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Predictors of mortality in solid-organ transplant recipients with bloodstream infections due to carbapenemase-producing *Enterobacterales*: the impact of cytomegalovirus disease and lymphopenia.

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Abbreviations

CPE, carbapenemase-producing *Enterobacterales;* BSI, bloodstream infection; SOT, solid organ transplantatation; CMV, cytomegalovirus; OR, odds ratio; CI, confidence interval; HR, hazard ratio; CI, confidence interval; TMP/SMX, Trimethoprim/Sulfamethoxazole; KPC, *Klebsiella pneumoniae* carbapenemase; OXA, oxacillinase; ESBL, extended-spectrum β-lactamase; ICU, intensive care unit; AUROC, area under the receiver operator curve; Se, sensitivity; Sp,

specificity; PPV, positive predictive value; NPV, negative predictive value; Ac, accuracy; TreeNet, Stochastic Gradient Boosting, Boosted Regression Tree Model; CART, Classification and Regression Tree.

Abstract

Treatment of carbapenemase-producing *Enterobacterales* bloodstream infections (CPE-BSI) in solid-organ transplant recipients (SOT) is challenging. The objective of this study was to develop a specific score to predict mortality in SOT recipients with CPE-BSI. A multinational, retrospective (2004-2016) cohort study (INCREMENT-SOT, ClinicalTrials.gov NCT02852902) was performed. The main outcome variable was 30-day all-cause mortality. The INCREMENT-SOT-CPE score was developed using logistic regression. The global cohort included 216 patients. The final logistic regression model included the following variables: INCREMENT-CPE mortality score ≥8 (8 points), no source control (3 points), inappropriate empirical therapy (2 points), cytomegalovirus disease (7 points), lymphopenia (4 points), and the interaction between INCREMENT-CPE score ≥8 and CMV disease (minus 7 points). This score showed an area under the receiver operating characteristic curve of 0.82 (95% CI 0.76-0.88) and classified patients into three strata: 0–7 (low mortality), 8-11 (high mortality) and 12-17 (very-high mortality). We performed a stratified analysis of the effect of monotherapy versus combination therapy among 165 patients who received appropriate therapy. Monotherapy was associated with higher mortality only in the very-high (adjusted HR 2.82, 95% CI 1.13-7.06, P=0.03) and high (HR 9.93, 95% CI 2.08-47.40, P=0.004) mortality risk strata. A score-based algorithm is provided for therapy guidance.

1. Introduction

Infections due to carbapenemase-producing *Enterobacterales* (CPE) are dramatically increasing worldwide [1]. Numerous transplant centres have been affected by outbreaks and many suffer a subsequent endemic situation [2–4]. The extreme difficulty for their treatment and the high mortality (30-50%) associated with these infections explain their importance in the solid-organ transplant (SOT) setting [4,5]. Their epidemiology has been extensively studied and specific recommendations for infection control and clinical management of these infections in SOT recipients have been published [4–8]. Nevertheless, current recommendations are based on observational studies conducted in the general population [9–13], while the specific risk factors and clinical impact of infections due to CPE in SOT recipients remains to be elucidated. Large, multicenter studies, truly representative of the SOT patient population, are needed to develop risk-stratification tools to assist in guiding the management of these infections.

The objectives of this study were: (I) to validate the INCREMENT-CPE score to predict all-cause mortality of CPE bloodstream infections (CPE-BSI) in the SOT population; (II) to explore if a new predictive score, INCREMENT-SOT CPE score, improves the predictive capacity, and (III) to check the utility of the new score to guide antibiotic therapy (monotherapy or combination) in different mortality risk groups.

2. Methods

2.1. Study design and population

This report follows STROBE recommendations [14] (**Supplementary Table S1**). We conducted a retrospective (2004-2016), international (40 SOT centres in 16 countries) cohort study of consecutive cases of adult SOT recipients with clinically significant, monomicrobial bloodstream infections by carbapenemase and/or extended spectrum-β-lactamase-producing *Enterobacterales* (INCREMENT-SOT Project; ClinicalTrials.gov identifier NCT02852902). In this work, we present the analysis of the CPE-BSI episodes from this cohort, which were submitted by 26 centres (12 countries) within the **INCREMENT-SOT** Consortium. The study was approved by

the Spanish Agency for Medicines and Health Products (AEMPS, code FIB-COL-2015-01) and by the Hospital Universitario Reina Sofia Ethics Committee (code 2907). Exclusion criteria were unavailability of key data and death within 48 hours after the blood cultures were obtained.

2.2. Variables and definitions

Clinically significant BSI was defined as the isolation of a carbapenemase-producing *Enterobacterales* in blood [16]. Episodes were considered nosocomial if symptoms started later than 48 hours after hospital admission or within 48 hours of a previous hospital discharge. The main outcome variable was 30-day all-cause mortality. Independent variables included demographics and variables related to comorbidities: Charlson comorbidity index score [17], diabetes, chronic pulmonary disease, kidney disease, and McCabe classification, according to three categories: non-fatal (mild and only a few comorbidities), ultimately fatal (risk of death within four years or multiple comorbidities) and rapidly fatal (risk of death during stay, intensive or terminal care patients). SOT-related variables included time from transplant to bloodstream infection, basal and induction immunosuppression, and transplanted organ. Variables recorded in the 30 days previous to the BSI episode were: stay in an Intensive Care Unit (ICU), dialysis, acute rejection of the transplanted organ, cytomegalovirus (CMV) replication (any level of DNAemia), and CMV disease (presence of symptoms with evidence of CMV infection, including viral syndrome and organ disease), and trimethoprim/sulfamethoxazole prophylaxis. Variables recorded at the time of BSI onset included urinary stenosis (kidney), biliary stenosis (liver) and traqueal stenosis (lung), severity of acute condition at presentation according to Pitt bacteraemia score [18], severity of systemic inflammatory response syndrome on day 0 (blood culture date) [19], mental status (four categories: alert, disoriented, stuporeous and comatose), lymphocyte csource of infection according to clinical and microbiological data, source control and use of mechanical ventilation. Microbiological variables included *Enterobacterales* species, carbapenemase type, antimicrobial susceptibility data. Finally, we recorded INCREMENT-CPE mortality risk score [11,12] and the therapy administered (dates and doses of antibiotics). Empirical therapy was considered appropriate when an active drug was administered before the susceptibility profile. Targeted therapy was considered appropriate if it included an active drug and was administered within five days or earlier after the blood culture (day 0), and once the susceptibility profile was

