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Fungal infection characterization in a Peritoneal Dialysis Unit

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Exit-site infection characterization on a Peritoneal Dialysis Unit

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Abstract

Background: Exit-site infections remain a major clinical problem in peritoneal dialysis (PD). Although detailed descriptions about microbiologic epidemiology regarding exit-site infections are found in the literature, little is known about the different risk factors associated with Gram positive and Gram negative infections. **Objective:** To retrospectively evaluate the factors associated with the presence and clinical behavior of exit-site infections caused by Gram positive and Gram negative agents in PD patients. **Methods:** This study included all cases of PD catheter exit-site infections diagnosed in patients followed in a PD Unit during 2011 and 2012. Patients with exit-site infection caused by Gram positive and Gram negative agents were compared regarding demographic, clinical and analytical variables. This analysis was extended to specific episode etiologies (*Staphylococcus aureus* and *Pseudomonas aeruginosa*) and distinct clinical behaviours, such as prolonged treatments and recurrent events. Outcome differences were additionally described among all etiologic groups. **Results:** A total of 225 events were diagnosed in 117 patients (corresponding to 0.96 events/patient-year). Infections were predominantly caused by Gram positive agents (47.6%), namely *Staphylococcus aureus* (18.2%) and *Corynebacterium spp* (15.6%). Reduced adequacy parameters were more often associated with Gram positive bacterial events than with Gram negative infections. However, similar outcomes were observed between both groups. *Staphylococcus aureus* infections associated to lower percentages of supplementation with vitamin D, lower levels of HDL cholesterol, preferentially occurred early after peritoneal dialysis initiation, required prolonged treatments and more frequently associated to tunnel infections and peritonitis. **Conclusion:** Exit-site infections in PD patients are still common events, related to substantial morbidity. *Staphylococcus* episodes represented, in our population, a subgroup of infections with a particular clinical profile and were associated with a significant clinical burden.

Resumo

Introdução: As infeções do orifício de saída do cateter peritoneal constituem ainda um problema clínico relevante em diálise peritoneal. Apesar da epidemiologia associada a estas infeções já ter sido abordada em trabalhos prévios, os fatores de risco especificamente relacionados com infeções causadas por agentes Gram positivos e Gram negativos permanecem ainda por esclarecer. **Objetivo:** Avaliar retrospetivamente os fatores associados à presença e evolução das infeções do orifício de saída causadas por agentes Gram positivos e Gram negativos. **Métodos:** Incluíram-se todos os casos de infeção do orifício de saída do cateter peritoneal diagnosticados em doentes seguidos numa Unidade de Diálise Peritoneal do Hospital S.João entre 2011 e 2012. Os doentes com infeção Gram positivo e Gram negativo foram comparados relativamente a variáveis demográficas, clínicas e analíticas. A abordagem foi alargada ao estudo de infeções com etiologias específicas (*Staphylococcus aureus* e *Pseudomonas aeruginosa*) e evoluções distintas (tratamentos prolongados e eventos recorrentes). Foi registada e comparada a evolução clínica dos vários grupos etiológicos. **Resultados:** Diagnosticaram-se 225 eventos em 117 pacientes (0.96 eventos/paciente-ano). As infeções foram causadas predominantemente por agentes Gram positivos (47.6%), nomeadamente *Staphylococcus aureus* (18.2%) e *Corynebacterium spp* (15.6%). Os episódios causados por bactérias Gram positivas relacionaram-se com parâmetros de adequação dialítica inferiores aos observados nas infeções por bactérias Gram negativas. Contudo, a evolução clínica foi semelhante nestes dois grupos. As infeções por *Staphylococcus aureus* associaram-se a menor percentagem de doentes suplementados com vitamina D, a níveis inferiores de colesterol HDL, ocorreram precocemente após o início da diálise, implicaram tratamento antibiótico prolongado e resultaram mais frequentemente em infeções do túnel e peritonites. **Conclusão:** As infeções do orifício de saída em diálise peritoneal são um evento frequente, condicionando morbidade significativa. Os episódios causados por *Staphylococcus*

aureus constituíram, na nossa população, um subgrupo de infeção com perfil clínico singular associado a elevada carga assistencial.

Palavras-chave: Infeções do orifício de saída, Bactérias Gram-negativas, Bactérias Gram-positivas, Diálise peritoneal.

Introduction

Peritoneal dialysis (PD) is an effective form of renal replacement therapy. Despite the improvements in PD technology, infection remains one of the most important preventable cause of morbidity and mortality, as well as of hospitalization, in patients undergoing dialysis (1). PD infections include exit-site infections (ESI), tunnel infections (TI) and peritonitis, this last one considered the main undesired complication of PD. Despite numerous improvements in PD technique, exit-site care and infection prophylaxis, ESI are still clinically relevant since they are associated with prolonged antibiotic treatment, increased morbidity, catheter dysfunction, peritonitis and with PD discontinuation (2, 3). Overall, ESI are predominantly caused by Gram positive (G+) bacteria. Previous studies have shown that ESI and TI are most often caused by S*taphylococcus aureus* (*S. aureus*) (25-50%) followed by *Pseudomonas aeruginosa* (10-28%)*,* both of which tend to recur and frequently lead to peritonitis (4). Other microorganisms that colonize the skin are also involved, such as *Staphylococcus* coagulase negative (10-35%) and *Corynebacterium* (2-9%)(5, 6). Non-diphtheria *Corynebacteria* species are major agents of the normal flora of the skin and mucous membranes and are frequently discarded as contaminants. For this reason, *Corynebacterium* infection rates in PD are most probably underestimated in the literature. Nevertheless, they are considered pathogenic in high-risk populations, such as immunocompromised individuals and patients with indwelling catheters and should not be undervalued in the context of peritoneal dialysis.

In the most recent years the spectrum of bacteria causing infections in the PD population is changing, with a significant higher proportion of Gram negative (G-) agents. This is in part due to improvements made in connection systems, pre- and postoperative catheter care such as *S. aureus* prophylaxis, allowing an important reduction in the proportional incidence of PD infections caused by G+ bacteria. Additionally, it is well established that G- infections are associated with worse outcomes (7, 8).

Although detailed descriptions about microbiologic epidemiology associated to ESI are found in the literature, little is known about the risk factors associated to G- comparing to G+ infections. Here we report an observational study designed to examine if specific background parameters, such as demographic, clinical, analytical, pharmacological or PD-related factors are associated to ESI caused by G- *versus* G+ bacteria. This analysis is extended to specific ESI etiologies, such as *S. aureus,* other G+ bacteria or *Pseudomonas aeruginosa.* We also describe outcome differences among all etiologic groups. To go further, the same background parameters are also compared between groups of ESI with different outcomes, such as sequential infections, prolonged medical treatment, non-cured and recurrent ESI.

Subjects and Methods

This study describes a retrospective and observational analysis of all ESI episodes occurring in a population of prevalent PD patients followed in a single unit in Portugal (Nephrology Department of Centro Hospitalar S. João), between 2011 and 2012. All patients had a double-cuffed Tenckhoff catheter implanted using standard surgical techniques and were submitted to antibiotic prophylaxis with 1 gram of intravenous cefazolin on the day of the PD catheter insertion. On average, 15 days after PD catheter implantation patients initiated intensive training sessions for PD technique-related issues and exit-site care.

