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Urinary tract infection caused by *enterococcus spp*: risk factors and mortality.

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Abstract

Purpose: Complicated urinary tract infections (UTIs) are frequently caused by *Enterococcus* spp.

We aim to define the risk factors involved in UTIs caused by Enterococcus. Determine the overall mortality and predictive risk factors.

Methods: A retrospective study was conducted. We compared the results with those of a random sample of patients with complicated UTIs infection caused by *Escherichia coli*.

Results: We found 106 in-patients with UTIs caused by *Enterococcus* spp., 56 of whom had positive blood cultures. Distribution by species: 83% *E. faecalis* and 17% *E. faecium*, with a Charlson comorbidity index of 5.9±2.9. Only male sex with an OR of 2.8 (95%CI 1.2-6.4), nosocomial infection with an OR of 2.8 (95%CI 1.1-7), urinary catheter with an OR of 4.5 (95%CI 1.8-11.3), urinary cancer with an OR of 6.4 (2.1-19.4), and previous antimicrobial treatment with an OR of 4.3 (1.8-10.2) were independent predictors of *Enterococcus* infection. Overall, in-patient mortality was 16.5%, which was associated with a higher Sequential Organ Failure Assessment (SOFA) score (>4), severe comorbidity such as immunosuppression, malignant hemopathy and nephrostomy, or *Enterococcus faecium* species and its pattern or resistance to ampicillin or vancomycin ($p<0.05$). Appropriate empiric antibiotic therapy was not associated with a better prognosis ($p >0.05$).

Conclusions: *Enterococcus* spp. is a frequent cause of complicated UTI by a profile of risk factors. High mortality secondary to a severe clinical setting and high comorbidity may be sufficient reasons for implementing empiric treatment of patients at risk, although we did not show a higher survival rate in patients with this treatment strategy.

Backgroud

The Enterococcus genus is included in the Enterococcaceae family, in which there are more than 30 recognized species, although Enterococcus faecalis, Enterococcus faecium and Enterococcus durans are the three main species that affect humans(1)

E. fecalis and E. faecium are rare causes of urinary tract infections (UTIs) in young women. Nevertheless, they are frequently involved in complicated infections. Thus, recent epidemiological studies have detected that these species are the second cause of complicated UTIs, followed by Escherichia coli, reaching 7–25% of the total number of cases of UTIs(2,3).

Despite the high frequency of UTIs caused by Enterococcus spp., there is a low rate of bacteremia associated with infection(2,4). Moreover, in mixed UTIs, where other uropathogens are involved, isolation of Enterococcus spp. is considered a commensal pathogen and is usually not treated (5)

On the one hand, Enterococci are tolerant or intrinsically resistant (particularly E. faecium) to several antimicrobials, such as broad spectrum penicillins, cephalosporins and carbapenems, that are typically used in complicated UTIs.

Moreover, glycopeptides, linezolid or other antibiotics active against gram-positive bacteria are usually not included in empiric recommendations of guidelines for the treatment of urinary tract infections. In recent guidelines of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) about the management of UTIs and The European Association of Urology (EAU) Urological Infections Guidelines Panel, the empiric treatment of the enterococcus species has been suggested for patients with classic risk factors for this infection

(6–8)

Although risk factors for overall bacteremia by Enterococcus spp. have been defined in the literature, the risk factors for UTI have not been well defined, and the consequences of a delay in optimal treatment have also not been well demonstrated.

Thus, the aim of this work was to identify the risk factors involved in urinary tract infections caused by Enterococcus spp., the variables associated with bacteremia and, finally, the overall mortality and consequences of non-optimal empiric treatment.

Materials And Methods

Patients

A retrospective, observational study during the years 2012-2017 was carried out in two centers of Castilla y León: Complejo Asistencial de Palencia (CAUPA) and Complejo Asistencial Universitario de Salamanca (CAUSA). We reviewed the records of in-patients with a diagnosis of urinary tract infection caused by *Enterococcus* spp. (**figure 1**).