available. An active therapy was classified as monotherapy if included one single active drug and as combined therapy if included 2 or more active drugs. If the antibiotic regimen administered was changed, we considered that administered for ≥50% of the duration of therapy (for patients who died sooner than 48 hours after the start of therapy, one complete day of therapy was required). Meropenem and imipenem were considered active when MIC < 4mg/L (monotherapy) or MIC 8-16 mg/L and administered in combination with ertapenem (monotherapy) or other active drugs (combination therapy). Tigecycline was not considered active for urinary source. Variables were collected in a centralized electronic clinical research file. The database was curated and queries were sent to participating centres for missing or inconsistent data.

2.3. Microbiological studies

The identification of microorganisms and susceptibility testing were performed at each participating centre. The identification of microorganisms and susceptibility testing were performed at each participating center, using standard microbiological techniques. Susceptibility was studied using automated systems or disk diffusion at each local laboratory and interpreted using the 2015 CLSI break points [17]. For isolates obtained before 2015, minimum inhibitory concentrations (MICs) were reviewed and the susceptibility category was assigned accordingly; when the MIC was not available or the available data had a MIC less than or equal to the older susceptibility break point, these were considered as susceptible if so reported by the local laboratory. Isolates were considered to be carbapenemase producers if a carbapenemase gene was detected by a molecular method.

2.4. Statistical procedures

Continuous variables were compared using the Kruskal-Wallis test. Categorical variables were compared using the chi-squared test or Fisher's exact tests. Survival distributions were compared using the log-rank test and were graphically displayed using Kaplan-Meier curves.

Validation of the INCREMENT-CPE score [12] was performed by calculating the area under the receiver operating characteristic curve (AUROC) for observed data, the sensitivity (Se) and specificity (Sp).

Multivariable logistic regression was used to develop a new score. The original INCREMENT-CPE score (modified by excluding the variable "inappropriate empirical and early targeted therapy", since we aimed to investigate different aspects of treatment for the new score) was dichotomized into two previously validated categories of risk (<8, low-risk versus ≥8, high-risk) [11]. To control for the site effect, we classified centres into low-mortality-risk and high-mortality-risk using TreeNet (Salford Predictive Modeller software) and considering all other variables (**Supplementary Figure S1**). The study period (to control for changes in clinical management over time), the source of BSI and lymphocyte count were dichotomized by CART (Classification and Regression Tree, Salford Predictive Modeller Software; **Supplementary Table S2** and **Supplementary Figure S2**). The variance inflation factor (VIF) value for every variable was calculated to control the influence of multicollinearity. We assumed lack of multicollinearity if all variables had a VIF value <2. The variable "high-mortality risk centre" was included in the analysis to obtain a predictive model for which this effect was controlled but was not considered for the score. Potential interactions between variables were explored using TreeNet and those selected were included in the models. Variables with a $P \leq 0.20$ in the final models were selected for the assignment of a score provided their inclusion significantly improved the predictive capacity of the model. A weighted score for each variable was calculated dividing each regression coefficient by one-half of the smallest coefficient and rounding to the nearest integer. The prediction ability of a model was examined by calculating its AUROC with a 95% confidence interval; Se, Sp, positive predictive value (PPV), negative predictive value (NVP) and accuracy (Ac) were calculated for different breakpoints.

Sensitivity analysis for the INCREMENT-SOT-CPE score was performed using Salford Predictive Modeller Software to check the robustness of its predictive ability. Fifteen subgroups of the cohort with a 20% sample size were randomly extracted (43 cases per subgroup), and the AUROC of the score to predict 30-day all-cause mortality was calculated for each subgroup. A minimum, maximum, and median value of AUROC was obtained. The process was repeated

another 7 times, extracting 15 subgroups with sample sizes ranging 30% to 90% (10% intervals, thus obtaining 8 average AUROCs, maximum, and minimum values).

For the analysis of the association of monotherapy versus combination therapy with mortality, a propensity score for receiving combination therapy was calculated using a non-parsimonious logistic regression model. The impact of combination therapy was studied by Cox-regression, adjusting by propensity score and other potential confounders, after checking for collinearity.

The analyses were carried out using R software (version 3.0.1), SPSS 25.0 (SPSS Inc.), and Salford Predictive Modeller software 8.2 (includes CART and TreeNet).

3. Results

3.1. Cohort features and validation of the INCREMENT-CPE mortality score (objective I).

Among 228 patients included, 216 fulfilled inclusion criteria (Figure 1). Their characteristics are shown in **Table 1**. Most patients were men (75%), with a median (interquartile range) age of 56 (46-63). The most common types of transplant were liver (56%, including liver-other organs) and kidney (35%, including kidney-pancreas). Episodes occurred in the first month post-transplant in 45% of patients. The most common basal immunosuppression regimes included tacrolimus (85%), mycophenolic acid/mycophenolate (58%), and corticosteroids (83%). 43% of patients received induction of immunosuppression with thymoglobulin (21%) or basiliximab (22%). In the previous 30 days, 24% suffered CMV replication and 8% CMV disease. Lymphopenia was observed in 47% of cases. The most common sources of bloodstream infections were intrabdominal (21%), urinary tract (20%), biliary tract (18%), catheters (13%), and lung (10%). The most common organism involved was *Klebsiella pneumoniae* (83%) and the most common types of carbapenemases were KPC (66%) and OXA-48 (23%). Regarding treatment regimens, inappropriate empirical therapy was administered in 21% (45/216) of patients and appropriate targeted therapy in 88% (190/216), either monotherapy (118 patients) or combination therapy (72

patients). 30-day all-cause mortality was 37% (79/216; 95% CI, 31%-43%). Significant differences between types of SOT were observed in a number of variables, including Charlson index, chronic pulmonary disease, kidney disease, McCabe score, CMV replication, induction of immunosuppression, urinary and biliary stenosis, Pitt score, source of infection, administration of appropriate empirical therapy, and INCREMENT-CPE score (**Table 1**).

