



Original Article

A joint program of antimicrobial stewardship and hospital-acquired infection control to reduce healthcare-associated infections after kidney transplantation: The Hipomenes study



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ABSTRACT

Infection is a common complication in kidney transplant recipients (KTRs). The usefulness of antimicrobial stewardship programs (ASP) and hospital-acquired infection control (HAIC) initiatives in the general inpatient population is well established. We performed a quasi-experimental study to evaluate a joint ASP/HAIC initiative focused on KTRs. A dedicated ASP team optimized antimicrobial prescriptions in consecutive KTRs during the intervention period (June 2015–March 2016). A multifaceted, evidence-based HAIC program was concurrently implemented. Results were compared with the preceding period (June 2014–March 2015). We included 96 and 100 KTRs in the intervention and preintervention periods, respectively. There was a reduction in the consumption of meropenem (rate ratio [RR]: 0.63; 95% confidence interval [CI]: 0.53–0.75; $P < .0001$), ceftazidime (RR: 0.31; 95% CI:

Abbreviations: ASP, antimicrobial stewardship program; BSI, bloodstream infection; CDI, *Clostridioides difficile* infection; CI, confidence interval; CMV, cytomegalovirus; D, donor; DoT, day of therapy; EBNA, Epstein-Barr nuclear antigen; EMR, electronic medical record; ESBL, extended-spectrum β -lactamase; ESRD, end-stage renal disease; HAIC, hospital-acquired infection control; HCW, healthcare worker; ICU, intensive care unit; ID, infectious diseases; IgA, immunoglobulin A; IgG, immunoglobulin G; IQR, interquartile range; IV, intravenous; KT, kidney transplantation; KTRs, kidney transplant recipients; MDR, multidrug-resistant; mTOR, mammalian target of rapamycin; Q & A, question and answer; R, recipient; RR, rate ratio; SD, standard deviation; SOT, solid organ transplantation; SSI, surgical site infection; UTI, urinary tract infection; WHO, World Health Organization; XDR, extensively drug-resistant.

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0.21-0.45; $P < .0001$), vancomycin (RR: 0.65; 95% CI: 0.53-0.8; $P < .0001$), and ciprofloxacin (RR: 0.66; 95% CI: 0.55-0.81; $P < .0001$) and an increase of fosfomycin (RR: 1.80; 95% CI: 1.17-2.76; $P = .008$) during the intervention period. The incidence of cystitis (RR: 0.30; 95% CI: 0.28-0.33; $P < .001$) and upper urinary tract infection (RR: 0.56; 95% CI: 0.33-0.95; $P = .04$) decreased. A specific ASP/HAIC initiative was effective in optimizing antimicrobial use and reducing the incidence of common bacterial infections among KTRs.

1. Introduction

Solid organ transplantation (SOT) is currently the best option for patients with end-stage organ disease and limited therapeutic alternatives. This procedure has been demonstrated to restore health-associated quality of life, which is usually severely impaired on the waiting list.¹ Research in the field of transplantation has led to advances in surgical techniques² and new and more potent immunosuppressive agents,³ resulting in a reduction in rates of acute graft rejection and dysfunction. Furthermore, the elaboration of international and national guidelines has helped to improve strategies aimed at reducing the burden of opportunistic infections,⁴⁻⁶ such as tuberculosis, cytomegalovirus (CMV), or invasive mold disease.

Unfortunately, the past decades have also witnessed an increase in the occurrence of infections due to multidrug-resistant (MDR) and extensively drug-resistant (XDR) bacteria within the SOT population, including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, extended-spectrum β -lactamase (ESBL)-producing *Enterobacterales*, carbapenem-resistant Gram-negative bacteria, MDR *Pseudomonas aeruginosa*, carbapenem-resistant *Acinetobacter baumannii*, and *Burkholderia cepacia* complex.⁷⁻¹⁰ Management of MDR bacteria remains a clinical challenge due to the scarce number of active agents available and the limited experience of SOT recipients.¹¹ This complication is associated with poorer patient and graft survival, particularly in cases of inappropriate empirical therapy.¹² Finally, SOT recipients are at an increased risk of *Clostridioides difficile* infection (CDI) compared with other groups of patients, with high rates of associated morbidity and mortality.¹³⁻¹⁵ Antimicrobial exposure is one of the main drivers for developing CDI both in the general inpatient population and after SOT.^{16,17}

Over recent years, there has been a global call for the implementation of antimicrobial stewardship programs (ASP) in conjunction with hospital-acquired infection control (HAIC) initiatives in the setting of SOT.¹⁸⁻²⁰ Recent studies have shown that ASP initiatives are not only feasible for SOT recipients, but also linked to positive outcomes.²¹ A quasi-experimental study conducted in a Canadian tertiary-care institution from January 2010 to December 2014 found that a combined HAIC and ASP intervention decreased by 51.6% the rate of posttransplant surgical site infection (SSI),²² whereas the implementation of an antifungal ASP in an Italian center led to a significant improvement in the appropriateness of choice and duration of therapy compared with the preintervention period.²³

Despite the positive results from these preliminary experiences, ASP in the specific SOT setting remains logistically challenging,²⁴ and more data on the feasibility and usefulness of a bundle comprising a focused ASP and a multifaceted HAIC initiative is needed. Herein, we describe the results of a quasi-experimental study evaluating a combined ASP/HAIC intervention in the kidney transplantation (KT) program of our institution. We hypothesized that this joint effort, tailored to the KT population and implemented by a dedicated physician with specific expertise in transplant infectious diseases, would be well-accepted and would exert a synergistic effect in improving the quality of care and reducing the incidence of posttransplant infection.

2. Patients and Methods

2.1. Study population and design

The University Hospital “12 de Octubre” (Madrid, Spain) is a 1360-bed tertiary-care center with >30 years of experience in SOT. The KT program was established at our institution in 1978. As of January 2023, >4500 KT have been performed (including 240 living-donor procedures).

