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# Septic shock in chronic dialysis patients: clinical characteristics, antimicrobial therapy and mortality

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**Take-home message:** Chronic dialysis patients admitted to the ICU with septic shock undergo time-varying survival, with early improved survival followed by similar or worse survival compared to non-dialysis patients. The former also differ from non-dialysis patients in terms of causative organisms, site of infection and delayed empiric antimicrobials. Improvements in timely antimicrobial therapy could optimize outcomes.

**Electronic supplementary material**
The online version of this article (doi:10.1007/s00134-015-4147-9) contains supplementary material, which is available to authorized users.

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**Abstract** *Objectives:* To describe the clinical characteristics and in-hospital mortality of chronic dialysis-dependent end-stage kidney disease patients with septic shock in comparison to septic shock patients not receiving chronic dialysis. *Methods:* Using an international, multicenter database, we conducted a retrospective analysis of data collected from 10,414 patients admitted to the intensive care unit (ICU) with septic shock from 1989 to 2013, of which 800 (7.7 %) were chronic dialysis patients. Data on demographic characteristics, sites of infection, microbial pathogens, antimicrobial usage patterns, and in-hospital mortality were aggregated and compared for chronic dialysis and non-dialysis patients. Multivariate time-varying Cox models with and without propensity score matching were constructed to determine the association between dialysis and in-hospital death. *Results:* Septic shock secondary to central venous catheter infection, peritonitis, ischemic bowel, and cellulitis was more frequent in chronic dialysis patients. The isolation of resistant organisms (10.7 vs. 7.1 %; $p = 0.005$) and delays in receiving antimicrobials (6.0 vs. 5.0 h) were more common in chronic dialysis patients than in non-dialysis patients. Delayed appropriate antimicrobial therapy was associated with an increased risk of death in chronic dialysis patients

($p < 0.0001$). In-hospital death occurred in 54.8 and 49.0 % of chronic dialysis and non-dialysis patients, respectively. After propensity score matching, there was no difference in overall survival between chronic dialysis and non-dialysis patients, but survival in chronic dialysis patients decreased over time compared to non-dialysis patients. *Conclusions:* The demographic and clinical characteristics of chronic dialysis patients with septic shock differ from those of similar non-dialysis patients. However, there was no significant difference in mortality between the chronic dialysis and non-dialysis patients with septic shock enrolled in this analysis.

**Keywords** Dialysis · Kidney failure · Septic shock · Antimicrobials · In-hospital mortality · Epidemiology · Dialysis modality

## Introduction

Infection is leading cause of hospitalization, and death in chronic dialysis-dependent end-stage renal disease (ESRD) patients [1]. Multiple factors account for high infection rates and septic shock in this population, including skin disruption by central venous and peritoneal catheter use, predisposing co-morbidities, and immunosuppression related to uremia [2–6]. Accordingly, the risk of death from sepsis is up to 300 fold higher for chronic dialysis patients than the general population [7, 8].

While increased catheter-related infections (both peritoneal and central venous) are well-documented [9–12], fewer studies have reported on the broad causes of infection-related hospitalization in patients with chronic dialysis [13]. Even less is known about the characteristics of chronic dialysis patients admitted to the intensive care unit (ICU) with septic shock. A systematic review of 16 studies comprising 6591 ESKD patients admitted to the ICU reported sepsis as the primary diagnosis in up to 20.5 % of this patient population, a figure similar to that reported for the non-dialysis population [5, 14]. However, most studies of septic shock in chronic dialysis patients have been limited by little information on infection site, microbiology, antimicrobial therapy, and relatively small numbers of patients [15–30]. As such, it is unclear if the clinical characteristics and modifiable therapy of chronic dialysis patients admitted to ICU with septic shock differ significantly from those of the septic shock population without chronic dialysis.

We sought to examine a large cohort of chronic dialysis patients admitted to the ICU with septic shock and compare these patients to similar septic shock patients without chronic dialysis. Characteristics to be assessed included demographic factors, comorbidities, severity of illness, sites of infection, causative organisms, dialysis modality, treatment-related factors, such as timing of appropriate antimicrobial therapy, and in-hospital mortality.

## Methods

### Study population

We analyzed data from the Cooperative Antimicrobial Therapy of Septic Shock Database, which collects information on adult patients with septic shock from 32 medical centers in Canada, the USA, and the Middle East, from January 1989 to July 2012. We excluded cases obtained from four hospital sites where only fungal pathogens were collected. Septic shock was defined by the 1992 American College of Chest Physicians/Society of Critical Care Medicine consensus conference guidelines [31]. This study was approved by the Health Research Ethics Board at the University of Manitoba and all participating institutions. Data were collected by trained research personnel and included patient demographics, co-morbidities, physiological characteristics, ICU treatments, and ICU and in-hospital outcomes.

### Procedures and data definitions

Previous publications have described in detail the study methods and definitions used in this study [32–34]. The primary pathogen and site of infection were categorized according to modified definitions by the Centers for Disease Control and Prevention of the USA [35]. In order to qualify as potential pathogens causing shock, isolates from both local site and/or blood cultures were required to have been obtained within 48 h of onset of shock. Inappropriate antimicrobial therapy was defined as the provision of empiric drug therapy that did not demonstrate activity for the isolated pathogen(s), as previously described [32, 33]. Empiric antimicrobial therapy was considered to include all new antimicrobials administered within a 6-h window of the first new antimicrobial given to the patient after documentation of septic shock. For culture-negative septic shock, appropriate therapy was deemed to be initiated when antimicrobials consistent with broadly accepted guidelines for empiric management

of the typical pathogens for the clinical syndrome (in the context of host immune/health status, environmental factors and local flora) were given. For the purposes of this study, the appropriate therapy of culture-negative infections leading to septic shock was defined by the recommendations enumerated in Table 1 "Clinical approach to initial choice of antimicrobial therapy" in the most recently available "Sanford Guide to Antimicrobial Therapy" at the time of the occurrence of the case.

The delay in initiation of the appropriate antimicrobial therapy (i.e., therapy with the appropriate in vitro activity against the isolated pathogenic organisms or, if a pathogenic organism was not isolated, appropriate for treatment of the underlying clinical syndrome) after onset of recurrent or persistent hypotension was determined for all cases. The identification of recurrent/persistent hypotension as described further in the text included ambulance, paramedic, and/or nursing home records. Dialysis modality was defined at the time of hospitalization as peritoneal dialysis (PD) or hemodialysis (HD). For HD, information on vascular access was not available. 'Era' was defined as the period prior to or after 1 January 2005, respectively. Questionable cases or data elements were reviewed by the local and study principal investigators for adjudication. The laboratory and clinical variables collected were the most aberrant values within 24 h of diagnosis of septic shock and included values for the Acute Physiology and Chronic Health Evaluation (APACHE) II score of severity of illness [36].