The predictive value of the INCREMENT-CPE mortality score [12] was studied. We found that this score was associated with 30-day all-cause mortality (OR, 1.40 per unit; 95% CI, 1.27-1.56; $P<0.001$), showing an AUROC of 0.78 (95% CI, 0.71-0.85). The Se, Sp, PPV, NPV and Ac values for different breakpoints of each INCREMENT-CPE score and the proportion of patients are shown in **Supplementary Table S3**. For an INCREMENT-CPE score value ≥8, previously validated as a cut-off value predictive for low versus high mortality in non-SOT patients [11,12], the calculated NPV and PPV in the SOT cohort were 84.7% and 50.4%, respectively.

3.2. Development of the new INCREMENT-SOT-CPE mortality score (objective II).

We explored SOT-related variables that could improve the predictive capacity of the INCREMENT-CPE score in our population. Variables associated with 30-day mortality in the final model were: INCREMENT-CPE score ≥8 (excluding the variable about therapy from this score), CMV disease in the previous 30-days, lymphocytes ≤600 units per mm^3, and lack of source control (**Table 2**); the interaction between CMV disease and INCREMENT-CPE score ≥8 was negative and with a similar (but negative) β coefficient as CMV disease, indicating that CMV disease does not further increase the risk of death if the INCREMENT-CPE-score is ≥8, but do so only if the score is <8 (**Supplementary Figure S3**). The variable inappropriate empirical therapy was kept in the final model since its inclusion improved the predictive capacity. None of the final variables included in the multivariate model showed multicollinearity (VIF ≤ 1.06, **Supplementary Table S4**). The AUROC of the resulting logistic regression model was 0.84 (95% CI, 0.78-0.89). The score assigned to each variable according to its beta regression coefficient is shown in **Table 3**. The prediction rule based on the scores showed an AUROC of 0.82 (95% CI, 0.76-0.88) for 30-day mortality, improving the predictive ability of the non-transplant

INCREMENT-CPE score (previous section, objective I). We also developed an alternative model including variables independently of the INCREMENT-CPE score, nevertheless the resulting model showed a lower predictive capacity than our INCREMENT-CPE score-based model (AUROC=0.79, 95% CI 0.73-0.85).

The sensitivity, specificity positive predictive value (PPV), negative predictive value (NPV) and accuracy for different breakpoints of the new INCREMENT-SOT-CPE score and the proportion of patients are shown in **Supplementary Table S5.** The NPV and PPV for a score value ≥8 were 89.4% and 53.4%, respectively; and for a score ≥12, NPV and PPV were 78.8% and 72.3%, respectively. A classification into low (score 0-7), high (score 8-11), and very-high (score 12-17) mortality was developed, with mortality rates of 11.4% (10/87), 35.3% (23/65) and 71.8% (46/64), respectively (**Supplementary Table S6**). The sensitivity analysis (see Methods for details) confirmed the robustness of the model; the minimum value of the AUROCs for all subcohorts was always >0.70 and the average AUROC value >0.80 (**Supplementary Figure S4**).

3.3. Utility of the new score to guide antibiotic therapy. Impact of monotherapy versus combined therapy on 30-day all-cause mortality (objective III).

We analysed 165 patients who received appropriate targeted treatment (treatment cohort, **Figure 1**). Thirty-day all-cause mortality was 15.7% (11/70) in patients receiving combined therapy versus 43.1% (41/95, *P*<0.001) in patients receiving monotherapy. Mortality associated with each type of treatment in the different mortality risk groups, as defined by INCREMENT-SOT-CPE score, is shown in **Supplementary Table S7**. In a COX-regression model adjusted by the propensity score for receiving combination therapy, INCREMENT-SOT-CPE score and high-mortality risk centre, monotherapy was associated with higher mortality in the global cohort (HR 3.68; 95% CI, 1.83-7.40; *P*<0.001) and in the two higher INCREMENT-SOT-CPE mortality risk strata, i.e. very-high risk (adjusted HR 2.82, 95% CI, 1.13-7.06, *P*=0.03) and high risk (adjusted HR 9.93, 95% CI, 2.08-47.40, *P*=0.004] (**Table 4**). By contrast, in the low risk stratum, no significant differences were observed (adjusted HR 1.69, 95% CI, 0.32-8.89, *P*=0.54) (Table 4). Kaplan Meier curves are shown in **Supplementary Figure S5**. The specific antimicrobials administered to patients in the three INCREMENT-SOT-CPE risk groups were heterogeneous and preclude specific analyses; their related mortality are shown in **Supplementary Table S8**.

3.4. Proposed algorithm for clinical practice

In order to apply these results to the clinical management of SOT patients with CPE-BSI, we propose an algorithm which requires calculation of INCREMENT-CPE score [11,12] and identification of the number and type of risk factors present, without having to expressly calculate the new score (Figure 2). According to this algorithm, 86/165 (52.1%) patients in the therapy cohort received inadequate antibiotic therapy. Specifically, 57/165 (34.5%) of the patients who received monotherapy should have been treated with combined therapy. These patients had a 30-day mortality rate of 53.4% (31/57). On the other side, 29/165 (17.6%) of the patients who received combined therapy should have received monotherapy. The mortality rate in this second group was 3.8% (2/29). An expanded version of the algorithm, including the stratification of the risk of mortality, based on the INCREMENT-SOT score, is provided in **Supplementary Figure S6**.