ESI were diagnosed whenever clinical signs of infection were detected, as indicated in the International Society of Peritoneal Dialysis (ISPD) Guidelines/Recommendations (9). Sequential infection was diagnosed when different microorganisms were culturally isolated from the same ESI episode in a different microbiological culture. TI diagnosis was made taking in consideration the presence of clinical signs such as erythema, edema or tenderness along the subcutaneous catheter pathway and/or ultrasound results identifying suspicious subcutaneous collections. Peritonitis was considered in the presence of two of the following three findings: abdominal pain, cloudy effluent with ≥50% polymorphonuclear cells or positive microbiological culture of the dialysate fluid.

Data of ESI episodes were gathered from medical records for the following variables: (a) Demographic characteristics, such as age at the time of ESI diagnosis, gender, residence characteristics (city/rural), water supply (public network/well); (b) Previous comorbid diseases such as diabetes *mellitus* (DM), hypertension, cardiovascular disease (this group included cardiac, cerebrovascular and peripheral vascular disease), chronic kidney disease (CKD) etiology and duration, previous infectious episodes (ESI, peritonitis, respiratory infections or other) on the last 3 months and presence of constipation; (c) Analytical profile, including hemoglobin, albumin, A1c hemoglobin and lipid profile, calcium, phosphorus, pH, bicarbonate, B-type natriuretic peptide,

sedimentation rate and C reactive protein; (d) Pharmacological profile, including previous antibiotherapy in the last 3 months, immunossupressors, anti-platelet agents, anti-coagulants and vitamin D supplementation; (e) Characterization of PD technique, including PD modality, degree of residual renal function, diuresis, weekly creatinine clearance, weekly Kt/V and peritoneal transport status defined by the 4h creatinine D/P obtained by the peritoneal equilibration test; (f) ESI episode characterization, namely the presence of serous-hematic or purulent drainage, microbial culture result, antibiotic treatment duration and ESI outcome (TI, peritonitis, ESI cure, external cuff removal, catheter substitution or removal, hemodialysis transfer).

Ambiguous exit-sites were kept under close clinical surveillance with topical antibiotic, saline soak or silver nitrate solution and were treated with systemic oral antibiotic if no improvement was observed after approximately 1 week. Empiric treatment was usually initiated with cotrimoxazole, normally for 2 weeks. Once the microbial culture report was available, the patient was switched to a specific antibiotic agent directed by the susceptibility profile (9).

Prophylaxis of fungal peritonitis was undertaken with oral fluconazole in cases of prolonged antibiotic therapy (treatment duration superior to 1 month). If extended appropriate antibiotic treatment failed to resolve the infection, the patient was successively oriented for one of the following procedures: external cuff removal, catheter substitution or removal and hemodialysis transfer.

Statistical tests were applied to several sets of samples of ESI with different microbial etiologies, such as G- *vs.* G+ bacteria, *S. aureus vs. Pseudomonas aeruginosa*, *S. aureus vs.* other G+ bacteria or *S. aureus vs.* non-*S.aureus* bacteria. The same tests were used to compare samples related to different episode developments, such as those with *vs.* without sequential infections, those requiring >30 days *vs.* ≤30 days of medical treatment, non-cured *vs.* cured episodes and recurrent *vs.* single ESI episodes.

Statistical Analysis

The statistical analysis was performed using SPSS version 21 for Windows. Univariate analysis was conducted to identify potential correlations between variables and ESI. The association between two categorical variables was evaluated by Chi square test or Fisher's exact test, as appropriate. For continuous variables the Student's t-test (for normally distributed variables) or the non-parametric Mann-Whitney were used. Variables were considered to have statistically significant association with ESI if the p value was ≤ 0.050.

Results

Characterization of the population studied

Throughout the two-year period, a total of 225 ESI events were diagnosed, occurring in 117 patients. The follow-up of the group of patients studied represented a total of 246.15 patient-dialysis years of observation, resulting in an incidence of ESI during the period analysed of 0.91 ESI/patient-year. Table I shows the demographic and epidemiological data associated with the 117 patient sample. The population evaluated had median age of 47 years and was constituted by 65.8% of males. One hundred and five patients (89.7%) suffered from at least one comorbid disease (hypertension, DM or cardiovascular disease). Chronic kidney disease was most frequently caused by glomerulonephritis (17.9%) and diabetes *mellitus* (13.7%). The frequency of patients experiencing a single ESI (48.7%) was similar to the frequency of patients having multiple ESI (51.3%) during the two-year period. A median of 2 events *per* patient was registered (range: 1-9).

Characterization of the ESI sample

Among the total of 225 ESI analysed, the median age at the moment of diagnosis was 48 years (range: 19-84 years). PD duration had a median of 1 year (range: 0-6), 71.1% were on CAPD and 24.0% on APD (Table I) and all patients used standard bicarbonate based PD solutions with 1.25mmol/L of calcium. Preceding infections were present in the last 3 months in 41.8% of the episodes, of which 28.9% were due to ESI.

Concerning the relevant pharmacological profile, supplementation with vitamin D and immunossupressive therapy were prescribed in 54.7% and 7.6% of the cases, respectively. In 41.3% of the current ESI episodes, previous antibiotic treatment was prescribed for an infectious episode in the preceding 3 months.

Microbiologic cultures were positive in 66.7% of the ESI episodes, 23.1% resulted in non-specific bacterial growth and 4.4% were negative. In 64.0% of the cases the isolates

were purely bacterial and 2.7% were due to *Candida parapsilosis*, the only fungal agent isolated (Table II). G+ organisms were isolated in 47.6% of the cases and G- agents in 21.3%. *S. aureus* and *Corynebacterium* spp were the most commonly isolated bacteria (47.6% and 18.2%), followed by *Pseudomonas aeruginosa* (10.2%). Co-infections, *i.e.* simultaneous isolation with more than one agent, were observed in a small number of episodes (4.9%) and frequently due to growth of G+ bacterial species (2.7%), followed by G- bacteria (1.3%) and finally by a mixture of both (0.9%). No more than two species were isolated in each co-infection. Moreover, 16.4% of the events complicated with sequential infections a few days after diagnosis, *i.e.* new microbial agents isolated during a single ESI episode. Of these superimposed infections, G+ microorganisms were more frequently isolated (17.8% *vs.* 2.2% for G- bacteria), with only three cases (1.3%) of *Candida Parapsilosis* infection. These sequential infections were more often caused by *Staphylococcus* coagulase negative and *Corynebacterium* spp (9.8% and 4.4%, respectively).

Bacterial ESI were, in most cases, successfully controlled (85.0%) with antibiotic therapy for a median duration of 33 days (range: 13-199). Fungal infections were medically treated in 66.7% of the cases with anti-fungal drugs for a median duration of 74.0 days (range: 23-86). Patients with non-cured ESI were orderly proposed for external cuff removal (3.6%), catheter substitution/removal (9.3%) and hemodialysis transfer (0.9%), whenever indicated. Tunnel infections and peritonitis were reported in 12.9% and 3.6% of the cases, respectively.

Association of specific characteristics of the population according to ESI etiologies and outcomes

Comparison of specific characteristics of the population studied according to distinct ESI samples are described in Table III, IV and V.