### Exposure and outcome

Chronic dialysis was defined as the regular need for dialysis (either HD or PD) preceding the hospital admission. All others were not considered to be chronic dialysis patients (i.e. "non-dialysis"). This included any patients who developed acute kidney injury during septic shock who required acute in-patient dialysis. The primary outcome of interest was all-cause, in-hospital mortality.

### Statistical analysis

Continuous variables of interest were summarized as the mean ± standard deviation or median with inter-quartile range (IQR), as appropriate. Differences in baseline characteristics were determined by Student's *t* test for continuous variables and the chi-square test for dichotomous variables. We examined in-hospital mortality for chronic dialysis and non-dialysis patients using the Kaplan–Meier method and multivariable time-varying Cox models. Multivariable time-varying Cox proportional hazards models were created with the inclusion of covariate(s) based on clinical significance; the covariates included were age, sex, comorbidities [cancer, immunocompromised, congestive heart failure (CHF), coronary artery disease, elective or emergent surgery, chronic obstructive pulmonary disease (COPD), diabetes] and APACHE II score. Adjusted hazard ratios (HRs) were calculated for the survival time in quartiles (0–6 days, 6–14, 14–33, and >33 days) to illustrate time variation. In a sensitivity analysis, the models were repeated excluding all patients with acute kidney injury (AKI) requiring dialysis. Dialysis by age, sex, era, and diabetes interaction terms were created to examine for subgroup differences. In-hospital mortality in relation to provision of appropriate empiric antimicrobial therapy or delays in antimicrobial administration in chronic dialysis patients was assessed using separate multiple logistic regression models adjusted for the variables listed above. As there were significant differences in the baseline characteristics in chronic dialysis and non-dialysis patients, a propensity score-matched (PSM) cohort was created and the models repeated. The PSM cohort was created using the FUZZY extension bundle of the SPSS statistical package (ver. 1.4.7; IBM Corp., Armonk, NY) with Python plug-in and performed with 1:1 nearest neighbor matching at a maximum caliper of 0.03. The logistic regression created for PSM contained the following covariates: age, sex, comorbidities (cancer, immunocompromised, CHF, coronary artery disease, elective or emergent surgery, COPD, diabetes) and APACHE II score. The c-statistic for the regression model was 0.73. Standardized mean differences were calculated to contrast the two groups, with *P* values of >0.1 considered to be significantly different. *P* values of <0.05 were considered to be statistically significant for all tests. All analyses were conducted using PASW v. 23 (IBM Corp. http://www.ibm.com/SPSS_Statistics).

## Results

### Patient characteristics

We identified 11,167 septic shock patients between January 1989 and December 2013. Of these, 753 (6.7 %) cases were excluded as only fungal pathogen information was collected at the contributing site. Therefore, for the analytic study, the final cohort consisted of 10,414 patients, of whom 800 (7.7 %) were on chronic dialysis and 9614 (92.3 %) were not.

Chronic dialysis patients were more likely to be female and younger and to have a higher APACHE II score than non-dialysis patients (Table 1). They also had diabetes and cardiac disease more frequently but were less likely to have cancer and COPD. Chronic dialysis patients had a higher white blood cell count and marginally lower core temperature, respiratory rate, and heart rate than non-dialysis patients. There were also significant differences between the two patient groups in a number of laboratory indices, including Troponin T (Table 1). Pathogens were isolated from blood or at the primary anatomic infection

**Table 1** Baseline characteristics of the patient population of chronic dialysis and non-dialysis patients with septic shock

| Patient characteristics | Total cohort | | | Propensity score matched | | |
|---|---|---|---|---|---|---|
| | Chronic dialysis ($n$ = 800) | Non-dialysis ($n$ = 9,614) | $P$ value | Chronic dialysis ($n$ = 800) | Non-dialysis ($n$ = 800) | Standardized difference (%)[a] |
| Sex (% female) | 49.4 ($n$ = 395) | 43.6 ($n$ = 4196) | 0.006 | 49.3 ($n$ = 395) | 49.4 ($n$ = 386) | 0 |
| Age (years) | 61.1 ± 15.8 | 62.9 ± 17.2 | 0.003 | 61.1 ± 13.4 | 61.3 ± 15.8 | 1.37 |
| Body mass index (kg/m$^2$) | 27.2 ± 7.1 | 28.3 ± 8.2 | 0.010 | 27.2 ± 7.0 | 29.0 ± 8.5 | 2.57 |
| APACHE II score | 27.9 ± 7.1 | 25.0 ± 8.1 | <0.0001 | 27.8 ± 7.0 | 27.4 ± 8.5 | 5.14 |
| Co-morbidities, % ($n$) | | | | | | |
| Cancer | 8.0 (64) | 18.1 (1744) | <0.0001 | 8.0 (64) | 9.1 (73) | 0.94 |
| Immunocompromised | 15.1 (121) | 13.9 (1334) | 0.340 | 15.1 (121) | 15.0 (120) | 0.03 |
| Diabetes mellitus | 48.0 (384) | 25.9 (2490) | <0.0001 | 48.0 (384) | 46.6 (373) | 0.04 |
| Congestive heart failure | 16.9 (135) | 11.9 (1142) | <0.0001 | 16.9 (135) | 15.3 (122) | 0.36 |
| Coronary artery disease | 21.1 (169) | 13.0 (1251) | <0.0001 | 21.1 (169) | 19.4 (155) | 0.24 |
| Chronic obstructive pulmonary disease | 11.0 (88) | 15.4 (1478) | 0.001 | 11.0 (88) | 12.0 (96) | 0.46 |
| Surgical admission % ($n$) | | | | | | |
| Elective | 13.9 (111) | 15.0 (1445) | 0.408 | 13.9 (111) | 11.9 (95) | 0.72 |
| Emergent | 5.0 (40) | 6.6 (633) | 0.089 | 5.0 (40) | 6.3 (50) | 2.77 |
| Laboratory values on day 1 | | | | | | |
| Bicarbonate (mEq/L)[b] | 20.2 ± 4.8 | 20.3 ± 6.4 | 0.774 | 20.2 ± 5.5 | 18.5 ± 6.6 | 27.98 |
| Creatine kinase (U/L) | 118.0 (50–333) | 143 (53–463) | 0.0069 | 118.0 (49.8–333.5) | 164 (53–617) | 39.06 |
| Albumin (g/L) | 22.9 ± 7.2 | 21.9 ± 6.9 | 0.912 | 21.9 ± 7.2 | 22.0 ± 6.9 | 1.42 |
| Lactate (mmol/L)[b] | 4.7 ± 4.9 | 4.6 ± 4.2 | 0.666 | 4.7 ± 4.9 | 3.8 ± 4.5 | 19.12 |
| White blood cells (×10$^9$/L) | 18.2 ± 13.3 | 16.8 ± 15.2 | 0.018 | 18.2 ± 13.3 | 17.8 ± 17.4 | 3.21 |
| Troponin T (μg/L) | 0.20 (0.08–0.44) | 0.10 (0–0.22) | <0.0001 | 0.19 (0.08–0.53) | 0.08(0.01–0.30) | 70.40 |
| Platelets (×10$^9$/L) | 199.4 ± 118.0 | 201.2 ± 139.1 | 0.730 | 199.4 ± 118.0 | 206.5 ± 142.8 | 5.42 |
| International normalized rate | 2.0 ± 1.7 | 1.8 ± 1.3 | 0.001 | 2.0 ± 1.7 | 1.9 ± 1.5 | 6.24 |
| Bilirubin (μmol/L) | 11.0 (7–22) | 15.0 (9–32) | <0.0001 | | | |
| Cortisol (nmol/L) | 886.7 ± 519.3 | 1014.2 ± 843.4 | 0.031 | 886.7 ± 519.3 | 1013.0 ± 523.5 | 24.18 |
| Vital signs on day 1 | | | | | | |
| Temperature (°C) | 37.4 ± 1.7 | 37.6 ± 1.7 | 0.001 | 37.4 ± 1.7 | 37.4 ± 1.8 | 0 |
| Respiratory rate (/min) | 24.6 ± 8.9 | 26.8 ± 9.7 | <0.0001 | 24.6 ± 9.0 | 26.8 ± 10.2 | 22.87 |
| Heart rate (/min) | 106.7 ± 28.9 | 116.6 ± 29.3 | <0.0001 | 106.7 ± 28.9 | 115.5 ± 30.9 | 29.41 |
| Microorganism identified | 71.1 (569) | 67.5 (6494) | 0.041 | 71.1 (569) | 69.1 (553) | 0.02 |
| Positive blood culture | 33.3 (266) | 30.9 (1971) | 0.176 | 33.3 (266) | 32.8 (262) | 0.03 |
| Nosocomial infection | 42.5 (340) | 35.9 (3450) | <0.0001 | 42.5 (340) | 35.0 (280) | 0.29 |

