ORIGINAL ARTICLE

Changing trends in the aetiology, treatment and outcomes of bloodstream infection occurring in the first year after solid organ transplantation: a single-centre prospective cohort study

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SUMMARY

To analyse trends in the aetiology, treatment and outcomes of bloodstream infection (BSI) within the first year post-transplant over the last 10-year period, we prospectively recorded all episodes of BSI occurring in solid organ transplant (SOT) recipients during the first year post-transplant from 2007 to 2016. Trends of factors were analysed by 2-year periods. Of 475 consecutive episodes of BSI, 218 occurred within a year of SOT in 178 SOT recipients. Gram-positive BSI decreased over time (40.5–2.2%). In contrast, there was a steady increase in Gram-negative bacilli (GNB) BSI (54.1–93.3%; $P < 0.001$), mainly due to *Pseudomonas aeruginosa* (2.4–20.4%) and *Klebsiella pneumoniae* (7.1–26.5%). Multidrug-resistant (MDR) GNB (4.8–38.8%; $P < 0.001$) rose dramatically, especially due to extended-spectrum β-lactamase (ESBL) production (7.1–34.7%). There was a sharp rise in the use of carbapenems, both as empirical (11.9–55.3%; $P < 0.001$) and as targeted antibiotic treatment (11.9–46.9%; $P < 0.001$). In conclusion, today, GNB are the leading causative agents of BSI in SOT recipients within the first year after SOT. In addition, MDR GNB have emerged mainly due to ESBL-producing strains. In spite of these changes, length of hospital stay, days of treatment and mortality have remained stable over time.

Transplant International 2017; 30: 903–913

Key words
bacteraemia, multidrug resistance, organ transplantation, trends

Received: 16 March 2017; Revision requested: 24 April 2017; Accepted: 8 May 2017; Published online: 13 July 2017

doi:10.1111/tri.12984

Introduction

Bacterial infections now constitute the most frequent complication among solid organ transplant (SOT) recipients, having overtaken classical opportunistic infections [1,2]. In particular, bloodstream infections (BSI) occur in over one-third of SOT recipients and are associated with a higher rate of mortality, almost reaching 50% when accompanied by septic shock [3,4]. The management of BSI in SOT recipients is one of the most challenging clinical issues today.

In recent years, the emergence of multidrug-resistant (MDR) organisms has generated concern worldwide [5–8]. However, the changes over time in the aetiology of BSI in SOT recipients and the scale of the issue in this population have not been assessed in depth. This means that information has to be extrapolated from cohort studies reporting a high prevalence of BSI due to MDR Gram-negative bacilli (GNB) in their global series.

Understanding the changes over time in the epidemiology of BSI is imperative in order to allow prompt specific diagnostic testing and early empiric antibiotic therapy directed against these organisms in SOT recipients, and thus to improve short- and long-term patient outcomes. With this objective in mind, we aimed to analyse trends in aetiology, treatment and outcomes of BSI in the first year post-transplant over the last 10-year period.

Patients and methods

Setting and study population

We conducted a prospective observational study at a tertiary university referral hospital in Barcelona, Spain, with an active transplantation programme (annual average of 104 kidney transplants, 50 liver transplants and 15 heart transplants). From 1 January 2007 to 31 December 2016, all episodes of BSI occurring in the first year post-transplant in hospitalized adult SOT recipients were included. Data regarding baseline characteristics, including immunosuppressive treatment, occurrence of acute allograft rejection and opportunistic infections, clinical features, microbiological studies and outcomes were carefully recorded in a specific database. The study was approved by the ethics committee of our institution and conformed to the STROBE checklist.

At our hospital, the microbiology laboratory reports all positive results of blood cultures to the infectious disease team on a daily basis. All patients with BSI are visited by an infectious disease physician and followed up. Changes in antimicrobial treatment and general management are discussed when necessary.

Definitions

In accordance with the current standard definition, multidrug resistance was defined as acquired nonsusceptibility to at least one agent in three or more antimicrobial categories [9]. BSI was considered to be nosocomial-acquired or community-acquired according to previously described criteria [10].

The BSI source was determined on the basis of clinical criteria, and the isolation of any organism from a clinically significant site of infection matched with that obtained in blood cultures on the basis of the species identification and antibiotic susceptibility results. Catheter-related BSI was documented when the blood isolate was cultured from the catheter tip ($>10^3$ CFUs/ml). As the depth of infection was often difficult to determine, we combined surgical wound infections and abdominal organ/space infections into a single infectious source [11]. BSI was considered to be from a primary or unknown source in patients in whom no other BSI sites were identified.