4. Discussion

Our results indicate that being a recipient of SOT does not seem to worsen the prognosis of CPE-BSI. Thirty-day all-cause mortality in our INCREMENT-SOT cohort was 36.6%, higher that in pre-CPE era [15] and similar that previously reported in other series in SOT [4], and in the general population. [12]. Some studies and a meta-analysis have reported a higher mortality (>40%) when CPE-BSI is caused by *K. pneumoniae*. In our study, the type of *Enterobacterales* was not associated with mortality in the analysis after adjusting by other exposures, as previously observed [16–18].

The development of new INCREMENT-SOT-CPE score was based on the INCREMENT-CPE score, which had been previously validated in the general population in different studies [9,11,12,19,20]. We used this strategy because there are no specific studies in SOT and many transplant groups use this predictive model, which takes into account variables important in any type of patient with BSI, including SOT. Besides, the inclusion of this general model in our new score reinforces the utility of the new model in post-transplant periods, such as the postoperative

period, when the full impact of immunosuppression -derived from prolonged exposure to suppressive therapies- is still absent [21]. Finally, an alternative model including individual variables –transplant and non-transplant-, instead of the INCREMENT-CPE score, showed a lower predictive capacity and was thus not considered.

We additionally studied the impact of specific transplant variables that complemented the INCREMENT-CPE score on the prognosis of this type of infections in SOT-patients. So, our results indicate that the predictive capacity of INCREMENT-CPE score can be improved when it is combined with other mortality predictors such as source control, appropriate empirical therapy and variables related to immunosuppression, i.e. lymphopenia and CMV disease. The application of these additional predictors is very important in patients with INCREMENT-CPE score <8, when the score can be applied to indicate monotherapy or combined therapy (Figure 2).

It is obvious that an adequate control of the source and an appropriate empirical treatment can improve the prognosis of the bacterial infection. Lymphopenia can be a surrogate marker of over-immunosuppression. Nevertheless, some experts believe that a reduction in immunosuppression may lead to higher mortality by increasing the capacity of the immune system to induce a systemic inflammatory response [22].

CMV is an immunomodulatory virus that can favour bacterial infections [23]. Theoretically, CMV prevention could reduce this increased risk [24], although recent consensus do not recommend CMV prophylaxis is the scenario of solid-organ transplantation [23,25]. This is further complicated by the fact that sepsis may increase CMV reactivation [25,26]. Our results suggest that CMV disease increase mortality in SOT recipients with CPE-BSI, although CMV disease may also be a mere marker of the net-state of over-immunosuppression, which would be ultimately associated with all-cause mortality. Interestingly, the data from our study suggest that CMV disease does not increase the risk of death further in SOT recipients with a high underlying risk of death, as measured by the INCREMENT-CPE score, but only in patients with a lower underlying risk. Unfortunately, data on CMV prophylaxis was not collected in this study, but our results open the door to further research about whether prevention of CMV may be beneficial in SOT recipients colonized by CPE in order to improve their outcomes in case of an invasive infection due to these bacteria.

Our study has the limitations of retrospective studies, despite applying a rigorous definitions and statistical analyses to control biases. A second limitation is that we have analysed patients not treated with the newly available drugs (i.e. ceftazidime-avibactam or meropenem-vaborbactam). The impact of the new drugs on the applicability of risk scores to decision making will certainly need to be investigated, as it is not known if combination therapy would be needed in high-risk patients when the newer drugs are used, or if the new drugs are more effective in low-risk patients. However, it is important to bear in mind that accessibility to the new drugs is still limited in numerous countries, and therefore well-conducted observational studies in the SOT population treated with the "classic" drugs will still be relevant in many areas. Another limitation is that the sample size of our cohort precluded the selection of derivation and validation subcohorts (see [12]). The sensitivity analysis confirmed the internal robustness of our model, nevertheless, an external validation in a prospective cohort would be desirable. Finally, KPC carbapenemase may be overrepresented in our cohort, as compared to other carbapenemases.

To conclude, in transplant centers with outbreaks or endemia by CPE, identification of colonized patients is important so that empirical treatment with CPE coverage can be readily administered in case of BSI development. In this study, we have identified transplant-related variables specifically associated with the risk of mortality in SOT recipients with CPE-BSI. We expect this will help to identify patients at high risk of death and allow a more personalized clinical management, i.e. prevention of cytomegalovirus disease and the judicious use of immunosuppression in order to avoid lymphopenia.

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Figure Legends

Figure 1. Flow-chart of analysed solid-organ transplant patients with bloodstream infections due to carbapenemase-producing *Enterobacterales*.

Figure 2. Algorithm for clinical management of SOT patients with bloodstream infection due to carbapenemase-producing *Enterobacterales* (CPE-BSI), based on INCREMENT-SOT-CPE mortality risk score.

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

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Tables

Table 1. Characteristics of solid-organ transplant patients with bloodstream infections caused by carbapenemase–producing *Enterobacterales* included in the INCREMENT-SOT cohort, according to the transplanted organ.