Demographic, clinical and pharmacological parameters

Statistical tests applied to several sets of samples of ESI with different microbial etiologies showed no association with age, environment (city or rural) or type of water supply. However, a strong association with gender was observed among specific groups. *S. aureus* ESI were more prevalent in men (87.8%) and *Pseudomonas* in women (56.5%) (p<0.001). Similar results were found when comparing *S. aureus* events with other G+ bacterial ESI (p=0.003) or with non-*S.aureus* bacterial events (p=0.001). No obvious demographic differences were observed in the comparison of samples with different outcomes (with *vs.* without sequential infections, >30 days *vs.* ≤30 days of medical treatment, non-cured *vs.* cured episodes and recurrent *vs.* single ESI episodes). Clinical parameters, such as DM, hypertension, cardiovascular disease, smoking or CKD etiology, previous hemodialysis treatment, previous renal transplant or constipation were not associated to specific ESI etiologies or outcomes. Considering the pharmacological profile, *S. aureus* infections occurred less frequently in patients on vitamin D supplementation, comparing to non-*S. aureus* events (36.6% *vs.* 57.7%, p=0.022).

Biochemical parameters

Considering the analytical evaluation, significantly reduced levels of HDL cholesterol were reported in G+ bacterial ESI when comparing to infections caused by G- bacteria (45.0 *vs.* 49.0 mg/dL, p=0.039). These results were reproduced when specifically considering *S. aureus vs. Pseudomonas aeruginosa* events (41.7 *vs.* 50.6 mg/dL, p=0.003), *S. aureus vs.* other G+ bacterial infections (41.7 *vs.* 49.2, p=0.007) and *S. aureus vs.* non-*S. aureus* events (41.7 *vs.* 50.6, p=0.003). Lower levels of HDL were also significantly associated to ESI with sequential infections (42.5 *vs.* 46.0, p=0.030). Additionally, the levels of triglycerides were found to be higher in ESI with extended antibiotic treatment (158.0 *vs.* 133.0 mg/dL, p=0.047).

PD-related parameters

Considering PD therapy duration, *S. aureus* events occurred earlier after PD initiation (before completing a year of PD) when compared to other G+ ESI (p=0.002) or non-*S. aureus* infections (p=0.004). No correlations were reported between PD modalities (CAPD or APD) and specific ESI etiologies or outcomes.

G+ bacterial infections were associated to decreased levels of total Kt/V when compared to G- events (1.80 *vs.* 2.20, p=0.022). We also found lower levels of total Kt/V associated to *S. aureus* ESI in comparison to infections caused by *Pseudomonas aeruginosa* (1.68 *vs.* 2.27, p<0.001), other G+ bacterial ESI (1.70 *vs.* 2.00, p<0.001) or by non-*S. aureus* (1.70 *vs.* 2.10, p<0.001). Reduced levels of total creatinine clearance *per* week were additionally correlated with *S. aureus* infections in comparison to other G+ bacterial ESI (75.95 *vs.* 111.30 L/week, p=0.003) as between *S. aureus vs.* non-*S. aureus* (75.95 *vs.* 92.96 L/week, p=0.017). Moreover, a significant statistical difference of the total renal clearance was reported among *S. aureus vs.* other G+ bacterial ESI (2.40 *vs.* 4.99 ml/min, p=0.031). Statistical tests applied to PD-parameters comparing single *vs.* recurrent ESI also revealed lower levels of diuresis in the latter group (1175 *vs.* 950ml, p=0.023).

Previous infections/ antibiotic therapies

S. aureus events were not related to the presence of previous infections or ESI when considered individually. However, when present, previous ESI were longer than those preceding other G+ bacteria events (65.0 *vs.* 28.5 days, p=0.021) or non-*S. aureus* ESI (65.0 *vs.* 29.5 days, p=0.009). Similar findings were observed when analysing episodes treated for more than 30 days in comparison to those treated in a shorter period of time (42.0 *vs.* 23.0 days, p=0.001). Furthermore, when compared to the group of cured events, non-cured ESI were associated with reduced intervals between the previous infection and the current episode (19.5 *vs.* 36.0 days, p=0.026).

Although, *S. aureus* episodes were not related to previous ESI, considering the sample of all preceding episodes, this was not what we have observed when specifically considering previous *S. aureus* events. In fact, current *S. aureus* infections strongly correlated with preceding infections by the same agent (58.3% *vs.* 10.0%, p=0.006). Despite the fact that *S. aureus* ESI were not related to previous antibiotic therapy in the last 3 months, when present these were more frequently prolonged treatments requiring different antibiotic agents when comparing to the group of other G+ bacterial ESI (55.2 *vs.* 29.0 days, p=0.014; 3 *vs.* 1 antibiotic classes, p=0.005) and non-*S. aureus* ESI (58.5 *vs.* 25.5 days, p=0.017; 3 *vs.* 2 antibiotic classes, p=0.008). Similar results were obtained when comparing ESI treated for more than 30 days *vs.* those treated in a shorter period of time (37.0 *vs.* 21.0 days, p=0.005; 2.5 *vs.* 1 antibiotic classes, p=0.001) and non-cured *vs.* cured ESI (37.0 *vs.* 25.0 days, p=0.029; 3 *vs.* 2 antibiotic classes). Non-cured events also were significantly associated with shorter periods of time between the last antibiotic therapy and the actual event (18.0 *vs.* 40.0 days, p=0.006).

ESI clinical presentation

Overlapping clinical presentations (serous-hematic/purulent exsudates) were observed among different ESI etiologies. An exception was observed for *S. aureus* infections, which more frequently associated to serous-hematic exsudates than *Pseudomonas aeruginosa* ESI, despite the fact that no recognisable differences were documented among these microbial agents regarding the presence of purulent drainage. No specific clinical presentations associated to the presence of sequential infections, extended treatment events, non-cured or recurrent ESI.

Outcome

Although no statistical significant difference was demonstrated regarding treatment duration between G+ *vs.* G- infections, specific ESI etiologies, such as *S. aureus* infections were consistently related to prolonged treatments when compared to

Pseudomonas aeruginosa events (49.0 *vs.* 32.0 days, p=0.046), to other G+ bacterial infections (49.0 *vs.* 29.0 days, p=0.001) and to non-*S. aureus* events (49.0 *vs.* 31.0 days, p=0.001). Longer medical treatments were also required in ESI with sequential infections (67.5 *vs.* 27.5 days, p<0.001) and in those considered medically non-cured (51.5 *vs.* 29.0, p<0.001). G- ESI medical treatments required more antibiotic agents than G+ infections (3 *vs.* 2, p=0.029). Similar results were found among *S. aureus vs.* other G+ infections (3 *vs.* 2, p=0.001), *S. aureus vs.* non-*S. aureus* events (3 *vs.* 2, p=0.019), ESI with *vs.* without sequential infections (3 *vs.* 1, p<0.001) and non-cured *vs.* cured events (3 *vs.* 2, p<0.001).

No recognisable differences on ESI outcomes (such as TI, peritonitis, ESI cure, external cuff removal, catheter substitution/removal or HD transfer) were observed between ESI caused by G+ *vs.* G- bacteria, *S. aureus vs. Pseudomonas aeruginosa* or *S. aureus vs.* other G+ bacteria. A difference was however reported between *S. aureus* and the broader group of *non-S. aureus* infections, the former more frequently associated to TI (66.7% *vs.* 37.0%, p=0.050) and subsequent peritonitis events (9.8% *vs.* 1.0% ESI, p=0.023). Moreover, although a low frequency of peritonitis was reported in this study (3.6%), it strongly associated with the presence of TI (13.8% with TI *vs.* 0.0% without TI, p=0.020) and to the need for surgical catheter substitution/removal (14.3% with surgical intervention *vs.* 2.5% without surgical intervention, p=0.029). Accordingly, non-cured ESI strongly correlated to TI (84.6% *vs.* 29.0%, p<0.001).

