days of therapy (DOT) were 22 782 among the cohort, with a median of 5 days [interquartile range [IQR], 1–12]. Lung and liver transplants had the most total DOT (6571 vs. 5569 days), while lungs and small bowels had the highest median DOT (13 [IQR, 2–56] vs. 12 [IQR, 2–31]). The facility-wide DOT/1000 days were lowest in pancreas and highest in lung transplants (5.3 vs. 428.1). Small bowel transplants received the most resistant-Gram-positive infection and hospital-onset infection agents for facility-wide DOT/1000 days present. Pancreas and kidney transplants accounted for the most high-risk CDI agents. CDI occurred in 34 patients, with kidney and liver transplants experiencing 13 each.

Conclusion: This study represents one of the first reports of AU in SOTr utilizing the NHSN-AU framework. More studies are needed for further peer-to-peer comparison of AU in this complex patient population.

KEYWORDS
antimicrobial stewardship, antimicrobial use, solid organ transplant

List of Abbreviations: AMS, antimicrobial stewardship; ASPs, antimicrobial stewardship programs; AU, antimicrobial use; CDC, Centers for Disease Control and Prevention; CDI, *Clostridioides difficile* infection; DOT, days of therapy; EHR, electronic health record; HOI, hospital-onset infection; NHSN, National Healthcare Safety Network; SOTr, solid organ transplant recipient.

1 | INTRODUCTION

Antimicrobial stewardship programs (ASPs) involving multidisciplinary healthcare teams ensure patients receive the most appropriate antimicrobial, route of administration, dose, and duration of therapy. ASPs aid in optimizing patient outcomes, minimizing adverse effects, and preventing the development of antimicrobial resistance. Antimicrobial stewardship (AMS) has existed within patient care for decades; however, support for establishing formal ASPs within hospital systems escalated in response to the recognition of the necessity of AMS by the Centers for Disease Control and Prevention (CDC) in 2014 and the United States government in 2015.[1] Moreover, to provide national antimicrobial benchmarking metrics and use comparison, the CDC optimized the National Healthcare Safety Network (NHSN) as a method for institutions to participate in antimicrobial use (AU) reporting. NHSN-AU serves as a surveillance resource that can provide actionable data for ASPs. Data input into NHSN is obtained directly from electronic medication administration record and/or bar-coding medication record. The functionality of NHSN-AU is based on a variety of metrics including but not limited to patient location, patient days present, antimicrobial days of therapy (DOT), and classification of antimicrobial categories.[2] While the NHSN-AU supports the progression of ASP metric analysis and institution comparison, it does not require or provide pathways for analysis of AU specifically in solid organ transplant recipients (SOTr).

A white paper from the American Society of Transplantation described the current landscape and identified opportunities for ASP in SOTr.[3] The SOT population is uniquely at risk for infections in the setting of complex transplant surgery and immunosuppression. However, there is limited data on AMS practices in SOTr and hence no transplant-specific AMS metrics or benchmarks currently exist.[3] Analyzing AU metrics within SOTr is essential to track the progression of AU in this patient population and measure the effects of AMS efforts. This study aimed to describe local inpatient AU utilizing the NHSN-AU framework among SOTr within 12 months of transplant at a Midwestern US transplant center.

2 | METHODS

This institutional review board approved (IRB #13476), cross-sectional study included SOTr at least 18 years of age who underwent transplantation from January 2015 to December 2016 at Henry Ford Hospital, an academic medical center in southeast Michigan. Inpatient AU was followed for 12 months post-transplant. Patient demographics and transplant type were identified using the institution's transplant database. Antimicrobial use variables, *Clostridioides difficile* infection (CDI) occurrences, and hospital days present up to 12 months post-transplant were obtained using Microsoft SQL Server 2019 version 15.0.4198.2. Henry Ford Hospital utilizes Epic for its electronic health record (EHR). Information related to transplant patients was obtained through an internal quality improvement database, which was incorporated into the EHR server and cross-referenced against the EHR data. Patient- and encounter-level analysis of AU was performed to align with the NHSN-AU module. The accuracy of data was confirmed via a randomized chart review of 20 patients.