Prior antibiotic therapy was defined as the receipt of any systemic antibiotic for more than 48 h in the previous 3 months. We defined empirical antibiotic therapy as therapy used before the results of the antimicrobial susceptibility testing became available. Empirical antibiotic therapy was considered to be inadequate or inappropriate if the treatment regimen did not include at least one antibiotic active *in vitro* against the infecting microorganism.

Sepsis was defined as the presence (probable or documented) of infection together with systemic manifestations of infection. Septic shock was defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation, in accordance with the International Guidelines of the Surviving Sepsis Campaign [12].

Acute allograft rejection was considered to be present when proven by biopsy, and 30-day mortality was defined as death from any cause within the first 30 days of the onset of BSI.

Antimicrobial prophylaxis

Solid organ transplant patients received perioperative antibacterial prophylaxis for up to 48 h after transplantation. Specifically, kidney recipients received intravenous amoxicillin–clavulanate, and heart and liver recipients received intravenous vancomycin or teicoplanin plus aztreonam.

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Prophylaxis to prevent *Pneumocystis jirovecii* infection with trimethoprim–sulphamethoxazole (a double-strength tablet taken once three times a week in liver recipients and once a day in heart and kidney recipients) was given in the first 6 months after transplantation. However, the onset of treatment was usually delayed to the second week post-transplant in order to wait for post-transplant stabilization.

We used a prophylactic approach for patients at high risk of cytomegalovirus disease [D+/R− patients, and patients who received antithymocyte globulin (ATG)]. In the other cases, we used a pre-emptive therapy approach [13].

High-risk liver transplant recipients (multiple transfusions, prolonged ICU stay, post-transplant surgical intervention, retransplantation, known fungal colonization prior to transplantation, prolonged use of broad spectrum antibiotics or need for renal replacement therapy) were administered antifungal prophylaxis against *Candida* spp. The antifungal administered was either fluconazole or an echinocandin, depending on the risk of drug interactions and toxicity. In heart recipients with a high risk of invasive aspergillosis (*Aspergillus* spp. colonization of the respiratory tract, re-intervention, need for renal replacement therapy, hypogammaglobulinaemia (IgG <400 mg/dl), ICU readmission or rejection episodes), we used prophylaxis either with nebulized amphotericin B or an echinocandin [14].

Microbiological studies

Blood samples were processed with the BACTEC 9240 method (Becton-Dickinson Microbiology Systems, Sparks, MD, USA). The inoculated bottles were incubated for 5 days at 35 °C before being discharged. Microbial identification was performed with commercially available panels [MicroScan (Siemens Healthcare Diagnosis Inc, West Sacramento, CA, USA) or Vitek (bioMérieux SA, Marcy-L'Etoile, France)], with standard biochemical and/or enzymatic tests, or with matrix-assisted laser desorption ionization time-of-flight mass spectrometry (Bruker Daltonics, Bremen, Germany). EUCAST criteria were used to define susceptibility or resistance to antimicrobial agents.

Antibiotic susceptibility was tested with the microdilution method, following EUCAST guidelines. The screening of MDR phenotypes, including methicillin-resistant *Staphylococcus aureus*, ampicillin-resistant *enterococci*, extended-spectrum β-lactamase producers and carbapenemase producers, was performed according to EUCAST recommendations.

Statistical analysis

Data are presented as percentages and numbers or medians and interquartile ranges (IQR). To test for a linear trend, BSI were divided into five 2-year periods (2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016) defining 2007–2008 as the reference period.

We focused our trends analysis on selected variables based on the review of existing literature on the general population: rate of Gram-negative bacilli (GNB), rate of multidrug-resistant (MDR) GNB, rate of *Pseudomonas aeruginosa*, rate of ESBL-producing *Enterobacteriaceae*, rate of ESBL-producing *Klebsiella pneumoniae* strains, rates of empirical and targeted treatment with carbapenems and days of treatment. These selected variables did not have missing data. Trends of factors for these variables were analysed using the Mantel–Haenszel test for categorical variables and linear regression for continuous variables.

All statistical tests were two-tailed, and the threshold of statistical significance was $P < 0.05$. All statistical calculations were performed using STATA statistical software release 13.0 (STATA Corp., College Station, TX, USA).