Data are expressed as percentage, the mean ± standard deviation (SD), or median with the interquartile range (IQR) in parenthesis, as appropriate

APACHE, Acute Physiology and Chronic Health Evaluation score

[a] A standardized difference ≥10 % is considered to be significant

[b] Bicarbonate and lactate values were the most aberrant values of multiple assays performed first 24 h of the diagnosis of septic shock; all other laboratory test values are the initial values obtained at day 1 of septic shock diagnosis

site (i.e., culture positive) significantly more often in chronic dialysis (71.1 %) than in non-dialysis (67.5 %) patients ($P = 0.041$) (Table 1). A similar trend with respect to positive blood cultures (33.3 vs. 30.9 %; $P = 0.181$) did not reach significance. The occurrence of nosocomial infection was 6.6 % higher in the chronic dialysis group. After PSM, there was considerable improvement in the covariate imbalance, with no significant imbalance among the variables used to compose the score.

## Primary site of infection and microbiology among chronic dialysis and non-dialysis patients

The primary sites of infection differed between the two patient groups (see Fig. 1), with chronic dialysis patients experiencing more central venous catheter-associated infections (12.3 vs. 2.0 %; $P < 0.0001$), peritonitis (8.1 vs. 1.9 %; $P < 0.0001$), ischemic bowel (7.3 vs. 5.0 %; $P = 0.008$), and mediastinitis (3.1 vs. 1.0 %; $P = 0.002$). Non-dialysis patients experienced more respiratory infections (39.7 vs. 30.8 %; $P < 0.0001$), bowel perforations (8.1 vs. 1.9 %; $P < 0.0001$), urinary tract infections (11.7 vs. 4.9 %; $P < 0.0001$), biliary sepsis (4.0 vs. 2.5 %; $P = 0.021$), and central nervous system infections (0.9 vs. 0.1 %; $P = 0.020$).

Differences in the distribution of pathogens are presented in Fig. 2. *Staphylococcus aureus* and *Escherichia coli* were the two most common organisms in both groups, with *S. aureus* more common in the chronic dialysis group (26.5 vs. 16.5 %; $P < 0.0001$) but *E. coli* more common in the non-dialysis group (22.3 vs. 16.5 %; $P = 0.014$). Other organisms occurring more frequently in

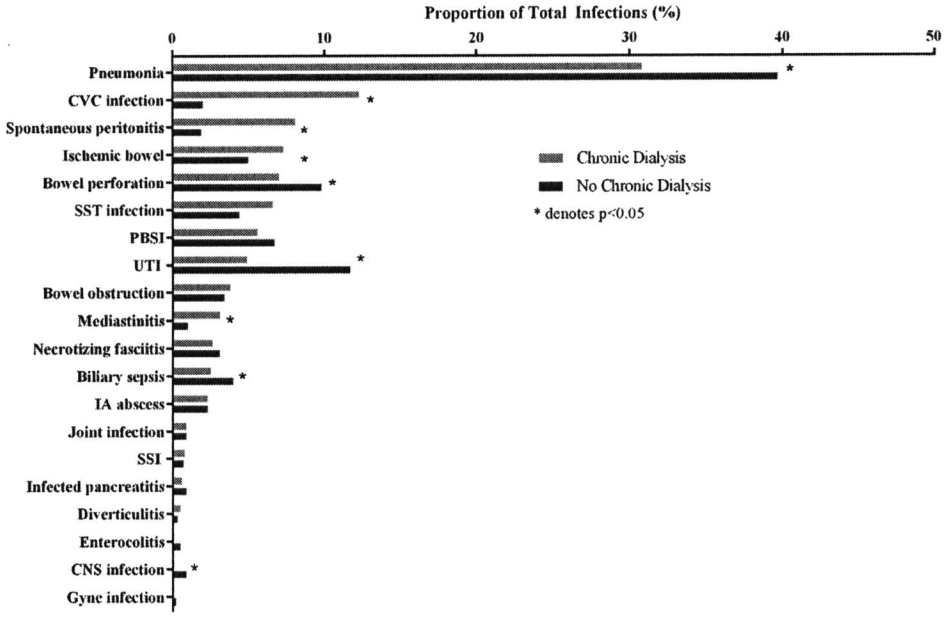


**Fig. 1** Primary source of infection in chronic dialysis and non-dialysis patients with septic shock. *CVC* Central venous catheter, *SST* skin and soft tissue, *PBSI* primary blood stream infection, *UTI* urinary tract infection, *IA* intra-abdominal, *SSI* surgical site infection, *CNS* central nervous system, *Gyne* gynecologic