Antimicrobial use variables included DOT, facility-wide DOT per 1000 patient days, antimicrobial-free days, and NHSN AU reporting targets of resistant Gram-positive infection agents, hospital-onset infection (HOI) agents, and high-risk CDI agents.[2] Antimicrobial was defined as antibacterial or antifungal agents included in the NHSN-AU module.[2] Antiviral agents used for the treatment of influenza are included in the NHSN-AU module but were excluded for the purposes of this study. A day of therapy was defined as at least 1 administration of a unique antimicrobial to a unique patient per calendar day.[2] Facility-wide DOT per 1000 patient days were accounted for using DOT divided by patient days of SOTr within 1 year of transplant multiplied by 1000.[2] Antimicrobial free days were accounted for by lack of administration of an antimicrobial to a patient on a given hospital day. Hospital days were further described as median hospital days and the number of encounters per transplant type was evaluated. Data were analyzed using descriptive statistics via Microsoft Excel.

3 | RESULTS

The final cohort was comprised of 530 SOTr 225 kidney (42.5%), 171 liver (32.3%), 45 lung (8.5%), 40 heart (7.5%), 39 multivisceral (7.4%), 7 small bowel (1.3%), and 3 pancreas (0.6%) transplants. Baseline characteristics are displayed in Table 1. Patients were primarily white and male with a median age of 61 years. Overall, there were 1672 hospital encounters among the 530 SOTr within 12 months of transplant, with kidney (39.7%) and liver (30%) transplants comprising most of the encounters (Table 2). Total DOT for antimicrobials was 22 782 among the cohort, with a median DOT of 5 days [interquartile range [IQR], 1–12]. Lung and liver transplants had the most total DOT (6571 days vs. 5569 days), while lungs and small bowels had the highest median DOT (13 [IQR, 2–56] vs. 12 [IQR, 2–31]) (Table 2). Lung transplants received the most antimicrobials for facility-wide DOT/1000 days present among the cohort (428.1), with pancreas transplants receiving the least (5.3). Of the NHSN classes evaluated (resistant Gram-positive agents, HOI agents, and high-risk CDI agents) facility-wide DOT/1000 patient days were lowest within 1 month of transplant (172, 231, 173 DOT/1000 patient days, respectively), increasing somewhat from 1–3 months post-transplant (275, 288, 216 DOT/1000 patient days), before significantly increasing 3–12 months post-transplant (380, 418, 292 DOT/1000 patient days). The greatest proportion of antimicrobial-free hospital days was observed for pancreas 29 (35.8%), liver 1463 (33.9%), and lung 1134 (33.3%) recipients.

HOI broad-spectrum agents were the most prescribed class of the three NHSN-AU categories evaluated (292.8 DOT/1000 days), followed by agents predominately used for resistant Gram-positive infections (e.g., methicillin-resistant *S. aureus* and vancomycin-resistant enterococcus) (252.7 DOT/1000 days), then high-risk CDI agents (214.3 DOT/1000 days) (Table 2). HOI agents use was most frequent in small bowel, multivisceral, and lung transplants. Small bowel, lung,

TABLE 1 Baseline characteristics

Variable - *N* (%), median [IQR]	(*n* = 530)
Age, year	61 [52–69]
Sex, male	337 (63.6)
Race	
Asian	12 (2.3)
Black	157 (29.6)
Other	25 (4.7)
White	336 (63.4)
Transplant type	
Heart	40 (7.5)
Kidney	225 (42.5)
Liver	171 (32.3)
Lung	45 (8.5)
Multivisceral	39 (7.4)
Pancreas	3 (0.6)
Small bowel	7 (1.3)
Charlson Comorbidity Index score	
Overall	5 [3–7]
Heart	4 [2.25–6]
Kidney	4 [3–6]
Liver	7 [5–8]
Lung	3 [2–4]
Multivisceral	6 [5–8]
Pancreas	4 [4–5]
Small bowel	1 [0–2]

Abbreviations: IQR, interquartile range.

and heart transplants received the most anti-resistant Gram-positive therapy (Table 2). The use of high-risk CDI agents was relatively lower compared to the other categories, and pancreas and kidney transplants accounted for the most use within this sector.