		Transplanted solid organ					
	Global (N=216)	**Liver (N=120)**	**Kidney (N=75)**	**Heart (N=13)**	**Lung (N=6)**	**Multiorgan (N=2)**	***P* value**
Age, median (IQR)	56 (46-63)	55 (46-63)	57 (46-64)	56 (40-60)	48 (35-62)	62 (52)	0.58[b]
Gender (Male)	162 (75)	92 (77)	56 (75)	8 (62)	4 (67)	2 (100)	0.68
Charlson index, median (IQR)	5 (3-7)	5 (4-7)	5 (3-6)	4 (5-7)	2 (1-5)	6 (5)	0.01[b]
Diabetes	87 (40)	46 (38)	35 (47)	4 (31)	2 (33)	0	0.49
Chronic pulmonary disease	15 (7)	3 (3)	6 (8)	1 (8)	5 (83)	0	<0.001
Kidney disease	120 (56)	37 (33)	64 (85)	8 (62)	1 (17)	2 (100)	<0.001
McCabe score							<0.001
Non-Fatal Disease	53 (25)	22 (18)	25 (33)	5 (39)	1 (17)	0	..
Rapidly Fatal Disease	47 (22)	36 (30)	4 (5)	6 (46)	1 (17)	0	..
Ultimately Fatal Disease	115 (53)	61 (51)	46 (61)	2 (15)	4 (67)	2 (100)	..
Days from transplant to bloodstream infection							0.10
≤30 days	97 (45)	63 (53)	24 (32)	6 (46)	3 (50)	1 (50)	..
31-180 days	75 (35)	37 (31)	32 (43)	5 (39)	0	1 (50)	..
≥ 181 days	44 (20)	20 (17)	19 (25)	2 (15)	3 (50)	0	..
Basal immunosuppression							
Cyclosporine	17 (8)	5 (4)	8 (11)	3 (23)	1 (17)	0	0.09
Tacrolimus	183 (85)	109 (91)	60 (80)	8 (62)	4 (67)	1 (50)	0.01
Mycophenolic acid/ Mycophenolate	125 (58)	54 (45)	57 (76)	10 (77)	2 (33)	2 (100)	<0.001
Corticosteroids	180 (83)	90 (75)	69 (92)	13 (100)	6 (100)	2 (100)	0.006
Azathioprine	6 (3)	0	3 (4)	1 (8)	2 (33)	0	<0.001
Everolimus	11 (5)	7 (6)	3 (4)	0	1 (17)	0	0.49[c]
Sirolimus	2 (1)	1 (1)	1 (1)	0	0	0	1[c]
Induction of immunosuppression	92 (43)	26 (22)	55 (73)	5 (39)	5 (83)	1 (50)	<0.001
Thymoglobulin	46 (21)	6 (5)	36 (48)	2 (15)	2 (33)	0	<0.001
Basiliximab	47 (22)	20 (17)	20 (27)	3 (23)	3 (50)	1 (50)	0.16
Nosocomial acquisition	180 (83)	102 (85)	57 (76)	13 (100)	6 (100)	2 (100)	0.12
ICU stay (previous 30 days)	149 (69)	92 (77)	37 (49)	12 (92)	6 (100)	2 (100)	<0.001
Dialysis (previous 30 days)	79 (36)	37 (31)	31 (41)	8 (62)	2 (33)	1 (50)	<0.001
Acute rejection (previous 30 days)	21 (10)	7 (6)	8 (11)	5 (39)	1 (17)	0	0.005
CMV disease (previous 30 days)	17 (8)	7 (6)	7 (9)	3 (23)	0	0	0.22
CMV replication (previous 30 days)	52 (24)	30 (25)	13 (17)	9 (69)	0	0	<0.001
TMP/SMX prophylaxis (previous 30 days)	119 (55)	62 (52)	43 (57.3)	8 (61.5)	4 (66.7)	2 (100)	0.58
Urinary stenosis (kidney)	11 (5)	0	11 (15)	0	0	0	<0.001[c]
Biliary stenosis (liver)	33 (15)	33 (28)	0	0	0	0	<0.001
Traqueal stenosis (lung)	1 (1)	0	0	0	1 (17)	0	0.04[c]

Pitt score	3 (1-6)	4 (1-6)	1 (0-4)	6 (2-11)	5 (3-9)	3	<0.001[b]
Systemic inflammatory response syndrome							0.004
Sepsis	99 (46)	47 (39)	45 (60)	4 (31)	3 (50)	0	..
Severe sepsis	54 (25)	36 (30)	9 (12)	3 (23)	3 (50)	2 (100)	..
Shock	63 (29)	37 (31)	21 (28)	6 (46)	0	0	..
Mental status							0.02
Alert	81 (38)	36 (30)	40 (53)	4 (31)	1 (17)	0	..
Disoriented	58 (27)	34 (28)	17 (21)	2 (15)	3 (50)	2 (100)	..
Stuporeous	31 (14)	20 (17)	7 (9)	3 (23)	1 (17)	0	..
Comatose	35 (16)	24 (20)	6 (8)	4 (31)	1 (17)	0	..
Lymphocytes <600/mm^3	101 (47)	56 (47)	35 (47)	7 (54)	3 (50)	0	0.73
Source of infection							<0.001
Intrabdominal	46 (21)	36 (30)	8 (11)	1 (8)	0	1 (50)	..
Urinary tract	44 (20)	4 (3)	39 (52)	1 (8)	0	0	..
Biliary tract	38 (18)	38 (32)	0	0	0	0	..
Vascular access	28 (13)	12 (10)	12 (16)	4 (31)	0	0	..
Pneumonia	21 (10)	6 (5)	6 (8)	3 (23)	6 (100)	0	..
Skin and soft tissue	5 (2)	0	4 (5)	0	0	1 (50)	..
Other	16 (7)	15 (13)	1 (1)	0	0	0	..
Unknown	18 (8)	9 (8)	5 (7)	4 (31)	0	0	..
No source control	55 (26)	29 (24)	23 (31)	1 (8)	2 (33)	0	0.38
Mechanical ventilation	92 (43)	57 (48)	20 (27)	9 (69)	5 (83)	0	0.001
Enterobacterales							0.05
Klebsiella sp.	180 (83)	99 (83)	64 (86)	11 (85)	5 (83)	1 (50)	..
Enterobacter sp.	16 (7)	8 (7)	6 (8)	1 (8)	0	0	..
Escherichia coli	15 (7)	10 (8.3)	4 (5)	0	1 (17)	0	..
Morganella morganii	1 (0.5)	1 (1)	0	0	0	0	..
Serratia sp.	4 (2)	2 (2)	1 (1)	1 (8)	0	1 (50)	..
Type of carbapenemase							0.29
KPC	143 (66)	79 (66)	51 (68)	8 (62)	4 (67)	1 (50)	..
OXA-48	50 (23)	31 (26)	15 (20)	4 (31)	0	0	..
Other	23 (11)	10 (8)	9 (12)	1 (8)	2 (33)	1 (50)	..
INCREMENT-CPE score[a], median (IQR)	8 (6-12)	11 (6-12)	6 (3-11)	13 (7-15)	11 (4-15)	11 (11-11)	0.005[b]
Inappropriate empirical therapy	45 (21)	24 (20)	18 (24)	2 (15)	1 (17)	0	0.86
Targeted therapy							0.64
Appropriate monotherapy	118 (55)	66 (55)	44(59)	5 (39)	3 (50)	0	..
Appropriate combination therapy	72 (33)	39 (33)	23 (31)	6 (46)	2 (33)	2 (100)	..
Inappropriate	26 (12)	15 (13)	8 (11)	2 (15)	1 (17)	0	..
Cure/Improvement at day 14	122 (57)	67 (56)	47 (63)	4 (31)	2 (33)	2 (100)	0.11
Mortality at day 30	79 (37)	47 (39)	21 (28)	8 (65)	3 (50)	0	0.10