Figure 1. Participant profile.

We included the following clinical criteria: i) Patients admitted to any services at these centers who needed hospitalization. ii) Patients with clinical manifestations compatible with a urinary infection. UTI is considered if the patient presents cystic syndrome (dysuria, frequency and/or nocturia) ó acute pyelonephritis (if there was pain in the renal fossa, fever >37.7ºC, involvement of the parenchyma during imaging techniques or criteria presented for systemic inflammatory response syndrome (SIRS)); or ancient patients (>65 years) with confusional syndrome and fever >37,7 without other other infectious foci. Sepsis or septic shock was considered if the recommendations of the Third International Consensus

Definitions for Sepsis and Septic Shock were met (9). The SOFA and Pitt bacteremia score (PBS) were systematically collected when samples were taken. The PBS was calculated for each patient at baseline when samples were taken(10). Hypotension, mechanical ventilation, mental status, and maximum temperature parameters of the PBS were measured for the baseline date. iii) Finally, the microbiological criteria for urinary infection were confirmed by isolation of *E. faecalis* or *E. faecium* in urine cultures (10^5 CFU/ml). STEP 2: we selected patients with concomitant urine and blood cultures. We also selected 55 patients without bacteremia. We used the Friedman criteria for the classification of UTIs as nosocomial, associated with care or community-acquired(11).

To establish the risk factors associated with enterococcus UTIs, we also selected a random sample of 100 patients with complicated UTIs infection caused by *E. coli* who needed hospitalization, stratified only by bacteremia. We used the same clinical and microbiological diagnostic criteria for *E. coli* as for *Enterococcus* spp.

The exclusion criteria for the study were as follows: i) patients who presented with symptoms typical of other infectious foci and ii) patients who fulfilled the definition of asymptomatic bacteriuria. All patients included in the study participated in a protocol that included the collection of demographics, epidemiological and clinical data. The empirical and directed antibiotic treatment and the carrying out of blood cultures and imaging studies were left to the clinician's discretion. The usual recommendations for taking samples according to the protocol were applied in the two centers. Urine specimens collected by clean catch were plated on agar blood (bioMérieux, España) and agar MacConkey (bioMérieux, España) using a 0.001-ml calibrated loop. Samples collected from indwelling catheters or transurethral catheterization were also plated on CLED agar (bioMérieux, España). All plates were incubated for 24 hours at 35-37 ºC. A colony count of 10^5 cfu/mL was considered positive. Identification and susceptibility were assessed with an automated MicroScan WalkAway system (Beckman Coulter, España). MIC was interpreted according to the cut-off points of the European Committee for Antimicrobial Susceptibility Testing (EUCAST). Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) was used for the identification of species of Enterococcus when the results of biochemical methods were doubtful.

Finally, the presence of endocarditis was analyzed collecting those patients with bacteremia in which echocardiography was performed.

Data analysis

The results obtained were expressed as the mean ± Standard Deviation (SD) and percentage. The risk factors were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). The X^2 test was used to evaluate the risk factors for urinary tract infections (UTIs) caused by Enterococcus. Moreover, we used the X^2 test for the analyses of mortality. A multivariate analysis was carried out, introducing only the variables with statistical significance ($p<0.05$) in the univariate analysis. Receiver operating characteristic (ROC) curves were performed to evaluate and compare the validity of the PBS and SOFA as predictors of

mortality. Binary logistic regression was carried out by introducing only the variables that were significant in the bivariant analysis. The odds ratio with 95% CI was assessed in all significant variables. Data analysis was performed using SPSS 25.0 (*Statistical Package for the Social Sciences*).

Results

In this study, we included one hundred and six patients with UTIs caused by *Enterococcus* spp. The main characteristics of the patients are shown in **table 1**.

Table 1. Characteristics of the patients included in the study with urinary tract infections caused by *Enterococcus* spp.