Of the 530 SOTr, 34 patients experienced an episode of CDI, kidney and liver transplants experienced the most cases at 13 each.

4 | DISCUSSION

The results of this study provide insight into AU metrics for SOTr at a large transplant facility in southeastern Michigan from January 2015 to December 2016. The study represents the first report of AU metrics in SOTr within the construct of NHSN-AU.

Although institutional ASPs and NHSN-AU reporting are strongly recommended by regulatory agencies in the United States, they are not specifically mandated for transplant programs.[3] ASPs also must account for variables unique to the SOT population including the type of organ transplanted, timing since transplantation, donor-derived infections, the intensity of immunosuppression, and presence of catheters, drains, and stents in the immediate post-transplant period, as well as colonization with drug-resistant organisms from pre-transplant antimicrobial exposure, when optimizing antimicrobial regimens.[4–6] To develop effective ASPs tailored to the SOT population, it is essential to track and disseminate metrics of antimicrobial consumption and patterns of use, as well as potential harm such as CDI and the emergence of antimicrobial resistance. Our study is novel as it demonstrates the development of measurements of AU specific to SOTr within the framework of NHSN-AU, utilizing available institutional analytics without the need for additional resources.

Additionally, a unique facility-wide DOT/1000 days present was employed in this study instead of a specific location, for example, a post-transplant unit. All analyses were limited to that of the SOTr cohort within 12 months of transplantation. Therefore, the days present metric was limited to that of the hospital days present for the cohort – excluding non-transplant inpatients and SOTr outside of the transplant window. Furthermore, analyses for days present per organ type were conducted using total hospital days present for respective organ types.

Kidney and liver transplants comprised 75% of our cohort. Despite kidney transplants holding the most encounters (39.7%), this group was only responsible for 249.3 facility-wide DOT /1000 days present among the cohort. (Table 2) Liver transplant recipients were the second leading encounter group (30%) and were responsible for 362.8 facility-wide DOT/1000 days present. In contrast, lung recipients accounted for only a small proportion of encounters (9.6%) but were the leading group for facility-wide DOT/1000 days present at 428.1. It should be noted lung recipient median hospital days present were approximately double that of any other transplant type. Lung and liver transplants had significantly more DOT compared to the other transplant types. Despite this, both groups retained >30% of their hospital days as antimicrobial-free.

These data highlight the variability of antimicrobial consumption and patterns of use within the SOT population reflecting the variables unique to the organ transplanted. This information is important to help tailor ASP programs specifically to the type of organ transplanted.

This analysis contains several limitations. The time period of the data 2015–2016 for this pilot study may be considered a limitation; however, this period was chosen to establish baseline AMS metrics. Since 2016, the institutional ASP implemented numerous quality initiatives to guide AU in SOTr. The creation of organ-specific transplant protocols by infectious diseases transplant providers, infectious diseases pharmacists, and organ-specific transplant teams now provides guidance for surgical prophylaxis, opportunistic infection prophylaxis, and immunosuppression. Additionally, close teamwork with the microbiology laboratory has provided pathways for stewardship interventions including but not limited to utilizing nares MRSA screening, T2 Candida assays, and Carba-R assays. The AMS team is assessing how these interventions may have affected baseline AMS metrics in SOTr. The lack of inclusion of antiviral use and assessment of the prevalence of multidrug-resistant organisms among the cohort is also a limitation. Consideration should be taken that the analysis accounted for both antimicrobial prophylaxis and treatment indications. Antimicrobial-free days may be the result of prolonged dosing intervals (e.g., thrice