Results

During the study period, 1829 solid organ transplants were performed at our centre (1113 kidney transplants, 547 liver transplants and 169 heart transplants). A total of 475 consecutive episodes of BSI were identified. Of these, 218 occurred during the first year after SOT (42 in 2007–2008; 24 in 2009–2010; 60 in 2011–2012; 43 in 2013–2014; and 49 in 2015–2016) in 178 patients.

Demographic characteristics and immunosuppressive treatment of SOT recipients presenting BSI within the first year of SOT compared by 2-year periods are shown in Table 1. Days between transplantation and the first episode of BSI increased throughout the study period. SOT recipients tended to present a greater number of comorbidities, including diabetes mellitus and chronic kidney disease. There were no temporal differences in terms of age, sex or immunosuppressive treatment.

Clinical characteristics of the episodes at the onset of BSI divided by 2-year periods are summarized in Table 2. The percentage of nosocomial-acquired episodes of BSI decreased significantly over time, as did the rate of episodes occurring in SOT recipients admitted to the intensive care unit (ICU). Likewise, the percentage of episodes in which the patient received antibiotic treatment in the previous 3 months declined, due to a significant reduction in prior use of β-lactamase inhibitors.

Table 1. Demographic characteristics and immunosuppressive treatment of solid organ transplant (SOT) recipients presenting bloodstream infection within the first year of SOT divided into 2-year periods.

Variable	All patients	2007–2008 (*N* = 34)	2009–2010 (*N* = 20)	2011–2012 (*N* = 50)	2013–2014 (*N* = 31)	2015–2016 (*N* = 43)
Age, years (median, IQR)	60 (52–66)	61 (51–65)	59 (46–66)	60 (52–66)	60 (53–67)	60 (51–68)
Male sex (*n*, %)	120 (67.4)	22 (64.7)	15 (75.0)	30 (60.0)	24 (77.4)	29 (67.4)
Type of transplant						
Liver (*n*, %)	49 (27.5)	12 (35.3)	7 (35.0)	15 (30.0)	6 (19.4)	9 (20.9)
Kidney (*n*, %)	91 (51.1)	17 (50.0)	11 (55.0)	22 (44.0)	16 (51.6)	25 (58.1)
Heart (*n*, %)	32 (18.0)	5 (14.7)	2 (10.0)	11 (22.0)	31 (25.8)	6 (14.0)
Multiorgan (*n*, %)	6 (3.8)	0	0	2 (4.0)	1 (3.2)	3 (7.0)
Prior transplant (*n*, %)	13 (7.3)	3 (8.8)	0	3 (6.0)	3 (9.7)	4 (9.3)
Acute allograft rejection within preceding 6 months (*n*, %)	19 (10.7)	4 (11.8)	2 (10.0)	5 (10.0)	4 (12.9)	4 (9.3)
Underlying diseases (*n*, %)	142 (80.2)	25 (73.5)	18 (90.0)	39 (78.0)	24 (76.7)	36 (85.7)
Diabetes mellitus (*n*, %)	45 (25.3)	9 (26.5)	2 (10.0)	11 (22.0)	8 (26.7)	15 (34.9)
Renal impairment* (*n*, %)	21 (11.8)	1 (2.9)	1 (5.0)	3 (6.0)	2 (6.5)	14 (32.6)
Chronic heart disease (*n*, %)	33 (18.5)	4 (11.8)	4 (20.0)	7 (14.0)	5 (16.1)	13 (30.2)
COPD (*n*, %)	9 (5.1)	2 (5.9)	2 (10.0)	2 (4.0)	0	2 (7.0)
TMT-SMZ prophylaxis (*n*, %)	73 (41.0)	8 (23.5)	4 (20.0)	20 (40.0)	18 (58.1)	23 (53.5)
Immunosuppressive regimens (*n*, %)						
Prednisone (*n*, %)	158 (88.8)	27 (79.4)	19 (95.0)	46 (92.0)	29 (93.5)	37 (86.0)
Mycophenolate mofetil (*n*, %)	148 (83.1)	26 (76.5)	14 (70.0)	43 (86.0)	29 (93.5)	36 (83.7)
Calcineurin inhibitors (*n*, %)	164 (92.1)	31 (91.2)	20 (100.0)	44 (88.0)	29 (93.5)	40 (93.0)
mTOR inhibitors (*n*, %)	9 (5.1)	3 (8.8)	1 (5.0)	2 (4.0)	1 (3.2)	2 (4.7)
ATG <6 m (*n*, %)	32 (18.1)	4 (11.8)	8 (40.0)	2 (4.0)	6 (19.4)	12 (28.6)
Lymphocyte-depleting antibody at transplant <6 m (*n*, %)	127 (71.3)	27 (79.4)	11 (55.0)	43 (86.0)	25 (80.6)	21 (48.8)
Days from transplantation (median, IQR)	28 (10–107)	24 (11–100)	27 (9–88)	30 (11–91)	21 (10–81)	49 (11–157)

TMP-SMZ, trimethoprim- sulfamethoxazole; COPD, chronic obstructive pulmonary disease; ATG, antithymocyte globulin; IQR, interquartile range.