Lower rates of exit-site cure and higher rates of external cuff removal were observed in the group of ESI with sequential infections (73.0% *vs.* 89.7%, p=0.013 for exit-site cure; 10.8% *vs.* 2.3%, p=0.033 for external cuff removal) and in episodes treated for more than 30 days (83.3% *vs.* 96.2%, p=0.002 for exit-site cure; 6.3% *vs.* 0.0%, p=0.011 for external cuff removal). Finally, recurrent ESI apparently did not correlated to worse outcomes when compared to single events.

Fungal infections

Although rare, fungal infections were still characterized. In order to increase the number of cases, fungal episodes included those with fungal isolates in the initial diagnosis and in subsequent sequential infections, making a total of 9 events (4.0%). Fungal infections were associated with a higher frequency of immunossupressive therapy (33.3% *vs.* 8.1%, p=0.043) and to higher sedimentation rate values (82.0 *vs.* 58.3 mm/h, p=0.031). Patients with these infections were on PD for a longer period of time (2.5 *vs.* 1.0 year in non-fungal ESI, p=0.008) and showed decreased adequacy PD parameters (diuresis, total renal clearance and total creatinine clearance). Moreover, these episodes were correlated to prolonged antibiotic treatment (74.0 *vs.* 35.0 days, p=0.005) and to higher rates of peritonitis (33.3% *vs.* 2.8%, p=0.005).

Discussion

In our PD population, ESI were a relatively common event, occurring with an incidence of 0.91 ESI/patient-year. ESI were mostly caused by G+ agents, of which *S. aureus* was the most commonly isolated microorganism, followed by *Corynebacterium* spp. *Staphylococcus aureus* infections occurred preferentially early after peritoneal dialysis initiation, required prolonged treatment periods, were more frequently associated to tunnel infections and peritonitis and represented, in our population, the subgroup of infections with the most particular clinical profile.

Agents and Incidence Rates

In our population we have documented an ESI incidence of 0.91 episodes/patient-year. Previous studies have demonstrated that ESI rates can vary from 0.05 to 1.02 episodes/patient-year (10-12). Some authors suggested that this apparent discrepancy are more likely related to differences in the diagnostic criteria used rather than to the real impact of prevention measures, namely exit-site management, *S. aureus* infection prophylaxis or patient training (13). Indeed, ESI diagnosis is not always a simple and straightforward task. Several definitions of ESI have been proposed during the past decades, and the clinical presentations from uninfected to infected exit-sites are wide and diverse. Different skin adaptive responses to the peritoneal dialysis catheter can also contribute to this heterogeneity (14). Moreover, some authors establish the diagnosis of ESI on the basis of a positive microbiologic culture, which does not necessarily correlate to the presence of infection, but may represent skin colonization instead. On the other hand, negative cultures may also be associated to ESI. This heterogeneity was probably the main reason why the ISPD 2010 Guidelines/Recommendations recommended the diagnosis of ESI mainly based on clinical findings and not on microbiological results (9). Taken together, all these

limitations pose several problems in the direct comparison of ESI incidences among different PD Units.

In our study, ESI were mostly caused by G+ agents (47.6%) in comparison to G- bacteria (21.3%). This result is corroborated by similar reports in the literature, which consensually document higher frequencies of G+ infections (11, 12, 15). Indeed, many of these G+ microorganisms are normal colonizing agents of the skin flora in healthy individuals, but may become pathogenic in immunosuppressive states like end-stage renal disease (ESRD). Despite the improvements observed in PD technology and in hygiene measures, the manipulation of the catheter in PD patients is still associated with a high risk of skin and oral cavity microbiota migration and, consequently, G+ infections. In the last years, the introduction of prophylactic measures has enabled PD programs to reduce the incidence of G+ infections, but have also led to a proportional increase of G- events relatively to all PD infections (7, 8, 16-18). G- ESI are thought to occur due to faecal contamination and poor hand washing techniques during the peritoneal exchange (16). Although, less frequent than G+ infections, G- bacteria are known for their increased virulence and worse outcomes (7, 19, 20), and they deserve careful attention in the context of exit-site management.

Regarding specific etiologic agents, *S. aureus* was the primary cause of ESI in our study (18.2%). Although not always pathogenic, *S. aureus* may be responsible for severe infections, especially in immunocompromised individuals. Several reports have confirmed that *S. aureus* prophylaxis measures with mupirocin significantly reduce the incidence of ESI and peritonitis caused by this microorganism in PD patients (15, 21, 22). Accordingly, these procedures have been recommended by the ISPD. Despite these efforts, previous studies have demonstrated that *S. aureus* still constitutes one of the main causes of ESI in PD, with rates varying from 19.7 to 29% (9, 11, 15, 23).

In our population *Corynebacterium* spp infections were the second most frequent cause of ESI, accounting for 15.6% of all episodes. Previous studies focusing on

Corynebacterium ESI showed frequencies of approximately 9% (5), somewhat inferior to those observed in our patients. Non-diphtheria *Corynebacteria* species are major agents of the normal flora of the skin and mucous membranes, therefore commonly dismissed as contaminants. Due to the relatively high incidence of these infections and to the significant clinical implications for PD patients when they occur, our study supports the importance of a close interaction with the local microbiology lab, aiming to optimize the identification of these microorganisms in the context of ESI.

In the present study, *Pseudomonas aeruginosa* ESI were reported in 10.2% of the cases. After *S. aureus*, *Pseudomonas aeruginosa* is usually described as the most frequent cause of ESI, with rates varying from 8 to 14.4% (11, 12, 15, 24). Some authors have recomended a daily basis application of a gentamicin cream to the exit-site to prevent both *Pseudomonas aeruginosa* and *S. aureus* infections (25). Despite this efforts, infections by *Pseudomonas* are still difficult to prevent. These infections are usually serious, particularly difficult to treat and frequently lead to peritonitis and thus should be managed aggressively.

Association of specific characteristics of the population according to ESI etiologies and outcomes

Clinical and pharmacological parameters

No significant association was observed between DM (including degree of glicemic control) or other comorbidities (hypertension or cardiovascular disease) and G+ or G- infections. Similar results were documented when considering specific ESI etiologies or outcomes. Previous studies have demonstrated that DM is associated with reduced innate and adaptive immune responses, increasing the susceptibility to infections (26-28). Furthermore, especially if complicated by poor glicemic control, DM increases the susceptibility to infection among patients in PD (12). In fact, poor glycemic control was considered a consistent predictor of subsequent risk for TI and ESI, but not for peritoneal

infection (29). In our population we have documented a low mean value of HbA1c (5.7%), suggesting a good glicemic control of our diabetic population. Additionally, diabetics accounted for less than 30% of the population studied. These facts, taken together, may help to explain why the expected association between diabetes and ESI episodes was not documented.

We have not identified a relation between vitamin D supplementation and type of ESI episodes, namely G+ or G- ESI. However, we did demonstrate that *S. aureus* infections occurred less frequently in cases associated with vitamin D supplementation, comparing to the sample of non-*S. aureus* events. An increasing number of studies are pointing to a crucial role of vitamin D in immune responses. Indeed, nearly all tissues in the body have receptors for the active form of vitamin D and this compound has been shown to have a pivotal function in the modulation of monocyte/macrophage response to infection and in several cellular immune mechanisms as well. Additionally, an anti-inflammatory role of vitamin D has been documented in several bacterial infections (30, 31). Recent publications have demonstrated an association between the treatment with oral vitamin D and a decreased risk of peritonitis in patients undergoing PD (32, 33). However, the role of vitamin D in other PD related infections, namely in ESI, is still very poorly understood. Despite the fact that serum vitamin D levels were not evaluated in our population of patients, our results may point to an eventual contribution of vitamin D oral supplementation in the protective immune response against *S. aureus* ESI. Further studies focusing on this subject are obviously needed.