Variables	Total, N 106
Age±SD; years	73.8 ± 19.0
Gender male n(%)	68 (64.2)
Acquisition n(%)	
Hospital	50 (47.2)
Community	33 (31.1)
Health care	23 (21.6)
Clinical setting n(%)	
Sepsis	34 (32.1)
Pyelonephritis	18 (20.5)
Shock	7 (6.7)
Cystitis	2 (2.3)
SOFA score±SD	2.1 ±2.2
Charlson index comorbidity±SD	5.9±2.9
Risk factors n(%)	
Uropathy (not renal failure)	68 (64.2)
Antibiotic 6 month ago	55 (67.1)
Bladder Catheter	19 (19.2)
Diabetes	27 (25.7)
Urinary cancer	18 (20.2)
Immunosuppression	17 (18.9)
Nephrostomy	12 (13.3)
Hemopathy malign	9 (10.1)
Double J stent	8 (9.5)
Solid organ transplantation	7 (8)
Neutropenia (<500/mm^3)	7 (8)
Species Enteroccus n(%)	
E.fecalis	88 (83)
E.faecium	18 (17)

Another coinfection	9 (10.2)
Blood culture positive n(%)	51 (48.1)
Antimicrobial resistance n (%)	
Ampicillin	21 (24.4)
Vancomycin	5 (5.3)
Endocarditis association n(%)	3 (2.8)
In-mortality n(%)	17 (16.5)

-

Sixty-eight (64.2%) patients were male, with an average age of 73.8±19 years and an average Charlson comorbidity index of 5.9±2.9. A total of 87.6% of the patients had a Charlson index > or = 3. Thirty-three (31.1%) patients had community-acquired UTIs, 23(21.7%) had healthcare-associated UTIs, and 50(47.2%) had hospital-acquired UTIs.

Of the patients with UTIs caused by *Enterococcus* spp, 51 (48.1%) had positive urine and blood cultures, and 55(51.9%) had negative blood cultures. *E. faec*alis was the most frequently detected isolation in 88 of the patients (83%), followed by *E. faecium* in 18 (17%) patients. A total of 9(10.2%) patients also had other simultaneous isolations. Patients demonstrated an average SOFA score of 2.1±2.2, and 15% demonstrated a SOFA score >5. Among the patients, 31(31%) had sepsis, and 7(6,6%) had septic shock. Twenty-one (24%) patients with UTIs caused by *Enterococcus* spp. were resistant to ampicillin, and 5.3% were resistant to vancomycin. Moreover, one-third of patients with UTIs caused by *E. faecium* were resistant to both types of antimicrobials. The risk factors associated with resistance to ampicillin were hematological neoplasia [OR 5.8 (95%CI 1.2-27.4) p<0.05], febrile neutropenia [OR 8.5 (IC 95 1.4-49) p<0.05], organ solid transplantation [OR 3.3 (IC 95 0.8-13.2) p>0.05] and immunosuppression treatment [OR 3.2 (IC 95 0.9-10.6) p>0.05].

To determine the risk factors associated with enterococcus UTI, we compared this cohort with a random sample of 100 patients with complicated UTI infections caused by *E. coli.* The results of the univariable analysis for UTIs caused by enterococcus is shown in **table 2**.

Table 2. Analysis of bivariable risk factors associated with tract urinary infection caused by Enterococcus spp. vs *E. coli.*