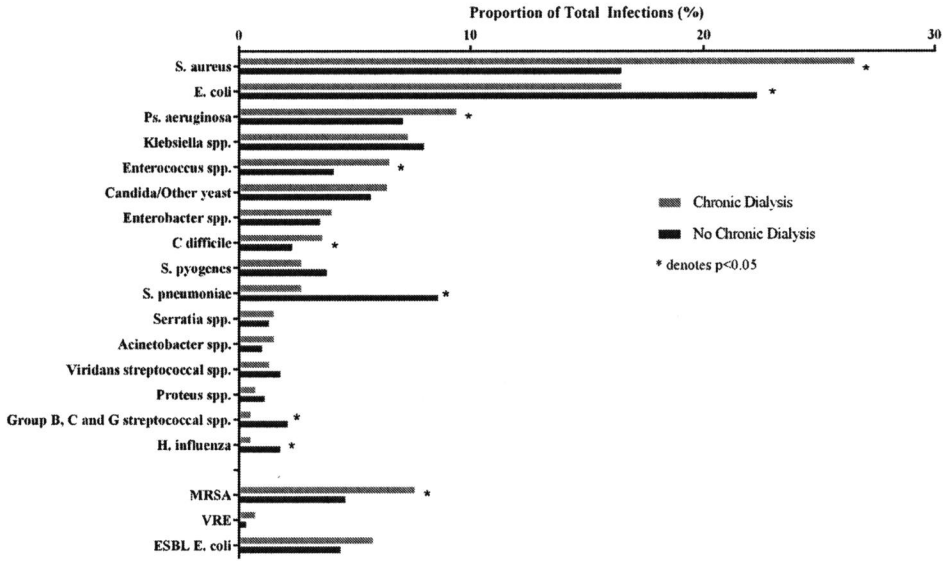


**Fig. 2** Primary causative pathogens in chronic dialysis and non-dialysis patients with septic shock. *MRSA* Methicillin-resistant *Staphylococcus* (*S.*) *aureus*, *VRE* vancomycin-resistant enterococci, *ESBL E. coli* extended spectrum beta-lactamase *Escherichia coli*, *C. Clostridium*, *Ps. Pseudomonas*, *S. pyogenes*, *S. pneumoniae* *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *H. Haemophilus*

chronic dialysis patients included *Pseudomonas aeruginosa* (9.4 vs. 7.1 %; $P = 0.022$), *Enterococcus* species (6.5 vs. 4.1 %; $P = 0.004$), *Clostridium difficile* (3.6 vs. 2.3 %; $P = 0.038$), and methicillin-resistant *S. aureus* (MRSA) (7.6 vs. 4.6 %; $P = 0.004$). *Streptococcus pneumonia* (8.6 vs. 2.7 %; $P < 0.0001$), group B, C and G streptococcal species (2.1 vs. 0.5 %; $P = 0.040$), and *Haemophilus influenza* (1.8 vs. 0.5 %; $P = 0.042$) were more frequent in non-dialysis patients. In aggregate, highly resistant organisms, including MRSA, vancomycin-resistant enterococci, and extended-spectrum β-lactamase *E. coli*, were more common in dialysis patients than in non-dialysis patients (10.4 vs. 7.1 %; $P = 0.005$).

## Antimicrobial treatment of septic shock

In the total cohort, chronic dialysis patients were less likely to receive appropriate and timely antimicrobial administration relative to non-dialysis patients [see Electronic Supplementary Material (ESM) Table 1]. Inappropriate initial empiric antimicrobials were given in 20.0 % of cases of chronic dialysis patients compared to 15.8 % ($P = 0.002$) of non-dialysis patients. No appropriate antimicrobial therapy before death was received by 5.6 % of chronic dialysis patients compared to 4.3 % of non-dialysis patients ($P = 0.068$). There was no difference between the two groups in the frequency of receipt

of appropriate antimicrobials before versus after the documented occurrence of hypotension ($P = 0.110$). The median time to receipt of appropriate antimicrobials was longer in chronic dialysis patients [6.0 (IQR 2.4–13.4) vs. 4.6 (IQR 1.8–11.2) h; $P < 0.0001$). After PSM, there was no significant difference in the administration of inappropriate antimicrobials [20.0 (chronic dialysis) vs. 18.5 % (no dialysis); standardized difference = 0.002]; however, the time to appropriate antimicrobial administration remained significant [6.0 (dialysis) vs. 5.0 (no dialysis) h; standardized difference 0.4).

The details of antimicrobial inappropriateness cannot be fully elucidated in this limited analysis. However, among the culture-positive chronic dialysis patients who received inappropriate therapy (22.8 %; 130/569), 24.6 % (32/130) had *Candida* or other fungi isolated as a pathogen (absent empiric antifungal therapy), and another 55.4 % (72/130) were patients with highly resistant isolates (as previously defined). The remainder of this patient group were patients who received overly narrow therapy (for example, a second- or non-pseudomonal third-generation cephalosporin for *Pseudomonas*; vancomycin only for a Gram-negative microorganism; a fluoroquinolone without anti-staphylococcal therapy for methicillin-sensitive *S. aureus*).

## Survival of chronic dialysis patients with septic shock

Among the total cohort of patients with septic shock, 5149 (49.4 %) died. Overall mortality improved steadily over time (mortality prior to 2000 = 60 %, steadily decreasing to 36 % in 2012). The mortality rate among chronic dialysis patients was 54.8 % (438/800), with a median survival time of 29 (IQR 24.9–33.1) days; among non-dialysis patients mortality was 49.0 % (4711/9614), with a median survival time of 35.0 (IQR 32.6–37.4) days. In the PSM cohort, there was no significant difference in mortality among the two groups as mortality was 46.2 % (861/1600) overall, 45.3 % for chronic dialysis patients, and 47.1 % for non-dialysis patients. In the PSM cohort, the median survival time was 29 (IQR 24.9–33.1) days for chronic dialysis patients and 27 (22.7–31.3) days for non-dialysis patients (log rank test $P = 0.377$; Fig. 3). Death due to septic shock or multisystem organ failure (MSOF) was similar between the two groups [septic shock: 59.1 (chronic dialysis) vs. 62.6 % (non-dialysis), $P = 0.149$; MSOF: 32.4 (chronic dialysis) vs. 30.4 % (non-dialysis); $P = 0.386$).