We conducted a quasi-experimental, preintervention, and postintervention study (Hipomenes study). The intervention period spanned from June 2015 to March 2016 and consisted of a joint initiative of ASP and HAIC, as described below. All consecutive adult patients (≥ 18 years old) with end-stage renal disease undergoing KT at our center during that period were included. The preintervention period comprised the immediately preceding 10-month interval (from June 2014 to March 2015). Consecutive patients undergoing KT during this period were retrospectively analyzed as a historical cohort and used as a comparison group. No changes in the attending medical or surgical teams, nursing staff, surgical techniques, immunosuppression, and prophylaxis regimens, or the spatial configuration of the ward were introduced between both periods. The 3-month gap between the end of the preintervention period and the initiation of the intervention period allowed us to include a comparable flu epidemic season in both study phases.

The study outcomes were the number of days of therapy (DoTs) for relevant antibiotic classes (penicillins, cephalosporins, carbapenems, aztreonam, fluoroquinolones, aminoglycosides, glycopeptides, linezolid, daptomycin, tigecycline, metronidazole, fosfomycin, and cotrimoxazole) and the incidence rate (per 1000 patient days of follow-up) over the first 6 posttransplant months of

major types of posttransplant infection (urinary tract infection [UTI], SSI, respiratory tract infection, intra-abdominal infection, bloodstream infection [BSI], and CDI). Follow-up was censored at month 6 for both the preintervention and intervention periods.

Detailed descriptions of the immunosuppression and prophylaxis regimens used are available as Supplementary Methods.

2.2. Description of ASP and HAIC

The ASP consisted of a prospective audit and feedback system that was developed by a dedicated infectious diseases (ID) specialist and performed at least 3 times per week. This physician, with long-term expertise in transplant infectious diseases, performed the intervention during the period. Data on antimicrobial prescriptions among KTRs were obtained using the unitary dose drug dispensation system, which was provided by the Department of Pharmacy. Recovered data included the patient's medical record number, the antimicrobial agent and route of administration, the prescribed dose, and the number of days of treatment. The Departments of Nephrology and Urology also collaborated in the process of implementing the ASP. A detailed description of the criteria used to select the therapeutic courses which needed revision and recommendations are shown in Table 1. Before issuing a recommendation, the dedicated ID physician reviewed the patient's electronic medical records (EMRs) and prescription charts. All the recommendations were discussed in person with the prescribing nephrologist or urologist and documented in writing in the EMR. Of note, the program was nonrestrictive in nature, and the recommendations were ultimately agreed upon with the prescriber. Finally, the corresponding EMR was reviewed within the following 48 hours to check the degree of compliance with the given recommendation. The content and result of each intervention were collected in a standardized case report form.

An intensive HAIC initiative was concurrently developed throughout the intervention period among healthcare workers (HCWs) assigned to the KT program, with the specific goal of reinforcing evidence-based measures aimed at reducing the risk of hospital-acquired infections. The ID physician that performed the ASP was also responsible for the HAIC interventions. A description of the content, timing, and target audience of the actions covered by the initiative is shown in Figure 1. First, several 45-minute small group sessions with media resources were held, focusing on hand hygiene, management of patients on transmission-based precautions, and care of surgical site wounds and intravascular catheters. Education on transmission-based precautions comprised the correct donning, wearing, and doffing of gloves and gowns (in the case of contact precautions) or personal protective equipment and the filtering face piece 2-type respirator (for droplet and airborne precautions, as required). All the sessions included a question-and-answer section. Media resources comprised educational slideshows and video presentations. We adapted the World Health Organization (WHO) Hand Hygiene Technical Reference Manual and the material provided by the WHO Infection Prevention and

Table 1

A detailed description of the activities carried out using the ASP.

Criteria used to select treatment courses needing revision^a
<ul style="list-style-type: none"> Any antimicrobial agent administered by the IV route for >5 days Any antimicrobial agent administered by the oral route for >10 days Fluoroquinolone antibiotics administered by the IV route, regardless of the length of treatment Any carbapenem-, piperacillin/tazobactam-, cefepime-, aminoglycoside-, or glycopeptide-containing regimen, regardless of the length of treatment Any combination regimen with > 2 antimicrobial agents concurrently prescribed
Recommendations issued^b
<ul style="list-style-type: none"> Switch from IV to oral route whenever possible (eg, agents with high oral bioavailability, such as levofloxacin, clindamycin, or metronidazole) De-escalate from a broad-spectrum to a narrower-spectrum agent guided by microbiological results and antimicrobial susceptibility testing Discontinue antimicrobial therapy in the absence of clinical and/or microbiological evidence of infection Avoid prolonged courses of therapy, whenever possible, by favoring compliance with clinical practice guidelines Use of a once-daily dosing regimen for aminoglycosides Avoid the use of antipseudomonal antibiotics when the involvement of <i>Pseudomonas aeruginosa</i> is deemed unlikely (eg, community-acquired infection with no previous antibiotic pressure) Restrict the use of glycopeptides to infections produced by bacteria resistant to other antibiotics or in the case of documented β-lactams allergy Restrict the use of piperacillin/tazobactam, cefepime, and carbapenems for hospital-acquired infections Discontinue inappropriate antimicrobial prophylaxis regimens

Abbreviations: ASP, antimicrobial stewardship program; ID, infectious disease; IV, intravenous.

^a The ASP consisted of a prospective audit and feedback system. Although some antimicrobials were systematically reviewed on the day of prescription, certain regimens were only reviewed depending on the length of treatment.

^b An ID specialist discussed in person with the attending nephrologist or urologist the nonmandatory recommendations issued. Recommendations were documented in the patient's electronic medical record.