Variables	*Enterococcus* spp *vs E. coli* n (%)	OR (CI 95%)	*p*
Age (<65 y)	20 (18.9) vs 10 (10.1)	2.1 (0.9-4.6)	0.076
Male	73 (68.9) vs 41 (41)	3.1 (1.7-5.6)	0.000
Diabetes	28 (26.7) vs 41 (41)	0.5 (0.2-0.9)	0.030
Uropathy (not renal failure)	68 (64.2) vs 46 (46)	2.1 (1.2-3.6)	0.009
Nosocomial infection	50 (47.2) vs 18 (18)	4.1 (2.1-7.6)	0.000
Bladder catheter	19 (19.2) vs 8 (8)	2.7 (1.1-6.5)	0.021
Double J stent	8 (9.4) vs 2 (2)	5.1(1.1-24.6)	0.046
Nephrostomy	12 (13.3) vs 1 (1)	15.2 (1.9-119.6)	0.001
Immunosuppression	17 (18.9) vs 4 (4)	5.5 (1.8-17.3)	0.001
Urinary cancer	18 (20.2) vs 2 (2)	12.4 (2.7-55.2)	0.000
Hemopathy malign	9 (10.1) vs 0 (0)	NC	-
Neutropenia (<xx /mm^3)	7 (8) vs 0 (0)	NC	-
Solid organ transplantation	7 (7.8) vs 0 (0)	NC	-
Antibiotic 6 month ago	56 (68.3) vs 31 (35.6)	4.6 (2.3-9.1)	0.000

According to the multivariable analyses, only male sex with an OR of 2.8 (95%CI 1.2-6.4), nosocomial infection with an OR of 2.8 (95%CI 1.1-7), urinary catheter with an OR of 4.5 (95%CI 1.8-11.3), urinary cancer with an OR of 6.4 (2.1-19.4), and previous antimicrobial treatment with an OR of 4.3 (1.8-10.2) were independent predictors of *Enterococcus* infection. We also studied the variables associated with UTIs with bacteremia. Urinary cancer [OR 3.4 (95%CI 1-11.3) p<0.05] and solid organ transplantation [OR 9.7 (95%CI 1.1- 79.8) p<0.05] were the only risk factors associated with bacteremia caused by enterococcus.

The overall in-patient mortality for UTIs caused by *Enterococcus* spp. was 17(16,5%). The predictive risk factors for mortality are shown in **table 3**: Malignant hemopathy [OR 4.8 (95%CI 1.1-20.7) p<0.05], immunosuppression treatment [OR 4.1 (95%CI 1.2-14.1) p<0.05], nephrostomy [OR 4.6 (95%CI 1.2-17.4) p<0.05], ampicillin resistance [OR 8.7 (95%CI 2.5-29.8) p<0.05], and vancomycin resistance [OR 9.3 (95%CI 1.4-62) p<0.05]. Moreover, a SOFA score >/= 2 was also associated with higher mortality, but these differences did not reach a significant level (OR 4.1 (0.8-21.5) p<0.05].

Table 3. Study of the bivariant variables associated with mortality

Variables	Mortality	OR (CI 95%)	*p*
Nephrostomy *vs* no-nephrostomy	41% *vs* 13%	4.6 (1.2-17.4)	0.030
Immunosuppression *vs* non immunosuppresion	37% *vs* 12%	4.1 (1.2-14.1)	0.028
Hemopathy malign *vs* no-hemopathy	44% *vs* 14%	4.8 (1.1-20.7)	0.046
Ampicillin resistant *vs* ampicilin sensible	47% *vs* 9%	8.7 (2.5-29.8)	0.001
Vancomycin resistant *vs* vancomycin sensible	60% *vs* 13 %	9.3 (1.4-62)	0.029
SOFA score 0-3 vs >4 *p*	10% *vs* 35%	0.2 (0.1-0.9)	0.026
E. fecalis vs E. faecium	10% *vs* 50%	0.1 (0.1-0.3)	0.0001

Among patients with bacteremia, the SOFA score was a better predictor of mortality than the PBS (AUC-ROC 0.8 vs 0.5), as shown in **figure 2**.

Figure 2. Area under the ROC curve (AUC) of the SOFA score and PBS as predictors of mortality.

We did not detect an association between bacteremia and mortality (p>0.05). A total of 49.4% of patients with UTIs caused by *Enterococcus* spp. achieved correct, empiric antibiotic therapy according to the final antibiogram, although we did not detect a lower mortality rate in this group of patients (p<0.05).