Data are % of patients, unless otherwise indicated.

*Renal impairment was defined as a serum creatinine level >1.5 mg/dl.

Table 2. Trends of clinical characteristics of all episodes at the onset of bloodstream infection compared by 2-year periods.

Variable	All episodes of BSI	2007–2008 (*N* = 42)	2009–2010 (*N* = 24)	2011–2012 (*N* = 60)	2013–2014 (*N* = 43)	2015–2016 (*N* = 49)
Source of BSI						
Primary source (*n*, %)	28 (13.1)	7 (16.7)	7 (29.2)	5 (8.3)	4 (9.3)	5 (10.4)
Catheter-related BSI (*n*, %)	30 (13.6)	9 (21.4)	5 (20.8)	12 (20.0)	4 (9.3)	0
Pneumonia (*n*, %)	6 (2.8)	0	1 (4.2)	1 (1.7)	3 (7.0)	1 (2.1)
Urinary tract infection (*n*, %)	97 (44.9)	18 (42.9)	8 (33.3)	19 (31.7)	19 (44.2)	33 (68.8)
Abdominal (*n*, %)	43 (19.6)	5 (11.9)	2 (8.3)	18 (30.0)	10 (23.3)	8 (16.7)
Other (*n*, %)	13 (6.1)	3 (7.1)	1 (4.2)	5 (8.3)	3 (7.0)	1 (2.1)
Prior antibiotic therapy* (*n*, %)	151 (69.6)	40 (95.2)	13 (54.2)	47 (78.3)	26 (61.9)	25 (51.0)
Prior use of carbapenem (*n*, %)	45 (20.6)	5 (11.9)	3 (12.5)	16 (26.7)	8 (18.6)	13 (26.5)
Prior use of cephalosporin (*n*, %)	16 (7.5)	3 (7.1)	3 (12.5)	5 (8.3)	1 (2.3)	4 (8.2)
Prior use of quinolone (*n*, %)	11 (5.0)	2 (4.8)	0	6 (10.0)	2 (4.7)	1 (2.0)
Prior use of β-lactam/β-lactamase inhibitors (*n*, %)	46 (21.5)	21 (50.0)	1 (4.2)	14 (23.3)	6 (14.0)	4 (8.2)
Use of urinary catheter (*n*, %)	109 (50.0)	21 (50.0)	15 (62.5)	29 (48.3)	20 (46.5)	24 (49.0)
Use of venous catheter (*n*, %)	134 (61.2)	27 (64.3)	17 (70.8)	41 (68.3)	25 (58.1)	24 (49.0)
Septic shock at presentation† (*n*, %)	38 (17.8)	2 (4.9)	4 (16.7)	17 (28.3)	5 (11.6)	10 (20.8)
Nosocomial acquisition (*n*, %)	167 (76.6)	38 (90.5)	20 (83.3)	50 (83.3)	25 (58.1)	34 (69.4)
Days since transplantation (median, IQR)	39 (12–133)	32 (13–143)	32 (11–94)	35 (15–92)	68 (11–132)	54 (11–205)
Days since hospital stay (median, IQR)	10 (0–28)	13 (0–27)	11 (2–31)	16 (3–35)	5 (0–14)	4 (0–12)

*Prior antibiotic therapy was defined as the administration of any systemic antibiotic in the preceding month.

†Septic shock was defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation.

Changing trends in the aetiology of episodes of BSI during the first year of SOT were documented throughout the study period (Table 3 and Fig. 1). The rates of Gram-positive bacteria as the cause of BSI fell significantly over the last 10 years, and in fact in the last period represented only 2.2% of all episodes.

In contrast, there was a steady increase in Gram-negative bacilli (GNB) BSI (54.1–93.3%; $P < 0.001$), mainly due to *P. aeruginosa* (2.4–20.4%; $P = 0.012$) and *Enterobacteriaceae* strains. *Klebsiella pneumoniae* (with an increase from 7.1% to 26.5%) was the causative agent of almost a quarter of the episodes of BSI in the last 2-year period. The rate of candidemia remained stable over time.