Control Technical and Clinical Hub to create the slide set used in these sessions.^{25,26} Two of these sessions were attended by the medical staff of the Departments of Nephrology and Urology, respectively, and 3 further sessions by the nursing staff of the KT program. The dedicated ID physician also joined the staff of the Department of Nephrology during their daily clinical rounds with KTRs admitted to the hospital. In these bedside meetings, the

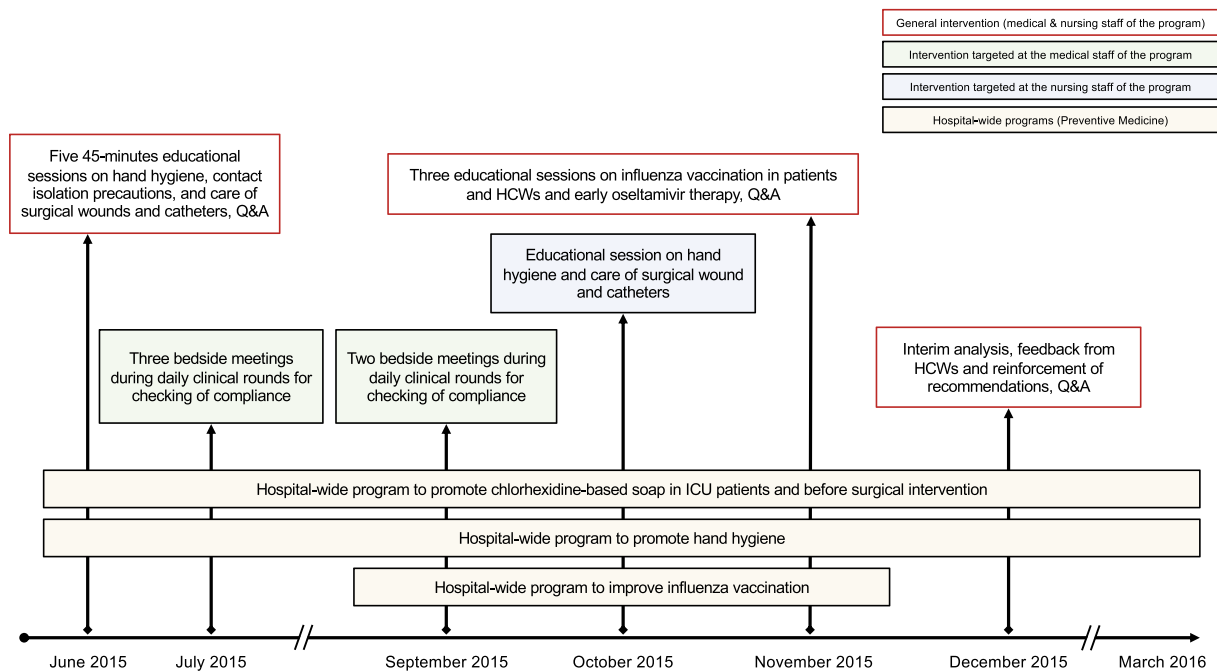


Figure 1. Timeline of activities programmed in the framework of the hospital-acquired infection control (HAIC) initiative during the intervention period. Abbreviation: HCW: healthcare worker; ICU, intensive care unit; Q & A, question and answer.

staff was directly observed to assess compliance with infection control recommendations (ie, hand hygiene practices, transmission-based precautions, and stethoscope disinfection). This activity was performed on 5 occasions during the intervention period. Standard contact isolation was implemented in the case of MDR bacteria colonization. An institutional program promoting the use of chlorhexidine-based soap for daily bathing in patients admitted to the intensive care unit and just before any type of surgical intervention (including transplant procedures) was simultaneously developed during the intervention period. Three meetings were organized in September–November 2015 with the medical and nursing staff to reinforce the importance of vaccination among KTRs and HCWs and the early initiation of oseltamivir therapy in patients with laboratory-confirmed influenza. In addition, a hospital-wide program to improve influenza vaccination uptake among HCWs was concurrently implemented. In addition, the Department of Preventive Medicine initiated, between June 2015 and December 2016, a hospital-wide program to encourage hand hygiene. Alcohol hand gel dispensers were located in the corridor of the ward and inside each patient room. A mid-study meeting was held with medical and nursing staff to share the initial results of the HAIC initiative, promote feedback sharing, and reinforce adherence to the promoted measures.

2.3. Study definitions

MDR bacteria were defined by their nonsusceptibility to ≥ 1 agent in ≥ 3 antimicrobial categories. XDR was defined as nonsusceptibility to ≥ 1 agent in all but 2 or fewer categories (ie, bacterial isolates remain susceptible to only 1 or 2 categories).²⁷ At least one of the following criteria should be met to establish the

diagnosis of posttransplant infection: (1) isolation of an unequivocal pathogenic microorganism from any clinical sample (eg, *Mycobacterium tuberculosis*); (2) isolation of any microorganism from a clinically relevant specimen obtained under sterile conditions; (3) isolation of a potentially pathogenic microorganism from any sample that was accompanied by signs and/or symptoms of a local or systemic infection; and (4) in the absence of microbiological documentation, a clinical picture suggestive of infection that was followed by complete clinical resolution after the initiation of empirical antimicrobial therapy. Febrile episodes with no documented causative agent not requiring antimicrobial treatment to obtain clinical resolution did not qualify as post-transplant infection. Specific infections (eg, pneumonia, BSI, UTI, CDI, or SSI) were diagnosed according to well-established criteria,^{28,29} as detailed in Supplementary Methods. Recurrent infection was defined by the diagnosis within the first 30 days of a new episode of infection at the same site with isolation of the same microorganism. DoT was defined as the number of days that a given patient received a certain antimicrobial agent, regardless of the dose and schedule of administration. Electronic charts were individually reviewed, and only those prescriptions in which the nursing notes documented that the drug had been effectively administered were taken into account.

2.4. Statistical analysis

Continuous variables were expressed as the mean (for those with a normal distribution) or the median (mostly for those with a skewed distribution), accompanied by the standard deviation (SD) and interquartile range (IQR), respectively. Discrete variables were expressed as absolute and relative frequencies. The student’s unpaired t-test was used to compare continuous

Table 2
Baseline and clinical characteristics of the 196 KTRs included in both periods.