Discussion

Enterococci species are part of the healthy human gut microbiota(12) and sometimes can also colonize in the urinary tract, causing different clinical settings from asymptomatic bacteriuria (AB) to UTIs. Bacteriuria caused by enterococci has a deleterious effect on the urinary tract, which promotes innate immune suppression and increases the risk of infection by other uropathogens(13), suggesting that the treatment of AB can be successful in terms of the prevention of the recurrence of urinary tract infection. Nevertheless, paradoxically, it has been shown that antibiotic treatment of AB caused by *Enterococcus,* in

patients with recurrent infection, increases the risk for recurrent urinary infection by other uropathogens(14).

Regarding UTIs, *Enterococcus* spp. is the cause of cystitis, prostatitis and epididymitis(1)

Experimental studies in mice have shown that enterococci can also affect the urinary tract, thus causing pyelonephritis(15), which is one of the most frequent pathogens involved in complicated UTIs. In a review, enterococci was the cause in 7-25% of patients with severe urinary sepsis and UTIs(3). Despite these data, pyelonephritis caused by *Enterococcus* spp. is not usually associated with bacteremia(2,4)

In this sense, empiric treatment against enterococci is not included in guidelines of UTIs management or is reserved only for patients at risk

(6-8)

Thus, the first aim of this work was to determine the risk factors associated with UTIs caused by enterococci Although there are several studies that have analyzed the risk factors for bacteremia, there have been few studies that have focused on urinary infections and how these risk factors affect infection.

Therefore, we reviewed the records from more than one hundred consecutive in-patient cases from different hospitals in Castilla y Leon (region of northwestern Spain) with a diagnosis of UTIs caused by Enterococcus, half of whom with positive blood cultures and the rest with negative blood cultures. In our cohort of patients, the main species that was detected was *E. faecalis*, whereas only fifteen percent of cases were due to *E. faecium*. This distribution, with a predominance of *E. faecalis*, was found in both a European study(15) and in a North-American series of complicated UTIs cases(16)

To establish the risk factors, we compared a cohort with Enterococcus UTIs with a randomized sample of 100 in-patients from a cohort with UTIs complicated by *E. coli,* stratified only by bacteremia.

Regarding demographic characteristics, male sex has been associated with Enterococcus spp. Thus, in a cohort of 700 patients with bacteremia, which included more than 180 patients with a urinary focus, there were twice as many males as females(15). Our results also support a predominance for male sex in complicated UTI cases, with or without bacteremia. In our work, nearly half of the cases of UTI caused by Enterococcus were acquired in a hospital. In a previous series of enterococcus infections, other authors have shown similar results(15) and have supported the fact that *Enterococcus* spp. must be considered, similar to *Pseudomonas aeruginosa*, especially in cases of nosocomial UTIs.

Enterococcus spp. are frequently associated with biofilms of both blood and urinary catheters. Thus, Enterococcus has been frequently referred to as the main cause of catheter urinary tract infection (CAUTI) in different studies. In a recent study, patients with an indwelling catheter had twice the risk for *Enterococcus* spp. than other patients with community-acquired UTIs(17). In our cohort, the patients

frequently had bladder, nephrostomy or double J catheters. It is possible, as is the case in other works, that the presence of a nephrostomy catheter is specifically involved in *Enterococcus* spp infection(18).

The population in this study had a high comorbidity Charlson index. Among the different comorbidities demonstrated by the patients, the most important were urinary disorders or severe systemic diseases. Among urological diseases, urological cancer has been described as a risk factor for Enterococcus UTIs(19,20). It is possible, as is the case in bacteremia associated with colorectal cancer(20), that lesions due to urinary epithelial colonization can be one of the most important predictive risk for urinary infections caused by Enterococcus.

Enterococcus species are considered by many authors an opportunistic pathogen(21), and factors such as immunosuppression, neutropenia or hemopathy are frequently detected as risk factors for bacteremia(16). The results of our work suggest that in this epidemiological setting, Enterococcus can be considered one of the most probable causes of UTI.