As regards antibiotic resistance, we observed a dramatic increase in multidrug-resistant GNB isolates (4.8–38.8%; $P < 0.001$), especially due to ESBL-producing *Enterobacteriaceae* (7.1–34.7%; $P < 0.001$) at the expense of ESBL-producing *K. pneumoniae* strains (0–24.5%; $P < 0.001$). Antimicrobial susceptibility testing showed marked increases in resistance to quinolones and β-lactamase inhibitors among those *Enterobacteriaceae* bloodstream isolates were susceptible to cephalosporins. Moreover, resistance to aminoglycosides rose in ESBL-producing *Enterobacteriaceae* strains (Fig. 2). The rate of MDR *P. aeruginosa* remained unchanged over time.

Table 4 shows the main changes in antibiotic therapy of the episodes of BSI during the study period. There was a significant linear trend towards an increase in the use of carbapenems as both empirical (11.9–55.3%; $P < 0.001$) and targeted antibiotic treatment (11.9–46.9%; $P < 0.001$). Likewise, the use of cephalosporins as a targeted treatment increased significantly. There were no changes in the rate of inadequate empirical antibiotic therapy or in days of antibiotic treatment ($P = 0.997$).

Outcomes of the episodes of BSI are shown in Table 5. The presence of acute renal failure increased over the study period, but length of hospital stay and ICU stay fell notably. There were no changes in 30-day mortality or 7-day mortality during the study period.

Discussion

This observational study of a prospective cohort of adult SOT recipients presenting BSI within the first year after SOT found a dramatic increase in GNB BSI, especially MDR strains, at the expense of ESBL-producing *K. pneumoniae* isolates over the last 10 years. This was in spite of notable reductions in nosocomial-acquired infections and in prior use of antibiotics.

Previous studies focusing on temporal changes in the aetiology of BSI are scarce. Singh *et al.* [15] described a shift towards GNB as the predominant pathogens in liver recipients with BSI between 1983 and 2003 and a lower rate of antibiotic resistance. Later, Al-Hasan *et al.* found a linear upward trend in resistance to quinolones among *Escherichia coli* isolates, detecting only three strains of ESBL-producing *E. coli* in their series. In contrast, Berenger *et al.* [16] reported that Gram-positive organisms were the most frequent aetiological agents in a large cohort of nosocomial BSI of SOT recipients from 2003 to 2012.

Our study provides comprehensive information on aetiological changes over time in SOT recipients with BSI. At the same time, the higher rates of antimicrobial resistance concur with data from recent studies, which report much higher rates of antibiotic resistance in GNB in their series [17–20] and reflect the growing concern with antibiotic resistance worldwide [8]. SOT patients are particularly prone to MDR bacterial infections, probably due to their frequent manipulation and the use of antibiotics and devices [21–23].

On the other hand, the sharp decrease in the pathogenic role of gram-positive bacteria could be related to the decrease in the incidence of catheter-related BSI during the study period. Remarkably, in 2003 a programme for the prevention of catheter-related bacteraemia was implemented in our centre. Moreover, the type of dressing was changed to a semi-permeable transparent one, and in 2013, the type of peripheral venous catheter was changed to other with a closed integral system. These initiatives as well as the awareness of all the hospital staff have allowed a progressive reduction of the catheter-related BSI in our series.

As regards antibiotic treatment, our study shows a marked increase in the use of carbapenems both as empirical and as targeted antibiotic treatment. This is probably the result of the rise in ESBL-producing strains as the aetiological agent of BSI in SOT. However, although carbapenems represent the cornerstone of treatment for ESBL-producing *Enterobacteriaceae*, their use has a number of drawbacks: for instance, their wide spectrum of activity which may promote bacterial infections and the potential selection of carbapenem-resistant variants, and the need for an intravenous route of administration [5,7].

Although some studies have proposed a combination of β-lactam/β-lactamase inhibitors as an alternative to carbapenems for treating these resistant strains in the general population [24], the usefulness of this approach

Table 3. Causative organisms of all episodes of bloodstream infection (BSI) occurring during the first year of solid organ transplant compared by 2-year periods.