Analytical parameters

We found no association between CRP, a well recognized inflammatory parameter, and G+ or G- infections. This was also documented when considering specific types of bacterial infections or episodes with distinct clinical outcomes. Chronic inflammation and concomitant increased levels of CRP are normally present in ESRD patients including those on PD (34, 35). Several studies have previously evaluated the relation of CRP

levels with the presence of PD-related infections, demonstrating an association of higher CRP levels with poor peritonitis outcomes. (36). The association of CRP with the presence of ESI has not yet been explored. ESI are usually controlled events, limited to the superficial tissues, what could help to explain the absence of relation between CRP levels and ESI incidence and outcome. Thus, it seems reasonable to suggest that CRP should not be used as a clinical instrument to identify the presence or predict the etiology or clinical behaviour of an ESI episode.

No obvious association was also documented between the levels of serum albumin and G+ or G- episodes. Albumin values were also similar between ESI samples with distinct etiologies and clinical outcomes. Low levels of serum albumin have been associated with increased mortality in the context of PD (37). The presence of comorbidities, possible ongoing losses of protein into the dialysate fluid, co-existing chronic inflammation and the volume status all may contribute to hypoalbuminemia in PD patients. Previous studies have demonstrated that initial serum albumin was an independent risk factor for peritonitis in PD patients (38). No relevant information about the relation between hypoalbuminemia and ESI episodes is reported in the literature. In PD patients ESI may be, therefore, mainly related to local risk factors and technical issues and not reflect the systemic predisposition to infection. Further studies on this matter, namely directed to the immune response characterization of patients with recurrent ESI, would be necessary.

In this study, G+ ESI were predominantly associated with lower levels of serum HDL cholesterol when compared to infections caused by G- agents. Further analysis revealed that, within the G+ episodes, these low levels of HDL were predominantly associated with *S. aureus* infections. Similar results were observed when considering ESI with sequential infections, which commonly required prolonged treatments and less frequently evolved to cure. Numerous studies have demonstrated that infection and inflammation are accompanied by cytokine-induced alterations in lipid and lipoprotein metabolism, decreasing both LDL and HDL-cholesterol, by mechanisms not yet fully

understood. Conversely, anti-inflammatory effects of HDL have been demonstrated both in *in vitro* and *in vivo* studies (39). HDL binds microorganisms or compounds derived from microbial agents (e.g. lipopolysaccharide from G-, lipoteichoic acid from G+ bacteria), thus blocking the activation of cytokine production by competing successfully with cellular receptors for microbial components. (39). Our observations suggest that low HDL may predispose the host to the virulent effects of specific microorganisms, like *S. aureus* and increase the risk of infection by this agent. The validity of this association and the mechanisms underlying this relation need to be further clarified.

PD-parameters

When considering the broader groups of G+ and G- episodes, no significant differences were reported concerning the elapsed time from PD initiation to the ESI diagnosis. On the contrary, specific *S. aureus* events preferentially occurred before completing 1 year of PD therapy. We thus suggest that, despite the worse clinical outcomes, *S. aureus* ESI do not necessarily correlate with long-standing PD treatments or its related complications. Several co-existing factors may contribute to this finding. It is well established that patient education and training positively influence the risk of PD infections (40, 41). Inadequate hygiene habits associated with technical inexperience in the early stages of PD might predispose patients to specific ESI etiologies, such as those caused by *S. aureus*. Moreover, the concomitant incomplete healing of the exit-site in the first weeks of PD may additionally contribute to this type of infection. We, thus reinforce the need to ensure early management of the exit-site, such as intensive training in the basic procedures for exit-site care and implementation of mupirocin prophylaxis soon after PD-catheter insertion.

In this study, specific PD modalities were not associated with any of the considered ESI agents. Meta-analysis studies have demonstrated that patients on APD had lower rates of peritonitis, but similar rates of ESI and TI where observed when comparing PD modalities (42). This may be explained by the fact that ESI is predominantly related to

the local skin care technique and not dependent on the connection procedure and reinforces the need to address prophylactic measures for ESI and peritonitis differentially.

In our sample, G+ ESI episodes were more often associated with reduced adequacy values than G- infections. Infections remain the major cause of morbidity and mortality in uremic patients, specially in those undergoing dialysis. In CKD patients the infectious risk is enhanced by, among other factors, uremic toxic retention and malnutrition. It is therefore reasonable to assume that efficiently dialysed patients may be more capable of deviating the immune response from a suppressive state towards a stronger reaction against infection. G+ bacteria are commonly present in the skin flora of healthy subjects and are generally less virulent than G- microorganisms. As a consequence of these weaker virulence mechanisms, G+ infections may be more frequently associated with poorer dialysis efficiency, which presumably correspond in PD patients to the worse scenarios of immunossupression.

A significant statistical difference in the levels of diuresis between single ESI events and recurrent infections was documented in our study. In fact, ESI episodes occurring more than once correlated with lower diuresis. The volume of diuresis usually reflects the residual renal function (RRF), which is characteristically preserved in PD patients. The loss of RRF has been demonstrated to contribute to anaemia (43), inflammation (44), malnutrition (45) and to the increase of mortality rates (46). Though previous studies have demonstrated that RRF is an independent risk factor for PD peritonitis, studies reporting the association of RRF with the rates of ESI are still missing in the literature (47). Although we cannot truly evaluate the effect of RRF in the rates of ESI, our results suggest that RRF may play a protective role against the relapse of ESI in patients undergoing PD.

Previous infections/ antibiotic therapies

We have not observed a relation between the existence of preceding infections (including ESI) or antibiotic therapies and current episodes caused by of G+ and G- bacteria. However, we could document that current *S. aureus* infections strongly correlated with preceding infections caused by the same agent. Studies in the literature have documented recurrent *S. aureus* infections in nasal carriers and in intermittent nasal carriers (48). In the case of intermittent carriers, *S. aureus* nasal screening may be associated with a false negative result. It is well established that *S. aureus* nasal carriers exhibit higher incidences of ESI, TI and peritonitis events (49). It is thus possible that recurrent *S. aureus* infections may associate with misdiagnosed carriers or intermittent carriers in our population. Alternatively, one may also consider re-infection of the exit-site by silent *S. aureus* bacteria remaining in the catheter from a previous clinically healed ESI. However, some studies have documented recurrent *S. aureus* events despite the removal of the infected catheter (50). This observation, thus, supports the idea of an intrinsic predisposition of some individuals to *S. aureus* infections.

Moreover, although we could not associate the presence of previous ESI/antibiotic therapies with current episodes requiring prolonged treatments (more than 30 days), if present, those preceding infections most frequently had similar durations. As suggested above, these cases may reflect a state of intrinsic susceptibility to infection and/or an immunossupressive basal profile that may predispose individuals to a weaker response to therapy in the presence of recurrent infections.