Finally, another risk factor detected in our work was previous antibiotic treatment. This finding is in accordance with other works in which patients treated with ceftriaxone were associated with an increased risk for reinfection by *Enterococcus* spp(22). The fact that more than one-half of our patients had been treated in the previous month with 3rd-generation cephalosporins may explain these results.

Another aim of this study was to evaluate the variables associated with bacteremia. Although there are several studies that have analyzed bacteremia caused by enterococcus and its risk factors, they included different types of infections, and the results were not focused on UTIs(16,20). In our study, we selected only patients with a clinical setting of UTIs and an isolation of enterococcus in urine culture, and we compared the risk factors in the two groups with and without bacteremia. Our results are consistent with other findings, and we showed that neutropenia, solid organ transplant, bone medullary transplant, and immunosuppression were also risk factors for bacteremia in patients with tract urinary infection caused by *Enterococcus* spp.(16,20). These are the same classic risk factors in patients with bacteremia, regardless of other origins(4). Moreover, we detected that urinary cancer was associated with bacteremia in patients with UTIs. In a recent study, urological cancer was also associated with bacteremia(20). These results support that regardless of *E. faecalis*- and *E. faecium*- colonizing urinary tract infections, it is difficult for these pathogens to cross the urinary epithelium when innate immunity is preserved, but when it exists, rupture of the epithelial barrier can result in bacteremia.

Another objective of this work was to study the mortality and morbidity following UTIs caused by Enterococcus. The mortality rates seen with this infection in our study were higher than those in other series of in-patients with UTIs(23,24) and were similar to those shown by Billinton *et al.*(16) in a subgroup of patients with urosepsis caused by Enterococcus. In our study, mortality was not different between patients with or without bacteremia. Factors that depend on the clinical setting, such as a high SOFA score and severe comorbidity (such as malignant hemopathy and immunosuppression), and factors that depend on the species involved (*E. faecium* vs E*. faecalis or* its pattern of resistance to ampicillin and

vancomycin) were the only factors associated with high mortality. Similar data have been reported by other authors regarding bacteremia(15). We did not detect a lower mortality rate for patients with correct empiric treatment for *Enterococcus* spp. This result could be due to the small number of patients included in the study and to the heterogenicity in the empirical treatments performed. However, because our study was retrospective, it is also possible that there was a selection bias, so patients with optimal empirical treatment according to the last antibiogram could also be the most critical.

Finally, we evaluated infectious endocarditis, a frequent morbidity detected in patients with bacteremia caused by *Enterococcus* spp. In a Danish cohort, 6% of patients with nosocomial infections and 25% of patients with community-acquired infections had infectious endocarditis. In our study, we found endocarditis in 5.8% of patients with UTIs and bacteremia with a urinary origin (2.8% of the total patients included in the study). These data support that in patients with bacteremia and a urinary focus, echocardiography must be performed to diagnose this severe complication(15)

We believe that our work can help to better define a group of patients with urinary infection that have a high mortality, thus requiring a differentiated antimicrobial treatment from the one included in the current guidelines. Nevertheless, we also recognize that our work has some limitations. It was a retrospective study of in-patients, with a relatively low number of patients and with selection bias, so risk factors or mortality may not be similar in other populations of patients.

In conclusion, Enterococcus is one of the most frequent causes of UTIs complicated by a profile of risk factors, in which male sex, a high Charlson index, urinary catheter, previous antibiotic treatment, urological cancer or several types of immunosuppression are the main predictive factors. These last two factors are also risk factors for bacteremia. High mortality secondary to a severe clinical setting and high comorbidity may be sufficient reasons for implementing empiric treatment of patients at risk, although we did not show a higher survival rate in patients with this treatment strategy.