Variable	Preintervention period (n = 100)	Intervention period (n = 96)	P value
Recipient age, y (mean ± SD)	52.8 ± 15.6	53.7 ± 15.6	.69
Recipient gender, male (n [%])	70 (70.0)	69 (71.9)	.77
Donor age, y (mean ± SD)	50.4 ± 14.8	52.7 ± 17.5	.33
Pretransplant diabetes mellitus (n [%])	37 (37.0)	29 (30.2)	.31
Previous transplantation (n [%])	14 (14.0)	15 (15.6)	.84
≥ 2 transplant procedures	2 (2.0)	6 (6.2)	.163
Previous kidney or pancreas-kidney transplantation	11 (11.0)	13 (13.5)	.587
Previous liver transplantation	4 (4.0)	1 (1.0)	.369
Cause of underlying ESRD (n [%])			.25
Diabetic nephropathy	29 (29.0)	21 (21.9)	
Polycystic kidney disease	12 (12.0)	10 (10.4)	
IgA nephropathy	13 (13.0)	7 (7.3)	
Hypertensive nephropathy	9 (9.0)	10 (10.4)	
Reflux nephropathy	5 (5.0)	7 (7.3)	
Focal segmental glomerulosclerosis	7 (7.0)	4 (4.2)	
Unknown	4 (4.0)	11 (11.5)	
Type of transplant (n [%])			.53
Single kidney	88 (88.0)	89 (92.7)	
Simultaneous kidney-pancreas	9 (9.0)	5 (5.2)	
Liver-kidney	3 (3.0)	2 (2.1)	
Induction therapy (n [%])	76 (76.0)	87 (90.6)	.006
Basiliximab	32 (32.0)	36 (37.5)	.92
Antithymocyte globulin	44 (44.0)	51 (53.1)	.92
Eculizumab ^a	0 (0.0)	1 (1.0)	1.00
None	24 (24.0)	7 (7.3)	0.001
Maintenance immunosuppression regimen (n [%])			
Corticosteroids	100 (100.0)	96 (100.0)	1.00
Tacrolimus	100 (100.0)	93 (96.9)	.12
Mycophenolate mofetil/mycophenolic acid	91 (91.0)	92 (95.8)	.17
Azathioprine	9 (9.0)	4 (4.2)	.17
mTOR inhibitor	0 (0.0)	0 (0.0)	—
AntiCMV IgG R+ serostatus (n [%])	85 (85.0)	84 (87.5)	.73
AntiEBNA IgG R+ serostatus (n [%])	89 (89.0)	86 (89.6)	.75
Delayed graft function (n [%])	49 (49.0)	47 (49.0)	.99
Hospital length of stay, d (median [IQR]) ^b	16 (11-23)	18 (15-28)	.07
Reintubation within the first 2 wk (n [%])	4 (4.0)	4 (4.2)	1.00
Major posttransplant events (n [%])			
Surgical reintervention			

(continued on next page)

Table 2 (continued)

Variable	Preintervention period (n = 100)	Intervention period (n = 96)	P value
Within the first 3 mo	19 (19.0)	20 (20.8)	0.748
Within the first 6 mo	24 (24.0)	21 (21.9)	0.724
Acute graft rejection	11 (11.0)	13 (13.5)	0.59
Graft loss	6 (6.0)	2 (2.1)	0.28
All-cause mortality	9 (9.0)	3 (3.1)	0.09
Infection-related mortality ^c	5 (5.0)	2 (2.1)	1.00

Abbreviations: CMV, cytomegalovirus; D, donor; EBNA, Epstein-Barr nuclear antigen; ESRD, end-stage renal disease; IgA, immunoglobulin A; IgG, immunoglobulin G; IQR, interquartile range; KTR, kidney transplant recipient; mTOR, mammalian target of rapamycin; R, recipient; SD, standard deviation.

^a One patient received antithymocyte globulin and eculizumab.

^b For the index hospitalization.

^c Causes of infection-related death in the preintervention group included pneumonia (2 patients), intraabdominal sepsis, skin and soft tissue infection, and acute graft pyelonephritis (1 patient each). Causes in the intervention period included the rupture of a mycotic aneurysm of the internal iliac artery due to *Rhizopus* spp. and healthcare-associated pneumonia (1 case each).

variables, the Mann-Whitney U test to compare continuous variables with a nonnormal distribution, and the χ^2 or Fisher exact test to analyze differences between proportions. All statistical tests were two-tailed, and the threshold of statistical significance was set at a $P < .05$. Antibiotic consumption was calculated as DoTs per 1000 patient days for each period on the basis of data provided by the unitary dose drug dispensation system. The incidence rates of posttransplant infection (per 1000 patient days) were also assessed. Rate ratios (RRs) with 95% confidence intervals (CIs) were used to compare both periods. To examine the effect of the ASP on the overall consumption of antibiotics and on the use of specific agents (meropenem, antipseudomonal antibiotics [piperacillin/tazobactam, meropenem, ceftazidime, aztreonam, colistin, and amikacin], and vancomycin) over time, interrupted time series analysis was performed using autoregressive integrated moving average models. Statistical analysis was performed with SPSS version 29.0.1.0 (IBM Corp).

3. Results

3.1. Study population and baseline characteristics

Out of a total of 201 eligible KTRs, 196 were included in the present study: 96 and 100 in the intervention and preintervention periods, respectively (a Consolidated Standards of Reporting Trials diagram is available in Supplementary Figure). The clinical characteristics of both cohorts, which were overall comparable, are shown in Table 2. Diabetic nephropathy is the most common cause of end-stage renal disease. Induction therapy was more commonly administered in the intervention than in the preintervention period (90.6% [87/96] vs 76.0% [76/100]; $P = .006$). Maintenance immunosuppression typically consisted of tacrolimus, mycophenolate mofetil, or mycophenolic acid, and prednisone. The incidence of acute graft rejection was comparable across both periods (11.0% [11/100] and 13.5% [13/96] in the preintervention and intervention cohorts, respectively).