Outcome

Regarding ESI medical treatment, in our study we have documented similar antibiotic therapy durations and outcomes between G+ and G- infections, although the latter frequently required more than one class of antibiotic agent. Descriptions in the literature have specifically emphasized outcome differences between G+ and G- peritonitis. In fact, peritonitis caused by G- bacteria has been associated with more hospital admissions,

catheter dysfunction episodes and PD discontinuation (7, 19, 20). In contrast to peritoneal infection outcomes, we have demonstrated that ESI caused by G- or G+ agents are equally likely to evolve to cure. Unlike peritonitis, which may lead to exuberant systemic responses that may contribute to a high morbidity and mortality, ESI are usually locally circumscribed events, confined to the superficial tissues. Accordingly, it is reasonable to speculate that despite the increased virulence mechanisms associated to G- bacteria, appropriate antibiotic therapies and exit-site care measures are capable of successfully restricting the infection to the boundary tissues, eventually leading to cure. Finally, we have demonstrated that *S. aureus* infections required extended antibiotic therapies and were more frequently associated to TI and peritonitis. *S. aureus* is responsible for severe infections in immunocompromised individuals, as those with ESRD. In the context of PD, it is considered one of the most serious and common exit-sit pathogens, since it is frequently associated to catheter-related infections, severe peritonitis and need for catheter removal (9, 51, 52). Dissemination to the peritoneal cavity frequently occurs through the catheter and is probably a more relevant route of infection than hand contamination. *S. aureus* nasal carriage constitutes a major risk factor for ESI, tunnel infection, peritonitis and catheter loss. Although the emergence of mupirocin-resistant *S. aureus* in PD patients has been documented (53), ISPD continues to recommend the use of mupirocin prophylaxis, provided that periodic surveillance is not neglected. The significant incidence of these infections in our population associated to a poorer clinical outcome and aggressive therapeutic regimens, all stress the need for reinforcing prevention measures against *S. aureus* infections, such as patient education, careful exit-site care management and *S. aureus* prophylaxis, without underestimating of course the possible emergence of antibiotic-resistant strains.

To the best of our knowledge this is the first report thoroughly describing factors associated with different ESI etiologies and distinct clinical outcomes. However, our study has some limitations, mainly related to its retrospective nature, and further prospective studies are needed to support our results.

In summary, although no significant differences were documented regarding the clinical outcome of G+ and G- ESI, we could identify some differences in these two types of infections. Lower HDL serum levels and reduced PD adequacy values were documented in patients with G+ events suggesting, as previously described in other clinical settings, a potential contributory role of HDL and dialysis efficacy to the regulation of the immune response of the patient undergoing PD. Moreover, we could find in our population that *S. aureus* infections were strongly correlated with worse outcomes and aggressive therapeutic approaches, supporting the idea that, despite all the improvements in PD technology and infection control measures, *S. aureus* ESI still represents a significant clinical burden for patients treated with PD.

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TABLE I: Characterization of the patient population

Demographic & Clinical profile	
Gender[a]	
Male	77 (65.8%)
Environment[a]	
City	39 (33.3%)
Rural	40 (34.2%)
Water Supply[a]	
Public Network	63 (53.8%)
Well	26 (22.2%)
Comorbid Diseases[a]	105 (89.7%)
Diabetes *mellitus*	34 (29.1%)
Type 2	23 (19.7%)
Duration (years)	19.9 ± 9.9
Hypertension	103 (88%)
Duration (years)	11.0 (0-45)
Cardiovascular Disease	39 (33.3%)
Duration (years)	7.0 (0-28)
Smoking[a]	22 (18.8%)
Chronic Kidney Disease (CKD) [a]	
Etiology	
Diabetes *mellitus*	16 (13.7%)
Hypertension	5 (4.3%)
Glomerulonephritis	21 (17.9%)
Polycystic Renal Disease	4 (3.4%)
Chronic Pyelonephritis	4 (3.4%)
Obstructive CKD	6 (5.1%)
Unknown	17 (14.5%)
Other	27 (23.1%)
Duration (years)	7.0 (0-32)
Previous Infections[b]	94 (41.8%)
ESI	65 (28.9%)
Peritonitis	15 (6.7%)
Respiratory infections	9 (4.0%)
Other	12 (5.3%)
Duration (days)	28.0 (4-199)
Days to event	35.0 (3-98)
Pharmacologic profile[b]	
Anti-platelet agents	71 (31.6%)
Warfarin	20 (8.9%)
Immunossupressors	17 (7.6%)
Vitamin D	123 (54.7%)
Previous antibiotic treatment	93 (41.3%)
Duration (days)	26.0 (5-119)
Days to event	35.0 (0-133)
Biochemical profile[b]	
Hemoglobin (g/dl)	11.4 ± 1.9
Leukocytes(n^ox10^9/L)	7.4 (3.47-52)
Sedimentation Speed (mm/h)	61.2 ± 28.2
Albumin (g/L)	37.5 (22.1-71.6)
Alkaline Phosphatase (U/L)	110 (44-483)

Total Cholesterol (mg/dl)	176.0 ± 38.7
HDL-Cholesterol (mg/dl)	45 (24-105)
LDL-Cholesterol (mg/dl)	95.8 ± 29.4
Triglycerides (mg/dl)	146 (41-598)
HbA1C (%)	5.6 (4.2-9.4)
Urea (mg/dl)	129.0 ± 37.3
Creatinin (mg/dl)	8.1 (2.0-17.8)
Calcium (mg/dl)	4.4 (2.1-10.0)
Phosphorus (mg/dl)	4.8 (1.9-11.0)
C-reactive protein (mg/L)	3.9 (2.0-187.3)
pH	7.321 (7.143-7.485)
Bicarbonate (mmol/L)	29.4 (18.1-36.3)
Brain Natriuretic Peptide (pg/ml)	93.4 (10.0-4574.8)
***PD-parameters*[b]**	
PD modality	
CAPD	160 (71.1%)
APD	54 (24.0%)
PD duration (years)	1.0 (0-6)
Adequacy parameters	
Total Renal Clearance (ml/min)	3.56 (0.00-20.68)
Diuresis (ml)	1000 (0-3950)
Total weekly Kt/V	2.00 (0.40-6.40)
Total Clearance (L/week)	88.83 (17.92-423.29)
D/P Cr (mg/dl)	0.78 (0.19-1.06)

Results are expressed in: frequency (percentage); median (range); mean ± standard deviation.

[a] Constant parameters among ESI. Values relative to the sample of patients (n=117)

[b] Variable parameters among ESI. Median or average values are displayed accordingly, relative to all ESI episodes (n=225).