In the adjusted models, the mortality rate of chronic dialysis patients varied with time compared to that of non-dialysis patients [admission day 0–6: HR 0.83, 95 % confidence interval (CI) 0.71–0.98; day 7–14: HR 1.08, 95 % CI 0.88–1.32, day 14–33: HR 1.35, 95 % CI 1.08–1.67, day >33: HR 1.17, 0.91–1.49; see Table 2]. Interaction terms for age ($P = 0.102$), sex ($P = 0.79$), era ($P = 0.390$), and diabetes ($P = 0.004$) were examined, revealing an increase in the in-hospital (>33 days) mortality for chronic dialysis patients with diabetes (HR 1.40, 95 % CI 1.01–1.93) (ESM Table 2). These findings were similar and consistent in the PSM models and when patients with AKI requiring dialysis were excluded. We adjusted for treatment center in the time-varying and PSM models, and although statistically significant ($P < 0.0001$), adjustment did not alter the HR for survival of dialysis patients; this variable was therefore not included in the final model (results not shown).

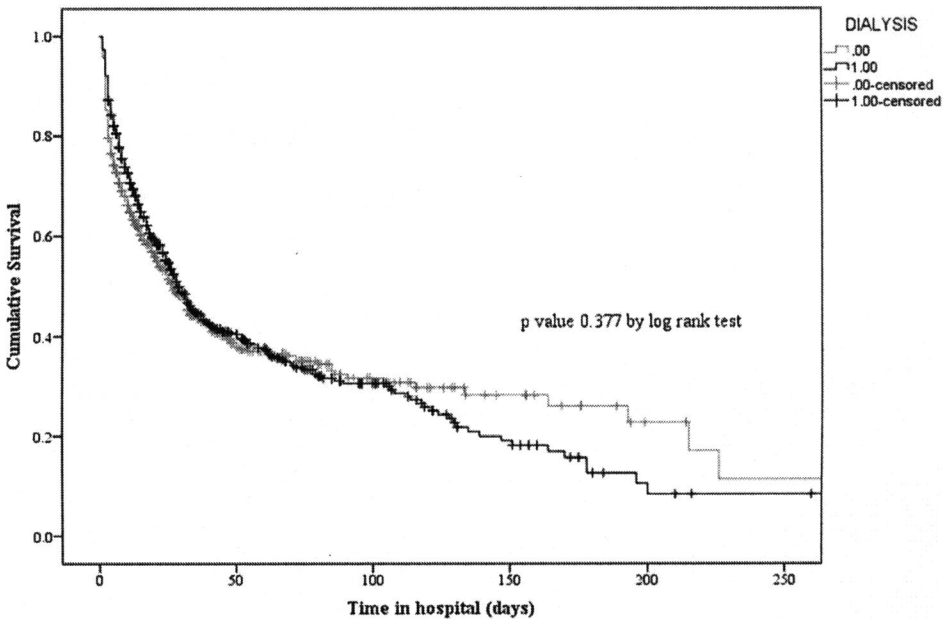


**Fig. 3** Kaplan–Meier plot of the propensity score-matched (PSM) survival for chronic dialysis and non-dialysis patients with septic shock (log rank tests $P$ value 0.377) with accompanying table of the number of patients at risk at various time points. *Black line* Dialysis patients, *Gray line* non-chronic dialysis patients

**Table 2** Total cohort and propensity score-matched crude and hazard ratio of mortality for chronic dialysis patients in quartiles of time following hospital admission

| Time quartile | Deaths (chronic dialysis/non-dialysis) | Hazard ratio (total cohort) | Deaths (chronic dialysis/non-dialysis) | Hazard ratio (PSM) |
|---|---|---|---|---|
| 0–6 days | Chronic dialysis: 155/183<br>Non-dialysis: 2196/2455 | 0.83 (0.71–0.98) | Chronic dialysis: 155/183<br>Non-dialysis: 218/235 | 0.76 (0.62–0.94) |
| 7–14 days | Chronic dialysis: 111/215<br>Non-dialysis: 1072/2353 | 1.08 (0.88–1.32) | Chronic dialysis: 111/215<br>Non-dialysis: 89/187 | 1.12(0.84–1.47) |
| 15–33 days | Chronic dialysis: 99/204<br>Non-dialysis: 847/2488 | 1.35 (1.08–1.67) | Chronic dialysis: 99/204<br>Non-dialysis: 78/211 | 1.28 (0.95–1.72) |
| >33 days | Chronic dialysis: 73/198<br>Non-dialysis: 595/2316 | 1.17 (0.91–1.49) | Chronic dialysis: 73/198<br>Non-dialysis: 138/165 | 1.54 (1.04–2.28) |

The total cohort model was adjusted, and the propensity score-matched (PMS) cohort was created using the following variables: age, sex, comorbidities (cancer, immunocompromised, congestive heart failure, coronary artery disease, elective or emergent surgery, chronic obstructive pulmonary disease, diabetes) and APACHE II score

*CI* confidence interval

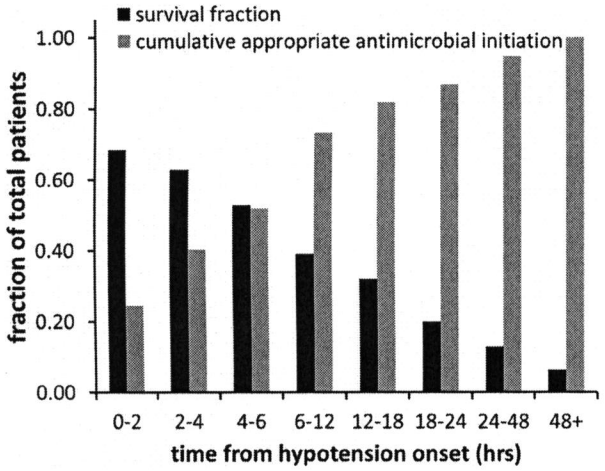


**Fig. 4** Cumulative appropriate antimicrobial initiation following onset of septic shock-associated hypotension and associated survival in chronic dialysis-dependent patients with end-stage renal disease. *x-axis* Time (hours) following first documentation of septic shock-associated hypotension, *black bars* fraction of patients surviving to hospital discharge who received the appropriate therapy initiated within the given time interval, *gray bars* cumulative fraction of patients who received the appropriate antimicrobials at any given time point. Only patients ($n = 597$) who received the appropriate antimicrobials after documentation of hypotension were included

Delays in initiating the appropriate antimicrobial therapy in chronic dialysis patients with septic shock was strongly associated with an increased mortality risk (adjusted OR 1.07, 95 % CI 1.05–1.10 per hour delay; $P < 0.0001$) (Fig. 4).

Information on dialysis modality was available for a limited number of chronic dialysis patients (368/800, 46 %). Of these 368 patients, 71.7 % were on HD and 28.2 % were on PD. In-hospital mortality was higher in those patients receiving PD than in those on HD (67.3 vs. 49.2 %; $P = 0.002$). Catheter-related infection was the primary site of infection in 94 HD patients, with an associated mortality of 36.2 %. There were 58 cases of peritonitis among the PD patients, with a subsequent associated mortality of 63.8 %. There were no differences in the frequency of nosocomial infections or in the receipt/delay of appropriate antimicrobials between the dialysis modality groups. Bacteremia was more common in HD patients (46.2 vs. 32.7 %; $P = 0.019$).