3.2. ASP activity

Overall, 291 discrete courses of antimicrobial treatment were prescribed to the 96 KT recipients included in the intervention period, with a median of 2.5 courses per patient (IQR: 1-4). In total, 12.3% (36/291) of the courses met the criteria for ASP review. These 36 courses reviewed were given to 36 patients (37.5% of those in the intervention period) and involved 55 different antibiotic or antifungal agents since 14 patients simultaneously received ≥ 2 antimicrobial agents. In 16.7% (6 instances), the prescribed agent was the most suitable option, whereas, in the remaining 83.3% (30 cases), the treatment could be optimized (Table 3). In detail, the ASP recommended discontinuation of therapy, switching to a narrower-spectrum agent (de-escalation), or switching to or adding on an alternative agent with a broader spectrum of activity (escalation) in 19.4% (7), 44.4% (16), and 16.7% (6) cases, respectively. In 2.8% (1) instances, the antimicrobial treatment was changed, as recommended by the ASP, due to a drug-induced adverse event. Meropenem and anidulafungin were the antimicrobials most frequently optimized. The ASP recommendations were accepted in 91.7% (33/36) of cases.

3.3. Antibiotic consumption

Compared with the preintervention period, there was a reduction in the consumption of meropenem (RR: 0.63; 95% CI: 0.53-0.75; $P < .0001$), amoxicillin/clavulanic acid (RR: 0.61; 95% CI: 0.44-0.82; $P = .001$), ceftazidime (RR: 0.31; 95% CI: 0.21-0.45; $P < .0001$), vancomycin (RR: 0.65; 95% CI: 0.52-0.80; $P < .0001$), and ciprofloxacin (RR: 0.66; 95% CI: 0.54-0.80; $P < .0001$), which was accompanied by an increase in the frequency of prescription of ceftriaxone (RR: 2.03; 95% CI: 1.654-2.493; $P < .0001$) and fosfomycin (RR: 1.80; 95% CI: 1.17-2.76; $P = .008$) (Table 4). Furthermore, we observed a significant decrease in the overall consumption of antibiotics during the intervention period (RR: 0.86; 95% CI: 0.81-0.91; $P < .0001$) (Table 4).

Table 3

Antimicrobial prescriptions were assessed using the antimicrobial stewardship program during the intervention period.

	Prescriptions reviewed (n = 36)
Antibiotics ^a	41
Meropenem	21
Vancomycin	6
Daptomycin	1
Linezolid	4
Amikacin	3
Ciprofloxacin	3
Levofloxacin	1
Amoxicillin/clavulanic acid	1
Metronidazole	1
Antifungals ^a	14
Anidulafungin	6
Micafungin	4
Liposomal amphotericin B	2
Fluconazole	2
Recommendations issued (n [%])	
Discontinuation of therapy	7 (19.4)
Escalation	6 (16.7)
De-escalation	16 (44.4)
No change	6 (16.7)
Change due to an adverse event	1 (2.8)
Acceptance of recommendations (n [%])	33 (91.7)

^a In 14 instances (38.9%) the patient was simultaneously receiving ≥ 2 antimicrobial agents.

3.4. Interrupted time series analysis

The interrupted time series analysis did not confirm the reduction in the overall use of antibiotics ($P = .583$; Fig. 2A), although significant differences were observed for the consumption of antipseudomonal agents ($P = .072$; Fig. 2B) and meropenem ($P = .003$; Fig. 2C). No significant changes were observed for vancomycin ($P = .681$; Fig. 2D).

3.5. Consumption of alcohol-based hand rub solution

Between June 2014 and March 2015 (preintervention period), the overall consumption of alcohol-based hand rub solution at the Department of Nephrology was 121 L. Between June 2015 and March 2016 (intervention period), this figure increased by consumption of alcohol-based hand rub solution increased by 10.7% to 134 L (Fig. 3).

3.6. Incidence of infection

We observed a reduction during the intervention period in the incidence rate of cystitis (RR: 0.30; 95% CI: 0.28–0.32; $P < .001$) and upper UTI (RR: 0.56; 95% CI: 0.33–0.95; $P = .04$) during the first 6 posttransplant months (Table 5). No significant differences were found in the overall incidence of bacterial and fungal infections, including CDI.

There was a reduction in the incidence of infections due to AmpC-producing *Enterobacterales* during the intervention period compared with the preceding period (RR: 0.19; 95% CI: 0.04–0.85; $P = .03$), with no differences in episodes due to ESBL-producing *Enterobacterales* or MDR *P. aeruginosa* (Table 6). No significant differences were observed in the cumulative incidence of recurrent infection by day 30 (8.0% [8/100] vs 3.1% [3/96] in the preintervention and intervention periods, respectively; $P = .138$).

3.7. Graft loss and mortality

Graft loss was reported in 6.0% (6/100) and 2.1% (2/96) of recipients in the preintervention and intervention periods, respectively (P value = 0.279). The all-cause mortality rate was 9.0% (9/100) in the preintervention period and 3.1% (3/96) in the intervention period ($P = .086$). Death was attributable to infection in 7 patients: 5.0% (5) and 2.1% (2) in each period ($P = 1.000$).

4. Discussion

A growing amount of literature supports the feasibility and usefulness of ASP to decrease the consumption of broad-spectrum antibiotics and antifungals in the overall population, as well as the incidence of related complications such as CDI, although maintaining the quality of care provided. A systematic review and meta-analysis reported that ASP is more effective to reduce the incidence of infection and colonization due to antibiotic-resistant bacteria (ie, ESBL-producing *Enterobacterales* and methicillin-resistant *Staphylococcus aureus*) when complemented with infection control measures than when implemented alone, in particular when bundled with hand hygiene program interventions (pooled incidence rate: 0.34, 95% CI: 0.21–0.54).³⁰ Since SOT recipients often receive antimicrobial therapy, there has been a recent interest in the implementation of ASP in this group of patients.^{18–20,31,32} Due to the lack of guidelines and formal recommendations issued by expert groups and ID societies concerning the use of antimicrobials in the SOT population, the diagnostic uncertainty, and the elevated risk of MDR and XDR bacteria, the choice of the empirical and targeted therapy and its duration are usually based on the sole criteria of the attending physician.³³ De-escalation by switching to narrow-spectrum agents whenever possible, shortening the duration of therapy, and prioritization of the oral over parenteral route are some of the standard recommendations typically issued by ASP teams that could be applied in the setting of SOT.³⁴

Some promising trends were observed in the present study. With the aim of optimizing the use of antimicrobials, the ASP

Table 4
Rates of antibiotic consumption in both study periods.