Data are number of patients (percentage), except where specified. *P* values represent global differences among the five types of solid organ transplant and were obtained by Chi-squared test, except when otherwise stated. [a] The INCREMENT-CPE mortality score included: severe sepsis or shock at presentation (5 points), Pitt

bacteraemia score ≥6 (4 points), Charlson index ≥2 (3 points), source of BSI other than urinary or biliary tracts (3 points) and receiving inappropriate empirical and early targeted therapy (2 points).[b] Kruskall-wallis test. [c] Fisher´s test. Abbreviations: IQR, interquartile range; ICU, intensive care unit; CMV, cytomegalovirus; TMP/SMX, Trimethoprim/Sulfamethoxazole; KPC, *Klebsiella pneumoniae* carbapenemase; OXA, oxacillinase;

Table 2. Multivariate logistic regression analysis of variables associated with 30-day all-cause mortality.

	Crude analysis		Adjusted analysis[b,c]	
Variable	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
Age (per unit)	0.99 (0.97-1.01)	0.36	..	..
Male gender	1.08 (0.57-2.09)	0.81	..	..
Klebsiella sp.	1.77 (0.83-4.04)	0.15	..	..
Carbapenemase			..	..
Carbapenemase	Reference			
Carbapenemase +*ESBL*	0.71 (0.35-1.42)	0.33	..	..
OXA-type carbapenemase	1.07 (0.56- 2.01)	0.84	..	..
Nosocomial acquisition	1.61 (0.75- 3.70)	0.23	..	..
ICU admission	4.92 (2.42-10.89)	<0.0001	..	..
Mechanical ventilation	7.48 (4.04-14.30)	<0.0001	..	..
Mental status, not alert	17.6 (6.80-51.18)	<0.0001	..	..
Chronic kidney disease	1.01 (0.58-1.77)	0.97	..	..
Chronic pulmonary disease	2.09 (0.72-6.19)	0.17	..	..
Severe liver disease	1.70 (0.92-3.15)	0.09	..	..
Any tumor	1.51 (0.61-3.68)	0.36	..	..
Charlson index, per unit	1.08 (0.95-1.22)	0.20	..	..
Pitt Score, per unit	1.55 (1.38-1.75)	<0.0001	..	..
Septic Shock	8.68 (0.46-16.90)	<0.0001	..	..
Days from transplant to positive blood culture				
≤30 days	Reference			
31-180 days	0.46 (0.24-0.90)	0.02	..	..
≥ 181 days	1.04 (0.51-2.13)	0.92	..	..
Type of SOT				
Kidney (including kidney-pancreas)	Reference			
Liver including (liver-kidney, liver-pancreas and multivisceral)	1.61 (0.87-3.00)	0.13	..	..
Others (lung and heart)	3.54 (1.25-10.01)	0.17	..	..
Source of infection in SOT				
High risk (pneumonia and others)	Reference			
Low risk (rest of sources)	0.36 (0.17-0.75)	0.006	..	..
Biliary stenosis	0.84 (0.37-1.82)	0.67	..	..
Previous dialysis	1.33 (0.75-2.36)	0.33	..	..
INCREMENT-CPE mortality score ≥8 [a]	6.72 (3.52-13.55)	<0.0001	13.74 (6.00-35.07)	<0.0001
CMV disease within 30 days before HC	2.69 (1.00-7.71)	0.05	10.87 (1.79-77.06)	0.01
Lymphocytes ≤600 units/mm^3	0.96 (0.91-0.99)	0.03	3.46 (1.73-7.16)	0.0006
No source control	2.00 (1.09-3.85)	0.03	2.66 (1.18-6.22)	0.02
Inappropriate empirical therapy	1.92 (0.99-3.70)	0.06	1.89 (0.77-4.26)	0.18
High-mortality risk centre	3.10 (1.75-5.56)	0.0001	3.72 (1.83-7.82)	0.0004
Study period 2007-2010 (reference: 2011-2016)	1.91 (0.87-4.17)	0.10	..	..
Interaction INCREMENT-CPE mortality score ≥8 x CMV disease	0.76 (0.63-0.93)	0.007	0.09 (0.007-0.90)	0.04

[a] The INCREMENT-CPE mortality score included the following variables: severe sepsis or shock at presentation (5 points), Pitt bacteremia score ≥6 (4 points), Charlson index ≥2 (3 points) and source of BSI other than urinary or biliary tracts (3). [b] Variables with a univariate p ≤0.2 for mortality were included. The interactions studied are specified in Results. [c] Lack of multicollinearity in the multivariate model was assesed with the Variance inflation factor (VIF), which was ≤1.06 for all variables included (Supplementary Table S4). Abbreviations: OR, odds ratio; CI, confidence interval; OXA, oxacillinase; ESBL, extended-spectrum β-lactamase; ICU, intensive care unit; SOT, solid-organ transplant; CMV, cytomegalovirus.