TABLE II: Microorganisms isolated from ESI and sequential infections (n=225)

Bacterial ESI	144 (64.0%)
Gram positive	107 (47.6%)
Staphylococcus aureus	41 (18.2%)
Corynebacterium spp	35 (15.6%)
Staphylococcus coagulase negative	16 (7.1%)
Streptococcus spp	2 (0.9%)
Other	13 (5.8%)
Gram negative	48 (21.3%)
Pseudomonas aeruginosa	23 (10.2%)
Enterobacteriaceae	20 (8.9%)
Other	5 (2.2%)
Fungal ESI	6 (2.7%)
Candida parapsilosis	6 (2.7%)
ESI co-infection	11 (4.9%)
Gram positive	6 (2.7%)
Gram negative	3 (1.3%)
Gram positive & Gram negative	2 (0.9%)
Sequential infections	37 (16.4%)
Nº agents isolated	1 (1-3)
Bacterial sequential infections	45 (20.0%)
Gram positive	40 (17.8%)
Staphylococcus aureus	2 (0.9%)
Corynebacterium spp	10 (4.4%)
Staphylococcus coagulase negative	22 (9.8%)
Streptococcus spp	1 (0.4%)
Other	5 (2.2%)
Gram negative	5 (2.2%)
Pseudomonas aeruginosa	2 (0.9%)
Enterobacteriaceae	2 (0.9%)
Other	1 (0.4%)
Fungal Sequential infections	3 (1.3%)
Candida parapsilosis	3 (1.3%)
Total fungal isolations (ESI & Sequential infection)	9 (4.0%)

Table III: Comparison of patient characteristics between ESI caused by Gram positive and Gram negative bacteria

Patient variable	Gram + ESI	Gram - ESI	p
Previous infections			
Previous Infections	42 (42.4%)	16 (38.1%)	0.633[b]
Duration (days)	47.0 ± 39.7	28.6 ± 14.1	0.161[d]
Days to event	43.4 ± 26.0	38.2 ± 22.2	0.577 [d]
Previous ESI	27 (27.6%)	9 (22.0%)	0.492[b]
Duration (days)	43.0 (6-199)	30.5 (13-56)	0.236[a]
Days to event	43.4 ± 26.9	42.8 ± 21.6	0.949[d]
Pharmacologic profile			
Vitamin D	47 (47.5%)	27 (62.8%)	0.093[b]
Previous antibiotic treatment	40 (40.4%)	15 (37.5%)	0.751[b]
Duration (days)	38.7 ± 30.8	32.9 ± 20.7	0.525[d]
Days to event	52.4 ± 32.6	30.9 ± 25.8	**0.035**[d]
Biochemical profile			
HDL-Cholesterol (mg/dl)	45.0 (24-105)	49.0 (27-94)	**0.039**[a]
Triglycerides (mg/dl)	150.0 (41-378)	153.0 (51-567)	0.568[a]
PD-related variables			
PD duration (years)	1.0 (0-5)	1.0 (0-6)	0.841[a]
Total Renal Clearance (ml/min)	4.17 (0.00-15.40)	2.81 (0.00-12.06)	0.107[a]
Diuresis (ml)	1000 (0-3950)	750 (0-2500)	0.199[a]
Total weekly Kt/V	1.80 (0.40-4.10)	2.20 (0.90-4.00)	**0.022**[a]
Total Clearance (L/week)	93.0 (17.9-423.3)	86.6 (40.5-206.2)	0.692[a]
D/P Cr (mg/dl)	0.78 (0.45-1.06)	0.79 (0.45-0.98)	0.683[a]
ESI Outcome			
ESI Treatment			
Nº Total Antibiotics	2 (1-9)	3 (1-6)	**0.029**[a]
Duration (days)	37.0 (14-198)	34.0 (14-199)	0.975[a]
Tunnel infection	17 (54.8%)	4 (33.3%)	0.206[b]
Peritonitis	5 (5.1%)	0 (0.0%)	0.323[c]
Exit site cure	85 (85.9%)	33 (76.7%)	0.183[b]
External Cuff Removal	5 (5.1%)	3 (7.0%)	0.698[c]
Catheter substitution/removal	9 (9.1%)	7 (16.3%)	0.251[c]
Hemodialysis/Renal Transplant	4 (4.0%)	1 (2.3%)	1.000[c]

Results are expressed in: frequency (percentage); median (range); mean ± standard deviation.

[a] Mann-Whitney U, [b] Chi-Square, [c] Fisher's Exact Test,[d] T-test (unpaired groups).

Patient characteristic	*S.aureus*	*P. aeruginosa*	*p*	*S. aureus*	Other G+	*p*	*S. aureus*	Non-*S. aureus*	*p*
Previous infections									
Previous Infections	14 (34.1%)	8 (36.4%)	0.860 [b]	14 (34.1%)	30 (49.2%)	0.133[C]	14 (34.1%)	44 (42.7%)	0.344[b]
Duration (days)	61.3 ± 31.0	29.0 ± 15.4	**0.022** [d]	65.0 (11-128)	26.5 (5-199)	**0.009**[a]	65.0 (11-128)	28.5 (5-199)	**0.003**[a]
Days to event	40.4 ± 29.5	33.0 ± 18.7	0.566[d]	40.4 ± 29.5	45.0 ± 24.5	0.643[d]	40.4 ± 29.5	42.7 ± 23.6	0.792[d]
Previous ESI	10 (24.4%)	6 (28.6%)	0.722[b]	10 (24.4%)	18 (30.0%)	0.536[b]	10 (24.4%)	26 (25.7%)	0.867[b]
Duration (days)	61.3 ± 31.0	34 ± 15.6	0.088[d]	65.0 (11-128)	28.5 (6-199)	**0.021**[a]	65.0 (11-128)	29.5 (6-199)	**0.009**[a]
Days to event	40.4 ± 29.5	38.2 ± 17.9	0.883[d]	40.4 ± 29.5	45.3 ± 25.8	0.641[d]	40.4 ± 29.5	44.5 ± 24.2	0.659[d]
Pharmacologic profile									
Vitamin D	15 (36.6%)	14 (60.9%)	0.061[b]	15 (36.6%)	33 (54.1%)	0.082[b]	15 (36.6%)	60 (57.7%)	**0.022**[b]
Previous antibiotic treatment	13 (31.7%)	8 (36.4%)	0.709[b]	13 (31.7%)	28 (46.7%)	0.133[b]	13 (31.7%)	42 (41.6%)	0.274[b]
Duration (days)	55.2 ± 31.5	41.4 ± 22.4	0.300[d]	55.2 ± 31.5	29.0 ± 25.7	**0.014**[d]	58.5 (5-116)	25.5 (5-119)	**0.017**[a]
Days to event	47.9 ± 38.9	31.4 ± 25.0	0.303[d]	47.9 ± 38.9	53.5 ± 29.1	0.644[d]	47.9 ± 38.9	45.2 ± 29.8	0.800[d]
Biochemical profile									
HDL-Cholesterol (mg/dl)	41.7 ± 9.0	50.6 ± 10.8	**0.003**[d]	41.7 ± 9.0	49.2 ± 15.6	**0.007**[d]	41.7 ± 9.0	50.6 ± 15.0	**0.003**[d]
Triglycerides (mg/dl)	159.0 (67-378)	179.5 (51-567)	0.537[a]	178.3 ± 89.4	156.7 ± 67.2	0.219[d]	159.0 (67-378)	143.0 (41-567)	0.529[a]
PD-related variables									
PD duration (years)	0.0 (0-2)	1.0 (0-6)	0.217[a]	0.0 (0-2)	1.0 (0-5)	**0.002**[a]	0.0 (0-2)	1.0 (0-6)	**0.004**[a]
Total Renal Clearance (ml/min)	2.40 (0.00-12.88)	0.79 (0.00-8.56)	0.059[a]	2.40 (0.00-12.88)	4.99 (0.00-15.40)	**0.031**[a]	2.40 (0.00-12.88)	3.90 (0.00-15.40)	0.249[a]
Diuresis (ml)	950 (0-3950)	300 (0-1950)	0.084[a]	950 (0-3950)	1150 (0-3000)	0.190[a]	950 (0-3950)	1100 (0-3000)	0.547[a]
Total weekly Kt/V	1.68 ± 0.51	2.27 ± 0.67	**<0.001**[a]	1.70 (0.40-3.20)	2.00 (1.10-4.10)	**<0.001**[a]	1.70 (0.40-3.20)	2.10 (0.90-4.10)	**<0.001**[a]
Total Clearance (L/week)	85.98 ± 44.33	83.91 ± 33.10	0.845[d]	75.95 (17.92-239.05)	111.30 (38.29-423.29)	**0.003**[a]	75.95 (17.92-239.05)	92.96 (38.29-423.29)	**0.017**[a]
D/P Cr (mg/dl)	0.79 (0.63-1.06)	0.83 (0.45-0.98)	0.686[a]	0.79 (0.63-1.06)	0.78 (0.45-1.00)	0.245[a]	0.79 (0.63-1.06)	0.78 (0.45-1.00)	0.337[a]
ESI Outcome									
ESI Treatment									
Nº Total Antibiotics	3 (1-9)	3 (1-5)	0.562[a]	3 (1-9)	2 (1-7)	**0.001**[a]	3 (1-9)	2 (1-7)	**0.019**[a]
Duration (days)	49.0 (16-165)	32.0 (20-128)	**0.046**[a]	49.0 (16-165)	29.0 (14-198)	**0.001**[a]	49.0 (16-165)	31.0 (14-199)	**0.001**[a]
Tunnel infection	12 (66.7%)	3 (33.3%)	0.127[b]	12 (66.7%)	6 (42.9%)	0.178[b]	12 (66.7%)	10 (37.0%)	**0.050**[b]
Peritonitis	4 (9.8%)	0 (0.0%)	0.288[c]	4 (9.8%)	1 (1.6%)	0.155[c]	4 (9.8%)	1 (1.0%)	**0.023**[c]
Exit site cure	32 (78.0%)	18 (78.3%)	0.984[b]	32 (78.0%)	55 (90.2%)	0.090[b]	32 (78.0%)	89 (85.6%)	0.272[b]
External Cuff Removal	3 (7.3%)	0 (0.0%)	0.547[c]	3 (7.3%)	3 (4.9%)	0.682[c]	3 (7.3%)	5 (4.8%)	0.688[C]
Catheter substitution/removal	6 (14.6%)	5 (21.7%)	0.505[c]	6 (14.6%)	4 (6.6%)	0.195[c]	6 (14.6%)	10 (9.6%)	0.389[C]
Hemodialysis/Renal Transplant	2 (4.9%)	1 (4.3%)	1.000[c]	2 (4.9%)	2 (3.3%)	1.000[c]	2 (4.9%)	4 (3.8%)	1.000[b]