Consumption (DoTs per 1000 patients d) ^a	Preintervention period (n = 100)	Intervention period (n = 96)	RR (95% CI)	P value
Overall antibiotic prescriptions	117.01	100.76	0.86 (0.81-0.91)	<.0001
Penicillins				
Ampicillin	2.24	1.31	0.58 (0.35-0.97)	.049
Amoxicillin/clavulanic acid	6.02	3.65	0.61 (0.44-0.82)	.001
Piperacillin/tazobactam	2.35	2.51	1.07 (0.70-1.62)	.85
Cephalosporins				
Cefuroxime	8.27	5.88	0.71 (0.55-0.91)	.008
Ceftriaxone	7.56	15.36	2.03 (1.65-2.49)	<.0001
Cefixime	0.38	0.97	2.53 (1.05-6.10)	.05
Cefditoren	0.38	0.23	0.59 (0.17-2.03)	.6
Ceftazidime	6.29	1.94	0.31 (0.21-0.45)	<.0001
Carbapenems				
Ertapenem	10.35	9.69	0.94 (0.76-1.15)	.57
Meropenem	19.16	12.07	0.63 (0.53-0.75)	<.0001
Fluoroquinolones				
Ciprofloxacin	14.23	9.47	0.67 (0.55-0.81)	<.0001
Levofloxacin	2.74	2.57	0.94 (0.63-1.40)	.83
Glycopeptides				
Teicoplanin	0.71	0.63	0.88 (0.39-0.97)	.92
Vancomycin	12.76	8.27	0.65 (0.53-0.80)	<.0001
Other groups				
Linezolid	1.69	1.43	0.84 (0.50-1.42)	.61
Daptomycin	1.15	1.19	1.04 (0.57-1.90)	.99
Metronidazole	3.18	2.91	0.92 (0.63-1.33)	.71
Fosfomicin	1.81	3.25	1.80 (1.17-2.76)	.008

Abbreviations: DoT, day of treatment; CI, confidence interval; RR, rate ratio.

^a It was not possible to calculate DoTs for aztreonam, moxifloxacin, gentamycin, tigecycline, and cotrimoxazole since the antibiotic agent was not prescribed in at least one of the periods. DoTs for amikacin were not assessed either because it was prescribed to only 2 patients in the preintervention period and one in the intervention period.

recommended a change in the prescribed agent in 83.3% of the courses reviewed. In most (63.8%) cases, the recommendation consisted of the discontinuation of treatment or the replacement by an agent with a narrower spectrum of activity. This ultimately led to a significant decrease in the consumption of vancomycin and meropenem, which were in most cases replaced by a 3rd-generation cephalosporin. Cefuroxime, amoxicillin/clavulanic acid, and ciprofloxacin have been progressively replaced in our institution by fosfomicin for the treatment of posttransplant asymptomatic bacteriuria and lower UTI in view of the progressive increase in antimicrobial resistance rates among uropathogens.¹⁰ A recent multicenter cohort study that included 14 Spanish transplant centers concluded that oral fosfomicin is a safe and effective alternative to β -lactams and fluoroquinolones for the treatment of

asymptomatic bacteriuria and lower UTI after KT, including episodes due to MDR microorganisms.^{35,36} It is also important to underline the extremely high (91.7%) acceptance rate of the ASP recommendations. Ours was one of the first institutions to implement an ASP in Spain. The noncompulsory hospital-wide program for the assessment and control of antibiotic treatment (PACTA, by its acronym in Spanish) was initiated in March 2002 and initially performed in 6 different departments of the hospital.³⁷ Since 2008, this noncompulsory ASP has been expanded to include antifungal prescriptions for adult patients.³⁸ Over these years, the ASP has become a valuable tool to guide the use of antimicrobials at our center, and the ASP activities are well acknowledged by the clinicians, who have confidence in the program and usually welcome its recommendations. Nevertheless, it must be clarified that these