TABLE 2 Outcomes by transplant type

Organ Type	Encounters (%)	Hospital days present (days)	Median hospital days present [IQR])	Antibiotic DOT (days)	Median DOT [IQR]	Cohort DOT/1000 days[a]	Antibiotic-free days (%)	Resistant Gram-positive agent * organ-specific DOT/1000 days[b]	HOI agent** organ-specific DOT/1000 days[b]	CDI high-risk agent*** organ-specific DOT/1000 days[b]
Heart	140 (8.4)	2298	6 [2–19]	3184	5 [1–7]	207.4	713 (31)	354.7	334.2	227.2
Kidney	664 (39.7)	3167	4 [1–6]	3827	4 [1–7]	249.3	518 (16.4)	129.1	135.8	268.4
Liver	501 (30)	4318	5 [1–12]	5569	4 [1–12]	362.8	1463 (33.9)	204	280.5	177
Lung	161 (9.6)	3407	10 [3–25]	6571	13 [2–56]	428.1	1134 (33.3)	362.5	371.6	183.2
Multivisceral	154 (9.2)	1468	5 [1–11]	2403	7 [1–18]	156.5	317 (21.6)	211.9	371.3	252
Pancreas	13 (0.8)	81	5 [3–10]	81	4 [2–12]	5.3	29 (35.8)	37	308.6	284
Small Bowel	39 (2.3)	611	7 [4– 23]	1147	12 [2–31]	74.7	130 (21.3)	368.2	407.5	222.6
Total	1672	15 350	5 [1–10]	22 782	5 [1–12]	1484.2	4304 (28)	252.7	292.8	214.3

Abbreviations: CDI, Clostridoides difficile infection; DOT, days of therapy; HOI, hospital-onset infection; IQR, interquartile range; MRSA, methicillin-resistant Staphylococcus aureus.

[a]Total days of antimicrobial therapy per organ type / total hospital days present of cohort x 1000.

[b]Total antimicrobial category specific days/hospital days present of specific organ x 1000.

*Resistant Gram-positive infection agents: ceftaroline, daptomycin, linezolid, and vancomycin.

**Hospital Onset Infection agents: aminoglycosides (amikacin, gentamicin, and tobramycin), aztreonam, cefepime, ceftazidime, imipenem/cilastatin, meropenem, and piperacillin/tazobactam.

***High-risk CDI agents: cefepime, ceftazidime, ceftriaxone, ciprofloxacin, clindamycin, levofloxacin, and moxifloxacin.

(Agents included within NHSN AU reporting targets of resistant Gram-positive infection agents, hospital-onset infection agents, and high-risk CDI agents that are not mentioned in the analysis were excluded due to zero administrations to the cohort within 12 months post-transplant).

weekly vs. daily) for agents such as sulfamethoxazole/trimethoprim and azithromycin or employment of agents not accounted for in the analysis (e.g., pentamidine and atovaquone).

The study has several strengths. This is one of the first AMS evaluations of AU in SOTr performed utilizing available institutional analytic resources and permits applicability to other institutions. The AU metrics can be used not only for internal benchmarking but also for comparison with transplant centers, given the lack of SOT-specific data from the current NHSN-AU platform. Additionally, a focus was on AU within the 12 months of transplantation the period with increased risk of infections as a consequence of surgical complications and intense immunosuppression. Lastly, data was validated via cross-matching query data with the transplant database of the institution.

5 | CONCLUSION

This study displays a novel approach to analyzing AU in SOTr within 12 months of transplantation using NHSN-AU metrics. The availability of these SOT population-specific metrics will help direct and assess ASP quality initiatives and peer-to-peer comparison.

AUTHOR CONTRIBUTIONS

Conceptualization/Methodology: Sage B. Greenlee, Tommy J. Parraga Acosta, Charles T. Makowski, Rachel M. Kenney, Mayur Ramesh, Jonathan D. Williams, and George J. Alangaden; Software/Validation/Analysis: Sage B. Greenlee, Tommy J. Parraga Acosta, and Charles T. Makowski; Manuscript Writing: SG, TP, RK, and GA; Manuscript Editing/Review/Final Approval: Sage B. Greenlee, Tommy J. Parraga Acosta, Charles T. Makowski, Rachel M. Kenney, Mayur Ramesh, Jonathan D. Williams, and George J. Alangaden.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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