## Discussion

In this large international cohort of patients with septic shock, overall mortality was similar in the groups of non-dialysis and chronic dialysis patients, but in the latter patient population it varied over time following ICU admission. In the early period after ICU admission (<6 days after admission), our analysis revealed a significant survival advantage; however, this was followed by progressively increasing mortality. Although physiological and laboratory values were generally similar for chronic dialysis and non-dialysis patients, important differences were observed with respect to demographics, comorbidities, sites of infection, infectious pathogens, and treatment-related factors. Most notably, chronic dialysis status was associated with infection with resistant organisms, particularly MRSA. In addition, chronic dialysis patients experienced a delay in receiving the appropriate antimicrobial therapy, and this delay was associated with increased mortality, similar to previous studies [32, 34].

The results from previously published, smaller studies are conflicting with respect to whether chronic dialysis is an independent risk factor for increased mortality following ICU admission [15, 16, 19, 20, 25, 28]. We believe that our study is the first to demonstrate that the survival of any group of chronic dialysis patients was significantly better than that of non-dialysis patients during the initial period following ICU admission.

Nonetheless, there was no significant difference in the survival rate following this initial period or overall. The validity of our findings is reinforced by the observation that our overall in-hospital survival rate of approximately 50 % for unselected patients with septic shock is very similar to that reported by recent, large, multinational, retrospective studies [41, 42]. Multiple factors could account for the variation in mortality we observed for the chronic dialysis patients during the period after ICU admission. It is well reported that ESKD and chronic dialysis patients are immunodeficient, which may blunt the overwhelming pro-inflammatory cytokine responsible for organ injury in early septic shock but which ultimately negatively impacts on the likelihood of longer-term survival [37]. A second, unrelated possibility is that relatively lower early mortality in chronic dialysis patients resulted from selection bias [38, 39]. Overall, the chronic dialysis population is older, with a higher number of comorbid illnesses, and fewer may have received admission to the ICU overall [39]. In support of this notion, there were significant demographic differences observed between chronic dialysis and non-dialysis patients. We believe that our study is the first to demonstrate that mortality risk is time-dependent for chronic dialysis patients, and further study to confirm and explain the early survival advantage that was noted for the chronic dialysis group is warranted.

To our knowledge, this is also the first study to assess the impact of antimicrobial timing and appropriateness for chronic dialysis patients who develop septic shock. Overall, chronic dialysis patients were more likely than non-dialysis patients to receive inappropriate antimicrobial therapy (20 vs. 15.8 %). However, this diminished after PSM, suggesting that illness severity, demographics, and comorbidities may mask important information regarding the presence, site, and microbials associated with septic shock. Chronic dialysis was associated with a significant delay in the initiation of antimicrobial treatment (median time 6.0 vs. 5.0 h), which likely contributes to mortality among chronic dialysis patients. Kumar et al. (2006) [43] demonstrated that the survival of patients with septic shock decreased by 7.6 % for each hour of delay in initiating the appropriate antimicrobial therapy over the first 6 h of documented hypotension. The absence of clinical symptoms and signs of infection, such as fever and/or localizing features, is more common among chronic dialysis patients and may play a role in delayed antimicrobial therapy [40, 44, 45]. Rojas et al. [46] recently reported that among chronic dialysis patients with bloodstream infection, lack of fever was associated with increased mortality. These results suggest that chronic dialysis patients may require a lower clinical threshold to initiate broad-spectrum antimicrobial coverage as compared with the non-dialysis population and that such an approach may improve mortality.

*Staphylococcus aureus* was the most prevalent pathogen among the chronic dialysis patients, whereas *E. coli* was the most prevalent pathogen present in non-dialysis patients. The finding that *S. aureus* was relatively more prevalent in chronic dialysis patients is consistent with studies showing that this microorganism is responsible for 21–43 % of HD catheter-related infections, of which 12–38 % are MRSA [47]. MRSA was also relatively more prevalent among dialysis patients, as were other resistant bacteria. These results reflect the large, previously documented burden of antimicrobial resistance that can be broadly found among the chronic dialysis population [48–50].

In general, the hospitalization rate among the chronic dialysis population is very high [1]. In our chronic dialysis and non-dialysis patients, respiratory infections were the most common infection. Not surprisingly, central venous catheter infections and peritonitis were much more prevalent in HD and PD patients, respectively, which is accounted for by increased infectious risks associated with vascular and peritoneal access [1]. In contrast to our results, previous studies of chronic dialysis patients admitted to hospital (but not necessarily ICU) with bloodstream infections found that access-related infections were more frequent than respiratory ones [3, 13, 46]. One possibility for this difference is that access-related infections less frequently progress than pneumonia to septic shock and/or respiratory compromise which require ICU admission. More generally, these results demonstrate that the range of infections leading to ICU admission for septic shock in this population are broadly distributed and not limited primarily to access-related infections as previously reported [13].

We found that chronic dialysis patients with septic shock were almost twofold more likely to be diabetic than non-dialysis patients (48 vs. 25.9 %). Diabetes among both HD and PD patients is associated with higher risks of hospital admission for septicemia [3]. Notably, we found a significant interaction between diabetes and chronic dialysis in which the relative risk of mortality for diabetic chronic dialysis patients was highest after 33 days and lowest during the initial 6-day period following admission. Similar to chronic dialysis, diabetes is also associated with immunodeficiency, with diabetes patients having a possible blunted immunologic response to sepsis. Conversely, our results may further provide evidence of selection bias as diabetic dialysis patients may be less likely to be admitted to the ICU. Given the strong male predominance of septic shock cases in sepsis datasets (including our own) and in the chronic dialysis population, an unexpected finding of our study was that, relative to non-dialysis patients, there was a more balanced gender ratio in chronic dialysis patients with septic shock [1, 33, 34, 52]. A previous large study of chronic dialysis patients admitted to the ICU found that chronic dialysis patients were significantly more likely to be women [29];

however, other studies have shown the opposite [19, 20]. The other notable demographic finding of our study was that, consistent with the findings of Hutchison et al. [20] and Strijack et al. [29], both of whom reported the characteristics of large cohorts of dialysis patients admitted to the ICU, we found that chronic dialysis patients were significantly younger than their non-dialysis counterparts. These findings further suggest that older chronic dialysis patients with septic shock may not be admitted to the ICU [20]. Severity of illness (as reflected by the APACHE II score) was greater in our chronic dialysis cohort compared to the non-dialysis one [18, 20, 23, 30]. This may be based on relatively late ICU referrals or acceptances of chronic dialysis patients, which would account for the increased illness severity [20]. After matching, no difference in APACHE II scores persisted; however, this result must be interpreted with caution as the presence of chronic dialysis alone mandates awarding of between 2 and 5 points to each patient in that group. Thus, the application of advanced matching techniques to attenuate differences in the APACHE II score may conversely lead to the matching of chronic dialysis to sicker non-chronic dialysis patients.