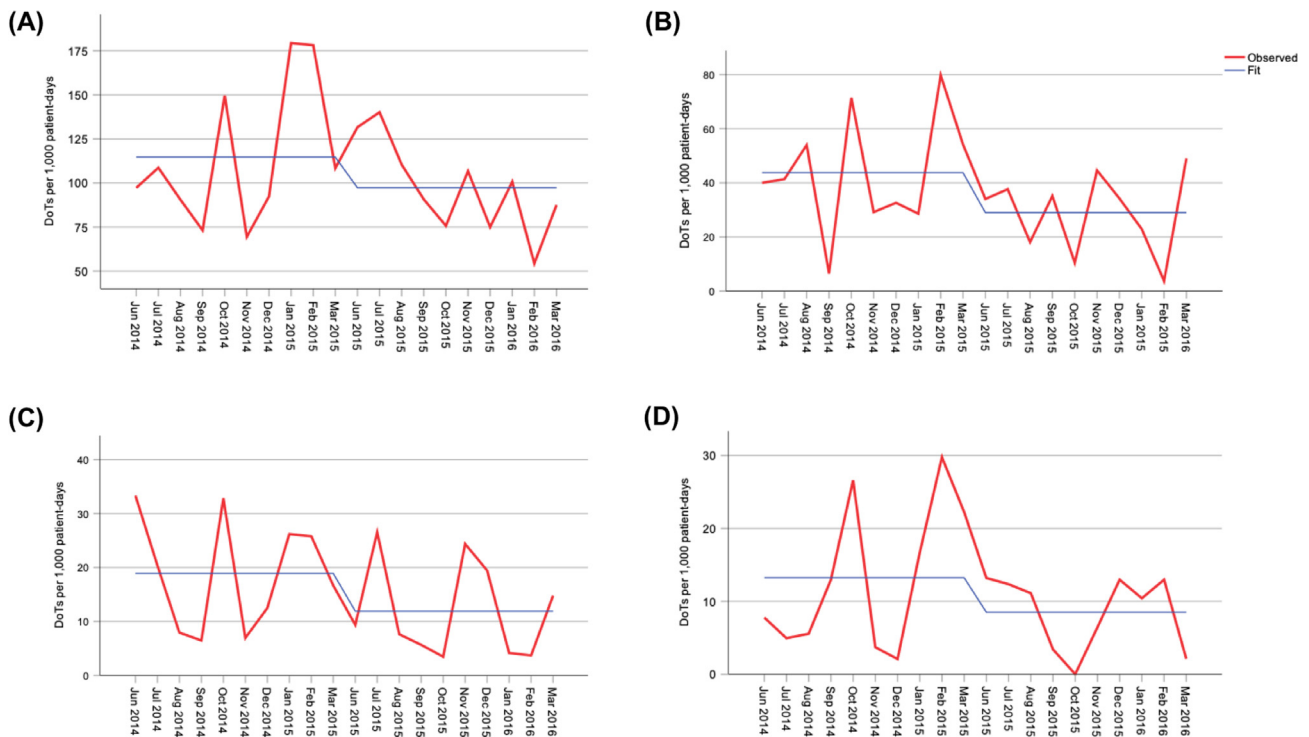


Figure 2. Interrupted time series analysis for monthly antibiotic consumption in days of therapy (DoTs) per 1000 patient-day: (A) all antibiotics; (B) antipseudomonal agents (piperacillin/tazobactam, meropenem, ceftazidime, aztreonam, colistin, and amikacin); (C) meropenem; and (D) vancomycin.

previous hospital-wide ASP initiatives were active for a limited period only and that both programs were not formally in place during the preintervention period due to the lack of personnel dedicated to this purpose. On the other hand, the KT program had an antimicrobial prophylaxis protocol (detailed in Supplementary Methods) that remained unchanged during both periods and essentially covered the use of cefazolin (or ciprofloxacin in the case of β -lactam allergy) as surgical prophylaxis and specific regimens for some

opportunistic infections. There were no local protocols for guiding empirical or targeted therapy during the study period.

We have observed an increase in the consumption of alcohol-based hand rub solutions throughout the intervention and in the following year. Of note, the institutional program promoted by the Department of Preventive Medicine encouraging hand hygiene practices remained in place during the next 9 months, until December 2016. A decrease in the incidence of cystitis and upper UTIs was also observed. Since there were no formal changes in the institutional protocols regarding the management of the Foley urinary catheter throughout the study period, it might be assumed that this reduction would be a consequence of the improvement in hand hygiene practices and infection control measures, both of which were exhaustively reinforced during the briefings and educational sessions attended by the medical and nursing staff. The importance of maintaining a sterile technique for the insertion and care of the urinary catheter was specifically highlighted, as was the need for prompt catheter removal as soon as it was no longer deemed necessary. There was also a nonsignificant decreasing trend in the incidence of SSI and catheter-related BSI. Adequate hand hygiene compliance and thorough maintenance of central and peripheral venous catheters, which were also comprehensively revised in the bedside meetings and sessions, would also account for these changes in local epidemiology. On the other hand, the tested intervention had no apparent unintended consequences in terms of 30-day recurrent infection, the need for surgical reintervention, or graft loss.

Some limitations must be acknowledged. The number of KTRs included and the 6-month follow-up could have been insufficient to

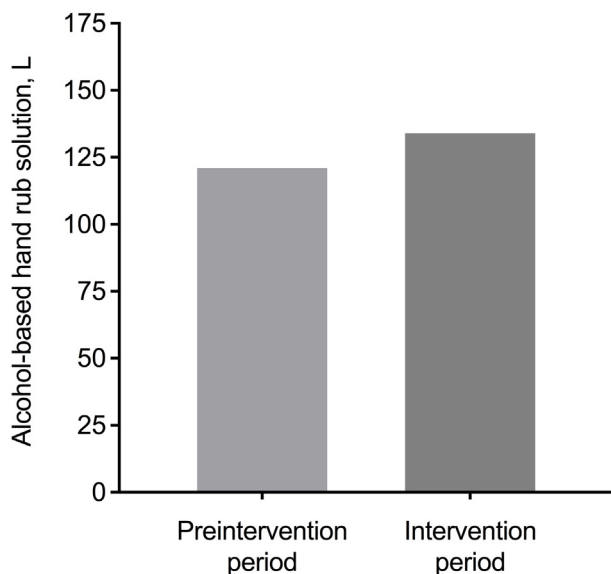


Figure 3. Comparison of the consumption of alcohol-based hand rub solution at the Department of Nephrology across the preintervention (June 2014 to March 2015) and the intervention period (June 2015 to March 2016).

Table 5
Incidence of posttransplant infection in both study periods.