Results are expressed in: frequency (percentage); median (range); mean ± standard deviation. [a] Mann-Whitney U, [b] Chi-Square, [c] Fisher's Exact Test, [d] T-test (unpaired groups).

Table IV: Comparison of patient characteristics between ESI caused by *S. aureus* and other agents

Table V: Comparison of patient characteristics between ESI with distinct outcomes

Patient characteristic	≤30 days	>30 days	p	Cured	Non-Cured	p
Previous infections						
Previous Infections	42 (40.8%)	39 (41.1%)	0.969[b]	80 (41.7%)	14 (50.0%)	0.405[b]
Duration (days)	22.0 (4-70)	41.0 (8-199)	**0.003[a]**	27.5 (4-199)	37 (14-77)	0.185[a]
Days to event	37.0 (10-94)	36.0 (5-93)	0.740[a]	36.0 (5-98)	19.5 (3-58)	**0.027[a]**
Previous ESI	24 (23.8%)	29 (30.9%)	0.266[b]	50 (26.5%)	12 (42.9%)	0.073
Duration (days)	23.0 (6-70)	42.0 (11-199)	**0.001[a]**	37.0 (14-77)	28.5 (6-199)	0.313[a]
Days to event	33.0 (10-94)	36.0 (5-93)	0.820[a]	36.0 (5-98)	19.5 (3-58)	**0.026[a]**
Pharmacologic profile						
Vitamin D	55 (51.9%)	55 (57.3%)	0.441[b]	109 (55.6%)	14 (48.3%)	0.459[b]
Previous antibiotic	44 (43.6%)	37 (38.9%)	0.512[b]	80 (41.9%)	13 (50.0%)	0.433[b]
Duration (days)	21.0 (5-72)	37.0 (5-119)	**0.005[a]**	25.0 (5-119)	37.0 (15-77)	**0.029[a]**
Days to event	35.0 (0-113)	36.0 (0-133)	0.862[a]	40.0 (0-133)	18.0 (0-58)	**0.006[a]**
Biochemical profile						
HDL-Cholesterol (mg/dl)	46.0 (27-105)	44.0 (24-105)	0.320[a]	45.0 (24-105)	49.0 (29-69)	0.547[a]
Triglycerides (mg/dl)	133.0 (41-378)	158.0 (51-598)	**0.047[a]**	138 (41-567)	195.0 (51-598)	0.076[a]
PD-related variables						
PD duration (years)	1.0 (0-6)	1.0 (0-6)	0.217[a]	1.0 (0-6)	1.0 (0-4)	0.581[a]
Total Renal Clearance (ml/min)	4.11 (0.00-16.99)	3.37 (0.00-20.68)	0.121[a]	3.56 (0.00-20.68)	3.50 (0.00-15.97)	0.999[a]
Diuresis (ml)	1125 (0-3950)	900 (0-2670)	0.187 [a]	950 (0-3950)	1150 (0-3000)	0.172[a]
Total weekly Kt/V	2.00 (0.60-4.10)	1.80 (0.40-6.40)	0.081[a]	2.00 (0.40-6.40)	1.85 (0.90-3.60)	0.365[a]
Total Clearance (L/week)	92.16 (19.46-423.29)	78.47 (17.92-284.34)	0.319[a]	87.78 (17.92-423.29)	89.99 (34.02-276.64)	0.800[a]
D/P Cr (mg/dl)	0.78 (0.45-1.06)	0.78 (0.19-1.06)	0.991[a]	0.78 (0.19-1.06)	0.83 (0.70-1.02)	**0.005[a]**
ESI Outcome						
ESI Treatment						
Nº Total Antibiotics	1 (1-4)	3 (1-9)	**<0.001[a]**	2 (1-9)	3 (1-5)	**<0.001[a]**
Duration (days)	-	-	-	29.0 (6-199)	51.5 (19-165)	**<0.001[a]**
Tunnel infection	9 (25.7%)	17 (47.2%)	0.060[b]	18 (29.0%)	11 (84.6%)	**<0.001[b]**
Peritonitis	3 (2.8%)	5 (5.2%)	0.481[b]	5 (2.6%)	3 (10.3%)	0.069[C]
Exit site cure	102 (96.2%)	80 (83.3%)	**0.002[b]**	-	-	-
External Cuff Removal	0 (0.0%)	6 (6.3%)	**0.011[c]**	-	-	-
Catheter substitution/removal	4 (3.8%)	10 (10.4%)	0.063[b]	-	-	-
Hemodialysis/Renal Transplant	2 (1.9%)	3 (3.1%)	0.670[c]	-	-	-

Results are expressed in: frequency (percentage); median (range); mean ± standard deviation.

[a] Mann-Whitney U, [b] Chi-Square, [c] Fisher's Exact Test, [d] T-test (unpaired groups).

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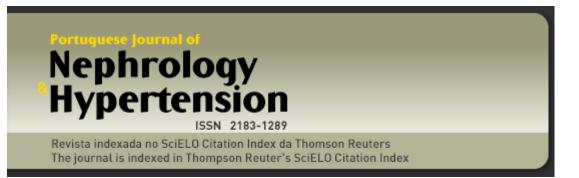
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