Table 3. INCREMENT-SOT-CPE score: assignment of scores based on the regression coefficients obtained for the selected variables using multivariable logistic regression.

Variable	Regression beta coefficients (95% CI)	Score
INCREMENT-CPE score ≥8	2.62 (1.79-3.56)	8
Cytomegalovirus disease in the previous 30 days	2.38 (0.58-4.34)	7
Lymphocytes ≤ 600 mm^3	1.24 (0.55-1.97)	4
No source control	0.98 (0.17-1.83)	3
Inappropriate empirical therapy	0.64 (-0.26-1.45)	2
Interaction INCREMENT-CPE score ≥ 8 * Cytomegalovirus disease in the previous 30 days[a]	-2.39 [-4.90 - (-0.10)]	-7
Maximum score [a]		**17**

[a] The negative interaction coefficient means that the effect of the combined action of two predictors is less than the sum of the individual effects. Consequently, in our model, the maximum score in a patient with all risk factors would be 17 [INCREMENT-CPE score ≥8 (+8), CMV disease (+7), lymphopenia (+4), no source control (+3), inappropriate empirical therapy (+2) and interaction INCREMENT-CPE score ≥8 with CMV (-7)].

Table 4. Adjusted Cox-regression analysis of the association of monotherapy versus combined therapy with 30-day all-cause mortality in the global cohort and in the different strata of risk, according to INCREMENT-SOT-CPE score.

Patient group	Variables	HR (95% CI)	*P* value
Global cohort receiving appropriate targeted treatment [a] (N=165; 95 monotherapy, 70 combined)	Monotherapy	3.68 (1.83-7.40)	<0.001
	Propensity score [b]	0.70 (0.12-4.19)	0.70
	High risk center	2.37 (1.37-4.10)	0.002
	INCREMENT-SOT-CPE score		
	Low risk	Reference	
	High risk	5.13 (2.02-13.05)	0.001
	Very high risk	12.54 (5.45-28.87)	<0.001
Very high risk patients (N=44; 30 monotherapy, 14 combined)	Monotherapy	2.82 (1.13-7.06)	0.03
	Propensity score [b]	0.48 (0.05-4.67)	0.53
	High risk center	1.23 (0.59-2.55)	0.58
High risk patients (N =47; 20 monotherapy, 27 combined)	Monotherapy	9.93 (2.08-47.40)	0.004
	Propensity score [b]	0.41 (0.004-45.42)	0.71
	High risk center	4.52 (1.38-14.79)	0.01
Low risk patients (N=74; 45 monotherapy, 29 combined)	Monotherapy	1.69 (0.32-8.89)	0.54
	Propensity score [b]	2.76 (0.02-316.64)	0.68
	High risk center	12.68 (1.50-107.49)	0.02

[a] All variables exhibited a variance inflation factor (VIF) <1.7. The model showed an area under the receiver operating characteristic curve of 0.73. Antimicrobials administered as monotherapy or combined therapy, both in the global cohort and in the three INCREMENT-SOT-CPE mortality risk groups, and their related mortality are shown in Supplementary Table S8. [b] The variables used to calculate the propensity score for combination therapy were centre, period, age, sex, acquisition, hospital service, days from transplant to blood culture, type of SOT, SIRS, Charlson index, Pitt score, source of infection, lymphocytes count, source control, CMV disease, kidney disease, diabetes, dialysis (previous 30 days), myocardial infarct, type of enzyme, type of carbapenemase, antibiogram showing resistance to group 2 carbapenems, gentamicin, and/or ciprofloxacin.