Abbreviations

1. Urinary tract infections (UTIs)
2. Sequential Organ Failure Assessment (SOFA)
3. Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)
4. The European Association of Urology (EAU)
5. Complejo Asistencial de Palencia (CAUPA)
6. Complejo Asistencial Universitario de Salamanca (CAUSA).
7. Systemic inflammatory response syndrome (SIRS)
8. Pitt bacteremia score (PBS)
9. CFU colony-forming unit

10. MIC minimum inhibitory concentration
11. European Committee for Antimicrobial Susceptibility Testing (EUCAST)
12. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS)
13. Standard Deviation (SD)
14. Odds ratios (ORs)
15. Confidence intervals (CIs).
16. Receiver operating characteristic (ROC)
17. SPSS 25.0 (*Statistical Package for the Social Sciences*).
18. Catheter urinary tract infection (CAUTI)

Declarations

Ethics approval and consent to participate

The procedures described here were carried out in accordance with the ethical standards described in the Helsinki Declaration revised in 2013. Additionally, this study was approvedby the Bioethics Committee of CAUPA. At all times, we maintained the confidentiality of the patients' personal data.

Informed consent

Non relevant

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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None declared.

Authors' contributions

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Figures

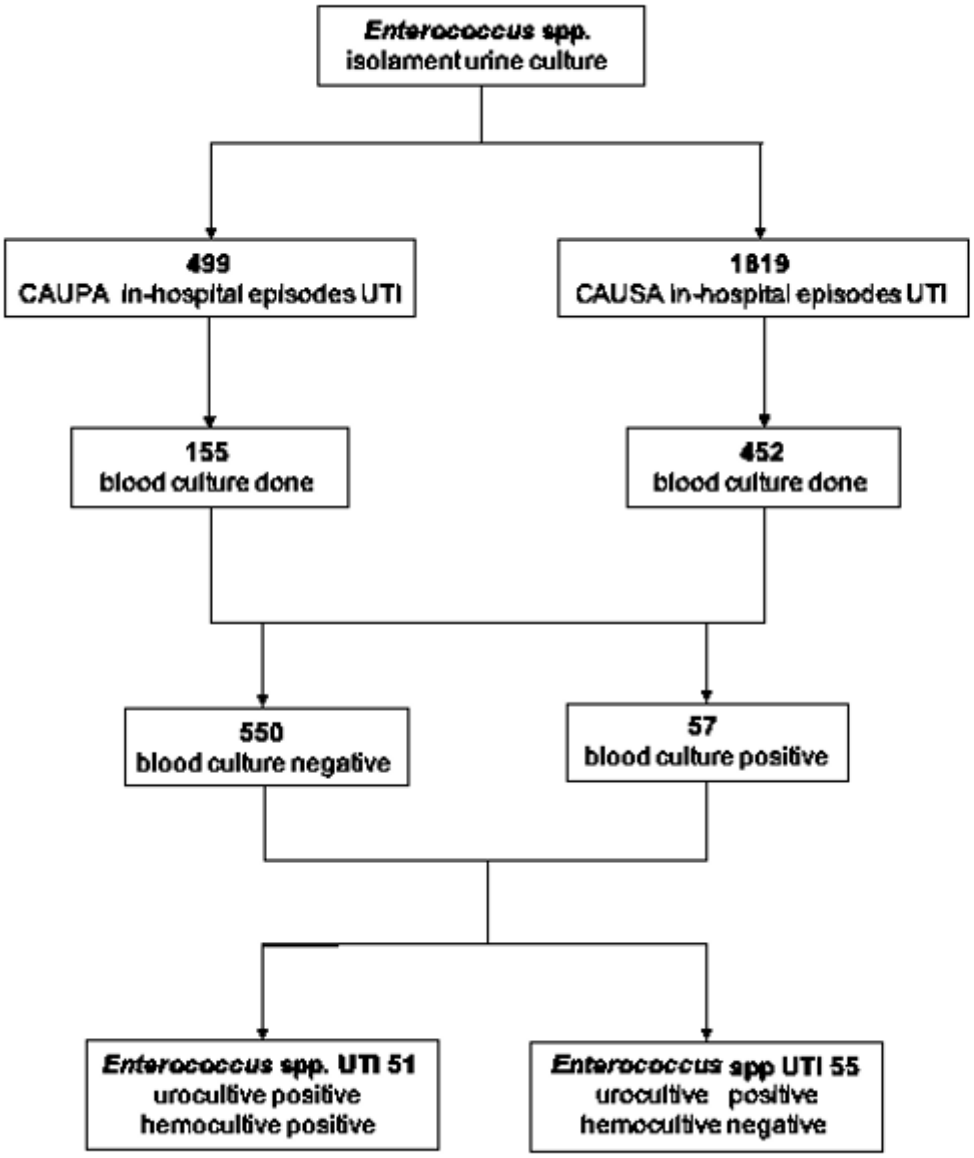

Figure 1

Participant profile.

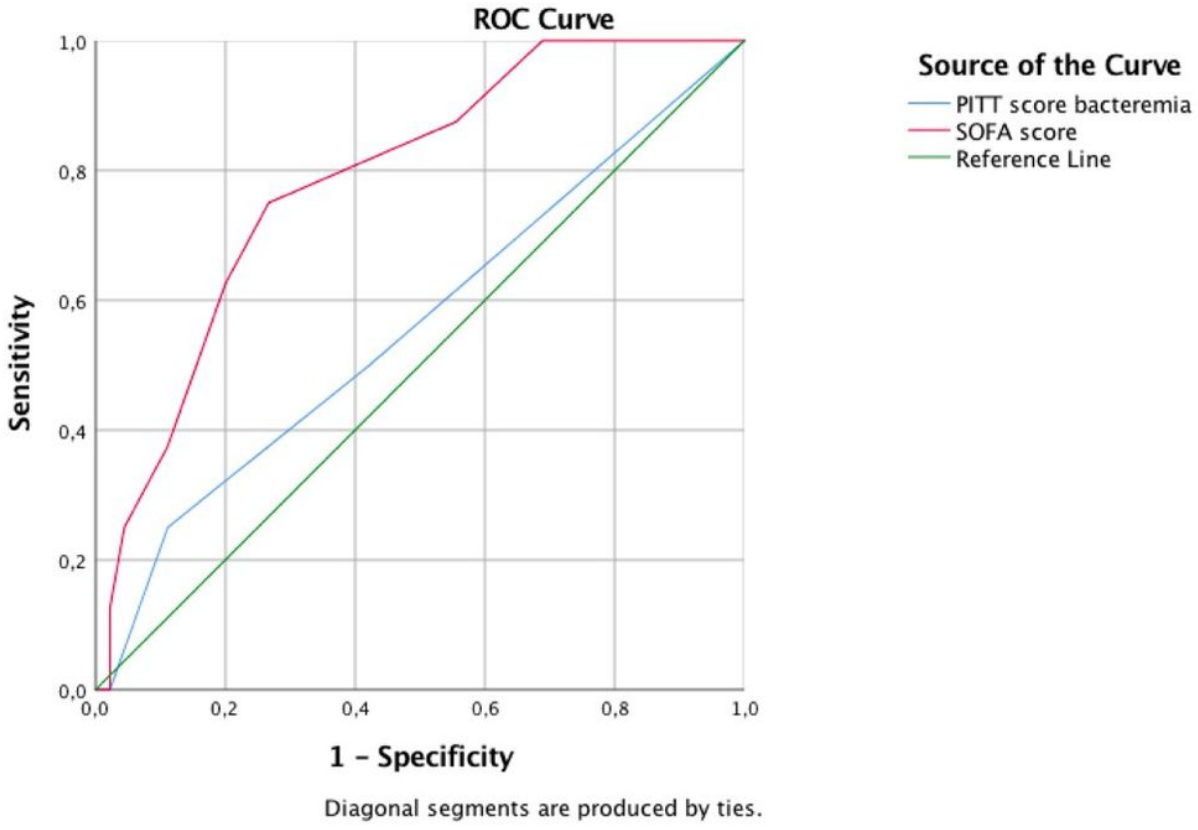

Figure 2

Area under the ROC curve (AUC) of the SOFA score and PBS as predictors of mortality.