Aetiology	All episodes of BSI	2007–2008 (*N* = 42)	2009–2010 (*N* = 24)	2011–2012 (*N* = 60)	2013–2014 (*N* = 43)	2015–2016 (*N* = 49)
Gram-positive bacteria (*n*, %)	42 (19.3)	15 (40.5)	7 (35.0)	11 (22.4)	8 (20.5)	1 (2.2)
Streptococci (*n*, %)	3 (1.4)	1 (2.4)	0	0	1 (2.3)	1 (2.0)
Staphylococcus aureus (*n*, %)	11 (5.0)	3 (7.1)	6 (25.0)	1 (1.7)	1 (2.3)	0
Enterococcus faecalis (*n*, %)	8 (3.7)	4 (9.5)	1 (4.2)	2 (3.3)	1 (2.3)	0
Enterococcus faecium (*n*, %)	3 (1.4)	0	0	2 (3.3)	1 (2.3)	0
CNS (*n*, %)	16 (7.3)	7 (16.7)	0	6 (10.0)	3 (7.0)	0
Gram-negative bacilli (*n*, %)	138 (63.3)	20 (54.1)	12 (60.0)	33 (67.3)	31 (79.5)	42 (93.3)
Multidrug-resistant GNB (*n*, %)	57 (26.1)	2 (4.8)	5 (20.8)	15 (25.0)	16 (37.2)	19 (38.8)
Enterobacteriaceae (*n*, %)	105 (48.2)	19 (45.2)	8 (33.3)	23 (38.3)	23 (53.5)	32 (65.3)
Klebsiella pneumoniae (*n*, %)	33 (15.1)	3 (7.1)	2 (8.3)	7 (11.7)	8 (18.6)	13 (26.5)
Escherichia coli (*n*, %)	52 (23.9)	9 (21.4)	4 (16.7)	15 (25.0)	11 (25.6)	13 (26.5)
ESBL-producing *Enterobacteriaceae* (*n*, %)	44 (20.2)	3 (7.1)	2 (8.3)	10 (16.7)	12 (27.9)	17 (34.7)
ESBL-producing *K. pneumoniae* (*n*, %)	24 (11.0)	0	0	5 (8.3)	7 (16.3)	12 (24.5)
ESBL-producing *E. coli* (*n*, %)	11 (5.0)	2 (4.7)	0	3 (5.0)	3 (6.9)	3 (6.1)
Other Enterobacteriaceae (*n*, %)	20 (9.2)	7 (16.7)	2 (8.3)	1 (1.7)	4 (9.3)	6 (12.2)
Nonfermenting GNB (*n*, %)	32 (14.7)	1 (2.4)	4 (16.7)	10 (16.7)	7 (16.3)	10 (20.4)
Pseudomonas aeruginosa (*n*, %)	29 (13.3)	1 (2.4)	3 (12.5)	8 (13.3)	7 (16.3)	10 (20.4)
MDR *P. aeruginosa* (*n*, %)	16 (7.3)	1 (2.4)	3 (12.5)	4 (6.7)	5 (11.6)	3 (6.1)
Nonfermenting GNB other than *P. aeruginosa* (*n*, %)	3 (1.4)	0	1 (4.2)	2 (3.3)	0	0
Candida spp. (*n*, %)	7 (3.2)	2 (5.4)	1 (5.0)	3 (6.1)	0	1 (2.2)
Anaerobes (*n*, %)	3 (1.4)	0	0	2 (4.1)	0	1 (2.2)
Polymicrobial (*n*, %)	28 (12.8)	5 (11.9)	4 (16.7)	11 (18.3)	4 (9.3)	4 (8.2)

CNS, Coagulase-negative staphylococci; MDR, multidrug-resistant; ESBL, extended-spectrum β-lactamase.

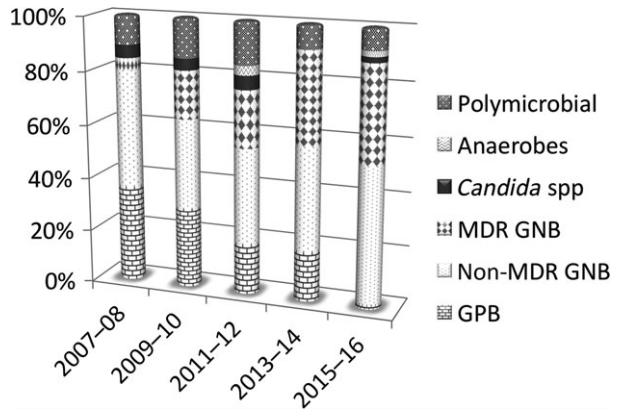

Figure 1 Changes in the aetiology of bloodstream infection by 2-year periods.

for the treatment of BSI in SOT recipients has not been conclusively demonstrated. The INCREMENT-SOT project, currently in progress, should shed light on this issue [25]. Nevertheless, it should be noted that our study showed *in vitro* resistance in more than 60% of the ESBL strains.