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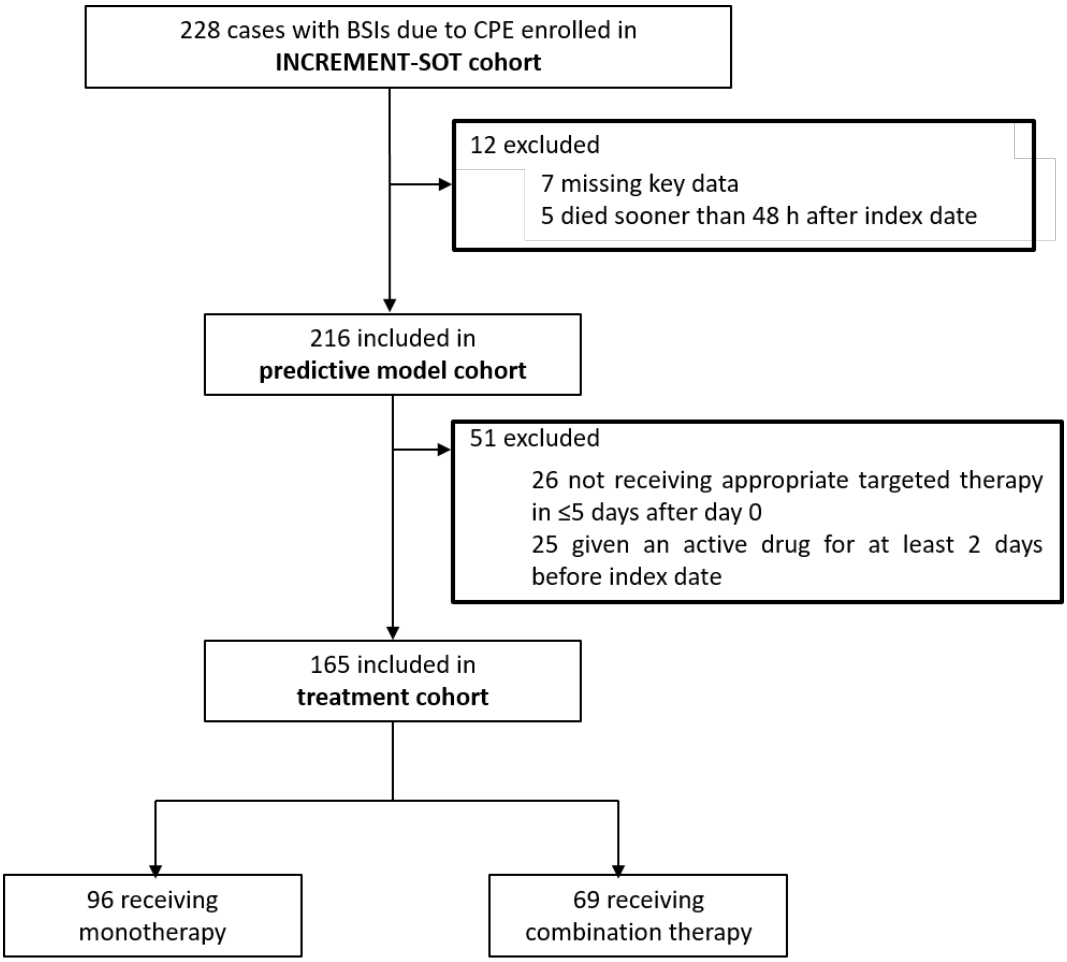
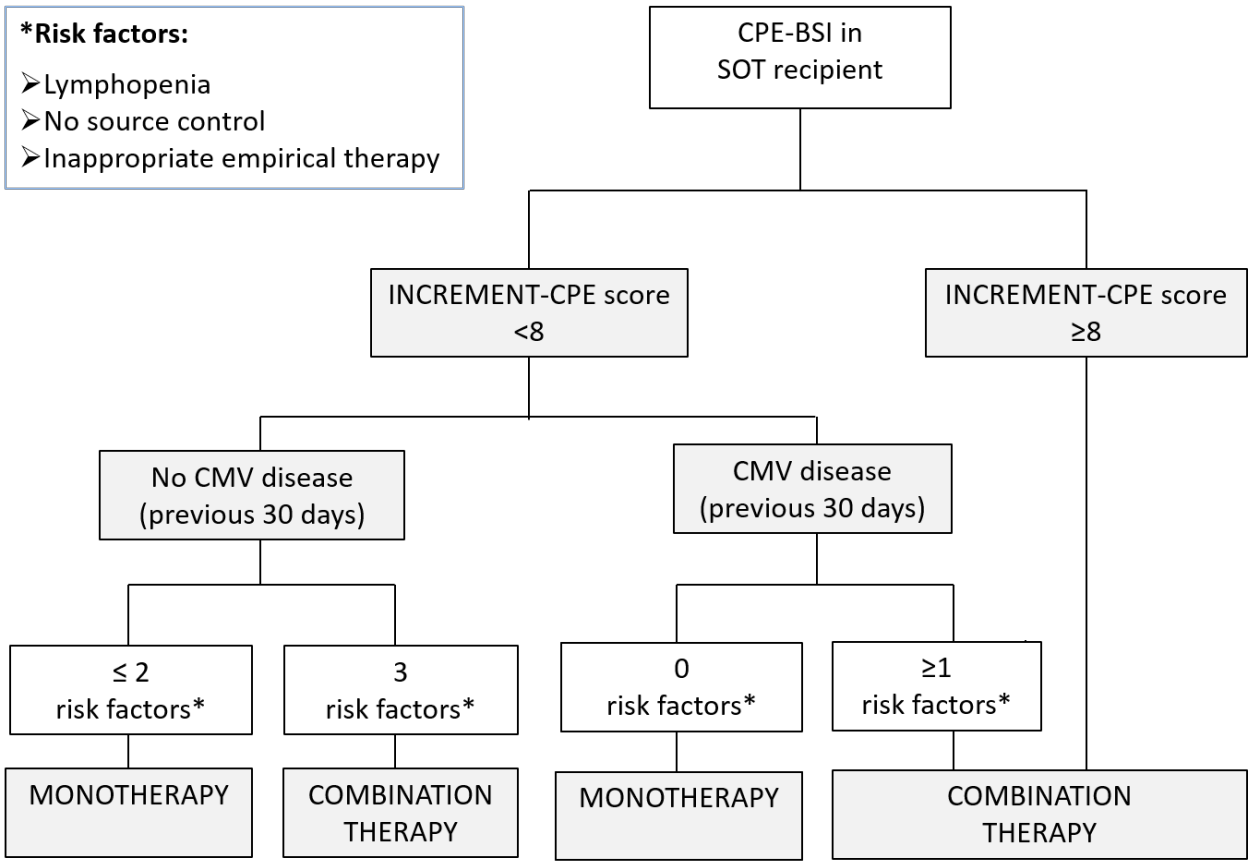
Figures

Figure 1. Flow-chart of analysed solid-organ transplant patients with bloodstream infections due to carbapenemase-producing *Enterobacterales*.



Abbreviations: BSI, bloodstream infections; CPE, carbapenemase-producing *Enterobacterales*.

Figure 2. Algorithm for clinical management of SOT patients with bloodstream infection due to carbapenemase-producing *Enterobacterales* (CPE-BSI), based on INCREMENT-SOT-CPE mortality risk score.



*Risk factors for INCREMENT-SOT-CPE score: cytomegalovirus (CMV) disease during the last 30 days; lymphopenia (<600 lymphocytes/mm^3) at BSI onset, no source control and inappropriate empirical therapy (in the first 3 days after blood culture).

Abbreviations: CPE-BSI, bloodstream infection due to carbapenemase-producing *Enterobacterales*; SOT, solid organ transplant.