This study has several important limitations. Patients were classified as chronic dialysis if they were on dialysis prior to hospital admission, with the duration of dialysis being unknown. The available data did not allow us to distinguish between vascular access type (central venous catheter or arteriovenous fistula or graft). Our results are international and multicenter (USA, Canada, and Saudi Arabia); however, they may not be generalizable to other jurisdictions. As this study was observational, there remains the possibility of residual confounding.

## Conclusions

Mortality among chronic dialysis patients with septic shock was similar overall to that of non-dialysis patients. However in chronic dialysis patients mortality varied over time following ICU admission with improved early survival and comparable or worse survival thereafter. Chronic dialysis patients with septic shock differ from those of similarly admitted non-dialysis patients: they are more likely to be younger, female, have more comorbidity, and to have a higher APACHE II score. Sepsis-related differences in chronic dialysis include an increased number of nosocomial infections, resistant microorganisms, and longer delays in receiving appropriate antimicrobial therapy. Chronic dialysis-specific protocols to prevent infection and shorten the delay in initiation of therapy with the appropriate antimicrobials could reduce mortality from septic shock in the chronic dialysis patient population.

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**Compliance with ethical standards**

**Conflicts of interest** None.

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## References

1. Harper AM (1966) Autoregulation of cerebral blood flow: influence of the arterial blood pressure on the blood flow though the cerebral cortex. J Neurol Neurosurg Psychiatry 29:398–403
2. Minnaganti VR, Cunha BA (2001) Infections associated with uremia and dialysis. Infect Dis Clin North Am 15:385–406, viii
3. Powe NR, Jaar B, Furth SL, Hermann J, Briggs W (1999) Septicemia in dialysis patients: incidence, risk factors, and prognosis. Kidney Int 55(3):1081–1090
4. Vanholder R, Ringoir S (1993) Infectious morbidity and defects of phagocytic function in end-stage renal disease: a review. J Am Soc Nephrol 3(9):1541–1554
5. Arulkumaran N, Annear NM, Singer M (2013) Patients with end-stage renal disease admitted to the intensive care unit: systematic review. Br J Anaesth 110(1):13–20
6. Antonelli M, Bonten M, Chastre J, Citerio G, Conti G, Curtis JR et al (2012) Year in review in Intensive Care Medicine 2011: I. Nephrology, epidemiology, nutrition and therapeutics, neurology, ethical and legal issues, experimentals. Intensive Care Med 38:192–209
7. Sarnak MJ, Jaber BL (2000) Mortality caused by sepsis in patients with end-stage renal disease compared with the general population. Kidney Int 58(4):1758–1764
8. Antonelli M, Bonten M, Chastre J, Citerio G, Conti G, Curtis JR et al. (2012) Year in review in Intensive Care Medicine 2011. II. Cardiovascular, infections, pneumonia and sepsis, critical care organization and outcome, education, ultrasonography, metabolism and coagulation. Intensive Care Med 38:345–358
9. Aslam N, Bernardini J, Fried L, Burr R, Piraino B (2006) Comparison of infectious complications between incident hemodialysis and peritoneal dialysis patients. Clin J Am Soc Nephrol 1(6):1226–1233
10. Lafrance JP, Rahme E, Iqbal S, Elftouh N, Vallee M, Laurin LP, Ouimet D (2012) Association of dialysis modality with risk for infection-related hospitalization: a propensity score-matched cohort analysis. Clin J Am Soc Nephrol 7(10):1598–1605