Although the reported experience in SOT recipients is very limited, other antibiotics are increasingly being used for the treatment of MDR GNB infections, including fosfomycin, tigecycline and above all colistin [26–28]. Regrettably, the use of colistin is associated with a higher risk of nephrotoxicity because of the use of nephrotoxic medications such as calcineurin inhibitors and the high rate of underlying renal impairment in SOT recipients. New combinations of cephalosporins/β-lactamase inhibitors have recently been introduced into clinical practice. Their role in MDR GNB infections in SOT recipients remains to be seen.

Surprisingly, in spite of the emergence of MDR GNB strains in our series and the increase in treatment with carbapenems over the study period, length of hospital stay and length of ICU stay after BSI experienced a marked decline. Nor were there were any changes in days of intravenous antibiotic or in days of antibiotic treatment. Probably this is due to the efforts made in recent years to avoid the overuse of antibiotics and to reduce the impact of BSI in SOT recipients [2]. Thirty-day mortality and 7-day mortality have remained stable over the last 10 years. Interestingly, some investigators have recently suggested that sepsis among SOT recipients could have a lower mortality than in the general population, due to the modulation of the inflammatory response secondary to immunosuppressive treatment [29,30].

The strengths of this study include the prospective nature of the cohort, the comprehensive data collection over a period of 10 years, and the large number of a wide spectrum of SOT recipients. However, it should be borne in mind that the study was conducted at a single centre and the extrapolation of our data to other settings should be performed with care.

In summary, we report significant changes in the aetiology of BSI within the first year after SOT. Today, GNB are the leading causative agents of BSI in SOT

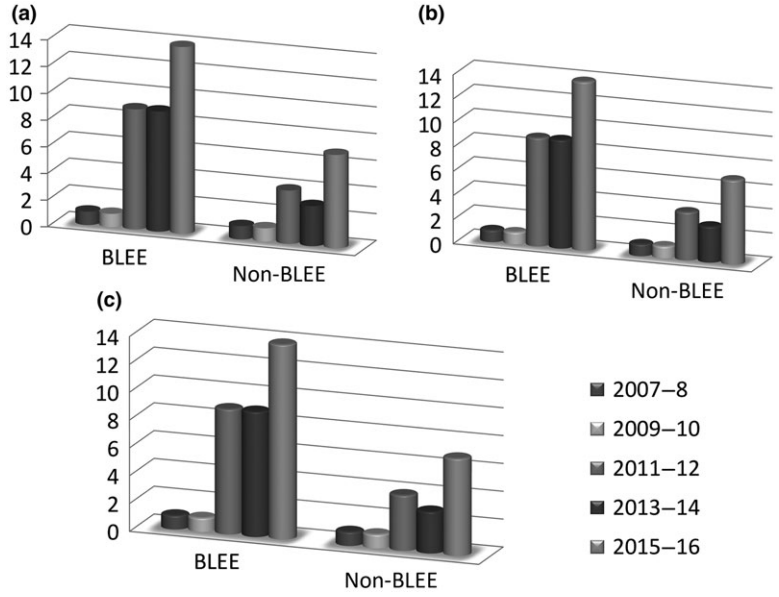

Figure 2 Number of Enterobacteriaceae isolates resistant to quinolones (a), betalactamase inhibitors (b) and aminoglycosides (c) by 2-year periods, divided into BLEE and Non-BLEE.

Table 4. Antibiotic treatment of all episodes of BSI occurring during the first year of SOT compared by 2-year periods.