Incidence rate (per 1000 patients d)	Preintervention period (n = 100)	Intervention period (n = 96)	RR (95% CI)	P value
Urinary tract infection	4.27	3.25	0.76 (0.54-1.07)	.12
Cystitis	1.69	0.51	0.30 (0.28-0.33)	<.001
Upper urinary tract infection ^a	2.14	1.19	0.56 (0.33-0.95)	.04
Surgical site infection	0.60	0.39	0.66 (0.26-1.71)	.55
Respiratory tract infection	0.27	0.34	1.25 (0.32-5.18)	.94
Pneumonia	0.22	0.23	1.05 (0.19-5.93)	1.23
Hospital-acquired pneumonia	0.16	0.23	1.39 (0.23-9.48)	.95
Intra-abdominal infection	0.16	0.06	0.35 (0.01-4.32)	.65
Bloodstream infection	1.26	1.37	1.09 (0.61-1.93)	.89
Catheter-related bloodstream infection	0.32	0.11	0.35 (0.03-1.94)	.31
MDR bacterial infection	0.08	0.11	1.43 (0.57-3.65)	.41
<i>Clostridioides difficile</i> infection	0.22	0.17	0.78 (0.11-4.62)	1.04

Abbreviations: CI, confidence interval; MDR, multidrug-resistant; RR, rate ratio.

^a Includes acute graft pyelonephritis and perinephric abscess.

show a reduction in the incidence of overall infection or, specifically, MDR bacterial or fungal infections. This would explain why the rate of ESBL-producing *Enterobacteriales* or MDR *Pseudomonas* remained stable despite the significant decrease in the incidence of episodes due to AmpC-producing Gram-negative bacilli. The preintervention period was based on a retrospective historical cohort. Therefore, we cannot rule out that the reduction

in antibiotic consumption and in the incidence of some events could have been due to factors unrelated to the ASP/HAIC initiative, such as secular trends in prescribing habits.³⁹ Nonetheless, both groups were comparable in their epidemiological characteristics and risk factors. On the other hand, beyond the practical difficulties of minimizing the spillover effect, we felt that the inclusion of a concurrent control group would have raised ethical

Table 6
Incidence of posttransplant infection according to the causative agent.

Incidence rate (per 1000 patients d)	Preintervention period (n = 100)	Intervention period (n = 96)	RR (95% CI)	P value
<i>Escherichia coli</i>	1.92	1.88	0.98 (0.61-1.60)	.96
ESBL-producing <i>E. coli</i>	0.60	0.45	0.76 (0.30-1.88)	.713
<i>Klebsiella pneumoniae</i>	0.60	0.68	1.14 (0.50-2.57)	.922
ESBL-producing <i>K. pneumoniae</i>	0.44	0.39	0.91 (0.33-2.51)	1.064
<i>Proteus</i> spp.	0.22	0.06	0.26 (0.005-2.63)	.401
ESBL-producing <i>Enterobacteriales</i>	1.04	0.86	0.82 (0.42-1.62)	.690
AmpC-producing <i>Enterobacteriales</i> ^a	0.60	0.11	0.19 (0.04-0.85)	.027
<i>Enterococcus</i> spp.	0.71	0.63	0.88 (0.39-1.97)	.917
<i>E. faecalis</i>	0.55	0.51	0.94 (0.38-2.31)	1.072
<i>E. faecium</i>	0.16	0.06	0.35 (0.007-4.32)	.656
<i>Pseudomonas aeruginosa</i>	0.82	0.63	0.76 (0.35-1.66)	.628
MDR <i>P. aeruginosa</i>	0.05	0.11	2.08 (0.11-122.91)	.969
Coagulase-negative staphylococci	0.27	0.11	0.42 (0.04-2.54)	.487
<i>Candida</i> spp.	0.22	0.23	1.04 (0.19-5.59)	1.228
<i>Candida albicans</i>	0.16	0.23	1.39 (0.23-9.48)	.955

Abbreviations: CI, confidence interval; ESBL, extended-spectrum β-lactamase; MDR, multidrug-resistant; RR, rate ratio.

^a Includes *Enterobacter* spp, *Citrobacter* spp., and *Serratia* spp.

concerns since the intervention was aimed at improving the quality of care in our program and reducing the adverse events related to the inadequate use of antimicrobials. The modification of prescribing habits once the involved medical staff became aware of antimicrobial stewardship monitoring (Hawthorne effect) cannot be completely ruled out,⁴⁰ although it should be noted that the prescribing nephrologists and urologists were not informed about the specific audit activities. In addition, direct in-room observations took place at specific points only throughout the 10-month duration of the intervention period, when the dedicated ID physician joined the medical staff during their clinical rounds. It is not possible to discern whether the decrease in antibiotic consumption was directly related to the ASP or indirectly depended on the reduction in the incidence of infections attributable to the HAIC initiative. Therefore, we would advocate for considering both interventions as a single bundle to be concurrently implemented on the grounds of efficiency and logistical convenience. Finally, a major limitation is that the effective compliance with several of the proposed HAIC interventions was not assessed. We were unable to directly quantify the degree of adherence to hand hygiene practices or transmission-based precautions (beyond the surrogate of consumption of alcohol-based hand rub solution), the appropriateness of use of personal protective equipment, or the rates of influenza vaccination uptake among HCWs. In addition, the potential long-term impact of the ASP and HAIC activities on the whole institution was not investigated.

Nevertheless, the present study has some strength. As mentioned above, the limited human resources available implied that a single ID specialist was responsible for carrying out the ASP/HAIC initiative during the entire intervention period. In addition, most of the nursing staff and all the physicians in the Departments of Nephrology and Urology also remained unchanged, thus minimizing the effect of unmeasured confounding due to behavioral and attitudinal variations secondary to staff turnover. Although there was some rotation among residents and nursing students, they were always under the direct supervision of trained staff. No structural changes have been implemented so far in our institution to ensure the long-term sustainability of the tested interventions, although the ASP has been included in the portfolio of clinical activities carried out by the Unit of Infectious Diseases, and targeted HAIC campaigns are periodically performed.

In conclusion, a joint approach based on an ASP and a HAIC initiative is effective in optimizing the use of antimicrobials and reducing the incidence of common bacterial infection among KTRs. Such a strategy may be extended to other SOT programs and should be considered as an opportunity for improving the outcomes of the transplant procedure.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose, as described by the American Journal of Transplantation.

Data availability

All data generated or analyzed during this study are included in this published article. The data that support the findings of this study are available on request from the corresponding author.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ajt.2023.07.009>.

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