11. Ng LJ, Chen F, Pisoni RL, Krishnan M, Mapes D, Keen M, Bradbury BD (2011) Hospitalization risks related to vascular access type among incident US hemodialysis patients. Nephrol Dial Transplant Off Publ Eur Dial Transplant Assoc Eur Ren Assoc 26(11):3659–3666
12. Williams VR, Quinn R, Callery S, Kiss A, Oliver MJ (2011) The impact of treatment modality on infection-related hospitalization rates in peritoneal dialysis and hemodialysis patients. Perit Dial Int J Int Soc Perit Dial 31(4):440–449
13. Dalrymple LS, Johansen KL, Chertow GM, Cheng SC, Grimes B, Gold EB, Kaysen GA (2010) Infection-related hospitalizations in older patients with ESRD. Am J Kidney Dis Off J Natl Kidney Found 56(3):522–530
14. Hotchkiss JR, Palevsky PM (2012) Care of the critically ill patient with advanced chronic kidney disease or end-stage renal disease. Curr Opin Crit Care 18(6):599–606
15. Apel M, Maia VP, Zeidan M, Schinkoethe C, Wolf G, Reinhart K et al (2013) End-stage renal disease and outcome in a surgical intensive care unit. Crit Care 17(6):R298
16. Bagshaw SM, Mortis G, Doig CJ, Godinez-Luna T, Fick GH, Laupland KB (2006) One-year mortality in critically ill patients by severity of kidney dysfunction: a population-based assessment. Am J Kidney Dis Off J Natl Kidney Found 48(3):402–409
17. Bell M, Granath F, Schon S, Lofberg E, Swing, Ekbom A et al (2008) End-stage renal disease patients on renal replacement therapy in the intensive care unit: short- and long-term outcome. Crit Care Med 36(10):2773–2778
18. Clermont G, Acker CG, Angus DC, Sirio CA, Pinsky MR, Johnson JP (2002) Renal failure in the ICU: comparison of the impact of acute renal failure and end-stage renal disease on ICU outcomes. Kidney Int 62(3):986–996
19. Dara SI, Afessa B, Bajwa AA, Albright RC (2004) Outcome of patients with end-stage renal disease admitted to the intensive care unit. Mayo Clin Proc 79(11):1385–1390
20. Hutchison CA, Crowe AV, Stevens PE, Harrison DA, Lipkin GW (2007) Case mix, outcome and activity for patients admitted to intensive care units requiring chronic renal dialysis: a secondary analysis of the ICNARC case mix programme database. Crit Care 11(2):R50
21. Juneja D, Prabhu MV, Gopal PB, Mohan S, Sridhar G, Nayak KS (2010) Outcome of patients with end stage renal disease admitted to an intensive care unit in India. Ren Fail 32(1):69–73
22. Khan A, Rigatto C, Verrelli M, Komenda P, Mojica J, Roberts D et al (2012) High rates of mortality and technique failure in peritoneal dialysis patients after critical illness. Perit Dial Int J Int Soc Perit Dial 32(1):29–36
23. Manhes G, Heng AE, Aublet-Cuvelier B, Gazuy N, Deteix P, Souweine B (2005) Clinical features and outcome of chronic dialysis patients admitted to an intensive care unit. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc Eur Ren Assoc 20(6):1127–1133
24. Ostermann M, Chang R (2008) Riyadh ICUPUG: renal failure in the intensive care unit: acute kidney injury compared to end-stage renal failure. Crit Care 12(5):432
25. Rocha E, Soares M, Valente C, Nogueira L, Bonomo H Jr, Godinho M et al (2009) Outcomes of critically ill patients with acute kidney injury and end-stage renal disease requiring renal replacement therapy: a case-control study. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc Eur Ren Assoc 24(6):1925–1930
26. Senthuran S, Bandeshe H, Ranganathan D, Boots R (2008) Outcomes for dialysis patients with end-stage renal failure admitted to an intensive care unit or high dependency unit. Med J Aust 188(5):292–295
27. Sood MM, Miller L, Komenda P, Reslerova M, Bueti J, Santhianathan C et al (2011) Long-term outcomes of end-stage renal disease patients admitted to the ICU. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc Eur Ren Assoc 26(9):2965–2970
28. Sood MM, Roberts D, Komenda P, Bueti J, Reslerova M, Mojica J et al (2011) End-stage renal disease status and critical illness in the elderly. Clin J Am Soc Nephrol 6(3):613–619
29. Strijack B, Mojica J, Sood M, Komenda P, Bueti J, Reslerova M et al (2009) Outcomes of chronic dialysis patients admitted to the intensive care unit. J Am Soc Nephrol 20(11):2441–2447
30. Uchino S, Morimatsu H, Bellomo R, Silvester W, Cole L (2003) End-stage renal failure patients requiring renal replacement therapy in the intensive care unit: incidence, clinical features, and outcome. Blood Purif 21(2):170–175
31. Knaus WA, Sun X, Nystrom O, Wagner DP (1992) Evaluation of definitions for sepsis. Chest 101(6):1656–1662
32. Kumar A, Ellis P, Arabi Y, Roberts D, Light B, Parrillo JE et al (2009) Initiation of inappropriate antimicrobial therapy results in a five-fold reduction of survival in human septic shock. Chest 136(5):1237–1248
33. Kumar A, Zarychanski R, Light B, Parrillo JE, Maki D, Simon D et al (2010) Early combination antibiotic therapy yields improved survival compared to monotherapy in septic shock: a propensity-matched analysis. Crit Care Med 38:1773–1785
34. Kumar ARD, Wood KE, Light RB, Parrillo JE, Sharma S, Suppes R et al (2006) Duration of hypotension prior to initiation of effective antimicrobial therapy is a critical determinant of survival in human septic shock. Crit Care Med 34:1589–1596
35. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM (1988) CDC definitions for nosocomial infections, 1988. Am J Infect Control 16(3):128–140
36. De Knaus WA (1985) APACHE II: a severity of disease classification system. Crit Care Med 13:818–829
37. Leentjens J, Kox M, van der Hoeven JG, Netea MG, Pickkers P (2013) Immunotherapy for the adjunctive treatment of sepsis: from immunosuppression to immunostimulation. Time for a paradigm change? Am J Respir Crit Care Med 187(12):1287–1293
38. Chertow GM, Normand SL, McNeil BJ (2004) "Renalism": inappropriately low rates of coronary angiography in elderly individuals with renal insufficiency. J Am Soc Nephrol 15(9):2462–2468
39. Covic A, Gusbeth-Tatomir P, Goldsmith D (2008) Negative outcome studies in end-stage renal disease: how dark are the storm clouds? Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc Eur Ren Assoc 23(1):56–61
40. Descamps-Latscha B (1993) The immune system in end-stage renal disease. Curr Opin Nephrol Hypertens 2(6):883–891
41. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R (2014) Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012. JAMA 311(13):1308–1316
42. Vincent JL, Marshall JC, Namendys-Silva SA, Francois B, Martin-Loeches I, Lipman J et al (2014) Assessment of the worldwide burden of critical illness: the intensive care over nations (ICON) audit. Lancet Respir Med 2(5):380–386

43. Kumar A, Haery C, Paladugu B, Kumar A, Symeoneides S, Taiberg L et al (2006) The duration of hypotension before the initiation of antibiotic treatment is a critical determinant of survival in a murine model of *Escherichia coli* septic shock: association with serum lactate and inflammatory cytokine levels. J Infect Dis 193(2):251–258
44. Jones PG, Kauffman CA, Port FK, Kluger MJ (1985) Fever in uremia: production of leukocytic pyrogen by chronic dialysis patients. Am J Kidney Dis Off J Natl Kidney Found 6(4):241–244
45. Lewis SL (1992) Fever: thermal regulation and alterations in end stage renal disease patients. ANNA J 19(1):13–18
46. Rojas L, Munoz P, Kestler M, Arroyo D, Guembe M, Rodriguez-Creixems M, Verde E, Bouza E (2013) Bloodstream infections in patients with kidney disease: risk factors for poor outcome and mortality. J Hosp Infect 85(3):196–205
47. Lok CE, Mokrzycki MH (2011) Prevention and management of catheter-related infection in hemodialysis patients. Kidney Int 79(6):587–598
48. Chang S, Sievert DM, Hageman JC, Boulton ML, Tenover FC, Downes FP, Shah S, Rudrik JT, Pupp GR, Brown WJ et al (2003) Infection with vancomycin-resistant *Staphylococcus aureus* containing the vanA resistance gene. N Engl J Med 348(14):1342–1347
49. Pop-Vicas A, Strom J, Stanley K, D'Agata EM (2008) Multidrug-resistant gram-negative bacteria among patients who require chronic hemodialysis. Clin J Am Soc Nephrol 3(3):752–758
50. Smith TL, Pearson ML, Wilcox KR, Cruz C, Lancaster MV, Robinson-Dunn B et al (1999) Emergence of vancomycin resistance in *Staphylococcus aureus*. Glycopeptide-intermediate *Staphylococcus aureus* Working Group. New Engl J Med 340(7):493–501
51. D'Agata EM (2002) Antimicrobial-resistant, Gram-positive bacteria among patients undergoing chronic hemodialysis. Clin Infect Dis Off Publ Infect Dis Soc Am 35(10):1212–1218
52. Kaukonen K-M, Bailey M, Pilcher D, Cooper DJ, Bellomo R (2015) Systemic inflammatory response syndrome criteria in defining severe sepsis. N Engl J Med 372(17):1629–1638