Variable	All episodes of BSI	2007–2008 (*N* = 42)	2009–2010 (*N* = 24)	2011–2012 (*N* = 60)	2013–2014 (*N* = 43)	2015–2016 (*N* = 49)
Empirical antibiotic therapy						
β-lactam/β-lactamase inhibitors (*n*, %)	56 (25.7)	22 (52.4)	7 (29.2)	7 (17.9)	9 (25.0)	11 (24.4)
Cephalosporins (*n*, %)	33 (15.1)	4 (9.5)	6 (25.0)	11 (28.2)	5 (13.9)	7 (15.2)
Quinolones (*n*, %)	9 (4.1)	5 (11.9)	1 (4.2)	1 (2.6)	0	2 (4.3)
Carbapenem (*n*, %)	63 (28.9)	5 (11.9)	5 (20.8)	12 (30.8)	15 (41.7)	26 (55.3)
Glycopeptide (*n*, %)	40 (18.3)	6 (14.3)	5 (20.8)	10 (25.6)	11 (30.6)	8 (17.4)
Colistin (*n*, %)	11 (5.0)	0	0	4 (10.3)	4 (11.1)	3 (6.5)
Inadequate empirical antibiotic therapy* (*n*, %)	69 (31.7)	12 (30.0)	7 (30.4)	19 (32.2)	14 (33.3)	17 (34.7)
Targeted antibiotic therapy						
β-lactam/β-lactamase inhibitors (*n*, %)	28 (12.8)	3 (7.1)	5 (20.8)	5 (8.3)	5 (11.6)	10 (20.4)
Cephalosporin (*n*, %)	39 (17.9)	6 (14.3)	1 (4.2)	10 (16.7)	9 (20.9)	13 (26.5)
Quinolone (*n*, %)	42 (19.3)	12 (28.6)	4 (16.7)	6 (10.0)	6 (14.0)	14 (28.6)
Carbapenem (*n*, %)	63 (28.9)	5 (11.9)	2 (8.3)	17 (28.3)	16 (37.2)	23 (46.9)
Colistin (*n*, %)	23 (10.6)	1 (2.4)	2 (8.3)	11 (18.3)	5 (11.6)	4 (8.2)
Days of intravenous antibiotic therapy (median, IQR)	11 (5–15)	11 (3–15)	9 (6–20)	12 (7–15)	11 (6–24)	11 (5–15)
Days of antibiotic therapy (median, IQR)	15 (14–21)	17 (14–21)	16 (12–23)	15 (13–21)	15 (11–24)	15 (14–21)

*Empirical antibiotic therapy was considered inadequate if the treatment regimen did not include at least one antibiotic active *in vitro* against the infecting microorganism.

Table 5. Outcomes of all episodes of bloodstream infection (BSI) compared by 2-year periods.

Outcome variables	All episodes of BSI	2007–2008 (*N* = 43)	2009–2010 (*N* = 24)	2011–2012 (*N* = 60)	2013–2014 (*N* = 43)	2015–2016 (*N* = 49)
Acute renal impairment* (*n*, %)	82 (37.6)	12 (29.3)	7 (29.2)	28 (46.7)	11 (25.6)	24 (49.0)
Respiratory insufficiency (*n*, %)	27 (12.4)	1 (2.4)	3 (12.5)	14 (23.3)	3 (7.0)	6 (12.5)
Multiorgan failure (*n*, %)	23 (10.6)	2 (4.8)	1 (4.2)	10 (16.7)	3 (7.0)	7 (14.6)
Days of ICU stay after the onset of BSI (median, IQR)	13 (3–37)	50 (32–79)	40 (11–60)	15 (5–40)	3 (3–7)	3 (2–13)
Length of hospitalization after the onset of BSI (median, IQR)	15 (8–32)	21 (12–40)	23 (10–50)	16 (8–26)	14 (8–36)	13 (7–22)
7-day mortality (*n*, %)	11 (5.0)	0	1 (4.2)	5 (8.3)	3 (7.0)	2 (4.1)
30-day mortality (*n*, %)	22 (10.1)	1 (2.4)	3 (12.5)	11 (18.3)	4 (9.3)	3 (6.1)

*Renal impairment was defined as a serum creatinine level >1.5 mg/dl. Renal impairment was considered to be present when occurring within the first 24 h after BSI.

recipients. In addition, there has been an increase in MDR GNB mainly due to ESBL-producing strains. As a result of these changes, the use of carbapenems has risen sharply. The application of stewardship programmes may have a key role to play in reducing the impact of antimicrobial resistance and in improving outcomes in SOT recipients with BSI.

Authorship

Author's specific contributions to the work: IO, NS, AS and JC: contributed to the conception and design of the article, as well as on the acquisition and interpretation of data for the work. Moreover, the authors draft the work and revised it critically for important intellectual content. Lll, AM, JG and FT: contributed to the acquisition and interpretation of data for the work. JC finally approves the version to be published.

Funding

This study was supported by research grants from the Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III [FIS 14/00935] and Ministerio de Ciencia e Innovación, Instituto de Salud Carlos III, cofinanced by European Development Regional Fund 'A way to achieve Europe' ERDF, Spanish Network for the Research in Infectious Diseases (REIPI) and the Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), Spain. Isabel Oriol is the recipient of a research grant from the University of Barcelona. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Conflict of interest

The authors of this manuscript have no conflict of interest to declare in relation to the material presented.

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