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Original Contributions

CLINICAL FACTORS AND OUTCOMES OF DIALYSIS-DEPENDENT END-STAGE RENAL DISEASE PATIENTS WITH EMERGENCY DEPARTMENT SEPTIC SHOCK

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☐ **Abstract—Background: Infection is the second leading cause of death in end-stage renal disease (ESRD) patients. Prior investigations of acute septic shock in this specific population are limited. Objective: We aimed to evaluate the clinical presentation and factors associated with outcome among ESRD patients with acute septic shock. Methods: We reviewed patients prospectively enrolled in an emergency department (ED) septic shock treatment pathway registry between January 2014 and May 2016. Clinical and treatment variables for ESRD patients were compared with non-ESRD patients. A second analysis focused on ESRD septic shock survivors and nonsurvivors. Results: Among 4126 registry enrollees, 3564 (86.4%) met inclusion for the study. End-stage renal disease was present in 3.8% (n = 137) of ED septic shock patients. Hospital mortality was 20.4% and 17.1% for the ESRD and non-ESRD septic shock patient groups ($p = 0.31$). Septic shock patients with ESRD had a higher burden of chronic illness, but similar admission clinical profiles to non-ESRD patients. End-stage renal disease status was independently associated with lower fluid resuscitation dose, even when controlling for severity of illness. Age and admission lactate were independently associated with mortality in ESRD septic shock patients. Conclusion: ESRD patients comprise a small but important portion of patients with ED septic shock. Although presentation clinical profiles are similar to patients without ESRD, ESRD status is independently associated with lower fluid dose and compliance with the 30-mL/kg fluid goal. Hyperlactatemia is a marker of mortality in ESRD septic shock.** © 2017 Elsevier Inc. All rights reserved.

☐ **Keywords—end-stage renal disease (ESRD); fluid resuscitation; septic shock; sepsis**

INTRODUCTION

Severe sepsis is a leading cause of death in the United States, with an incidence of approximately 300 cases per 100,000 (1). Similarly, infection is the second leading cause of death in patients with end-stage renal disease (ESRD) (2). Infections remain a common admission diagnosis for hemodialysis-dependent patients presenting to the emergency department (ED) (3). Despite this information, prior investigations of acute septic shock in the ESRD population are limited. We aimed to evaluate the clinical presentation, infection source, treatments, and outcomes of ESRD patients with acute septic shock and compare them with septic shock patients without ESRD.

METHODS

Design and Setting

Our health care system has a "Code Sepsis" clinical pathway for the management of adult patients with acute septic shock. Enrollment criteria are suspected infection plus persistent hypotension, defined as systolic blood pressure (SBP) < 90 mm Hg or mean arterial pressure

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(MAP) < 65 mm Hg after 20 mL/kg intravenous fluid bolus or serum lactate ≥ 4 mmol/L. The clinical pathway provides standardized management orders, fluid and hemodynamic resuscitation, clinical decision support for infection control measures, and serial monitoring to gauge response to resuscitation.

Enrolled patients are prospectively entered into a master quality improvement registry. Patients enrolled through the ED of one of 13 facilities in the Carolinas HealthCare System within metropolitan Charlotte, North Carolina served as the data source for this investigation. The Institutional Review Board and Privacy Board of Carolinas HealthCare System approved this study under waiver of informed consent.

Identification of Subjects

Clinical pathway enrollees registered between January 1, 2014 and May 31, 2016 served as the initial sample for this investigation. Subjects were divided into two groups based on the presence of ESRD on admission, as determined by International Classification of Diseases (ICD)-9 code 585.6 and ICD-10 code N18.6. We performed dedicated chart review on ESRD subjects to confirm chronic renal failure requiring renal replacement therapy as present on admission. Recognizing provider subjectivity in the clinical diagnosis of early infection, we then excluded patients without a final discharge diagnosis consistent with infection, sepsis, severe sepsis, or septic shock.

Data Collection and Analysis

We utilized a secure online Web application, Research Electronic Data Capture (REDCap) database, for data collection and organization. A single author performed chart reviews of the 219 ESRD patients using a standardized abstraction tool for additional data elements not included in the registry collection. Septic shock patients with ESRD were compared with septic shock patients without ESRD. A second analysis focused on clinical factors associated with hospital death in the ESRD septic shock group.

Continuous data are presented as means ± standard deviation using *t*-test for statistical differences. Categorical data presented as percentages and tested for significance using chi-squared tests of proportions. We considered $p \leq 0.05$ to be significant. In an attempt to identify factors independently associated with resuscitation, we used multiple variable linear regression modeling with fluid volume at 3 h as the dependent variable. A hierarchical logistic regression model was used to determine factors associated with ESRD septic shock death, where comorbidities, demographics, triage clinical markers, sepsis treatment variables, and treatment intensity models were generated. Variables from these models with $p \leq 0.15$ were included in the final model. The reduced final model includes variables significant at $p \leq 0.05$ level.

RESULTS

During the study period, 4126 patients were enrolled in our ED septic shock pathway (Figure 1). Of this group, 219 were coded with ESRD at admission, and 58 were excluded based on chart review that failed to confirm ESRD. We next excluded 504 (12.2% of total; 95% confidence interval [CI] 1.2–13.3) patients based on the absence of confirmed infection. This left a total cohort of 3564 study subjects for analysis. Overall, ESRD was a comorbid factor in 137 (3.8%; 95% CI 3.2–4.5) acute ED septic shock patients.

Comparison of ED Septic Shock with and without ESRD

Demographic and comorbid factors of the two groups are presented in Table 1. Compared with patients without ESRD, ESRD septic shock patients were younger ($p \leq 0.001$), more often female ($p = 0.01$), and more likely to have comorbid factors of diabetes, chronic obstructive pulmonary disease, and heart failure. ESRD patients were more likely to carry a "do not resuscitate" advanced directive status at admission ($p < 0.01$). There was no difference in hospital admission Premier CareScience® (Premier Inc., Charlotte, NC) Mortality Risk Model score or Acute Physiology and Chronic Health Evaluation (APACHE) IV score. ED presentation variables are reported in Table 1. ESRD patients had lower heart rates (96 vs. 106, $p < 0.001$) and triage shock index (0.9 vs. 1.0, $p = 0.01$). There was no significant difference in initial blood lactate between the two groups.

Table 2 demonstrates patient group treatment variables. ESRD patients were less likely to meet 3-h sepsis bundle treatment goals (35.0% vs. 56.3%, $p < 0.001$). Specifically, ESRD patients received less fluid at the 3- and 6-h treatment points ($p < 0.001$) and were less likely to meet the ≥ 30-mL/kg intravenous fluid (IVF) resuscitation goal within 3 h of ED arrival ($p < 0.001$). There was no difference in timeliness of initial antibiotic therapy. ESRD patients had higher rates of central venous catheter placement ($p = 0.001$), but no difference in vasopressor or mechanical ventilation requirements.

Hospital mortality for the entire cohort (n = 3564) was 17.3%. Mortality for septic shock patients with and without ESRD was 20.4% and 17.1%, respectively ($p = 0.31$; absolute difference: 3.3%; 95% CI of mortality difference: −10.2–3.6%). There was no difference in intensive care unit (ICU) length of stay (LOS) (3.3 ± 4.0 vs. 3.0 ± 3.5 days; $p = 0.58$) or hospital LOS (7.3 ± 7.7 vs. 7.6 ± 6.6 days; $p = 0.61$) between the groups.

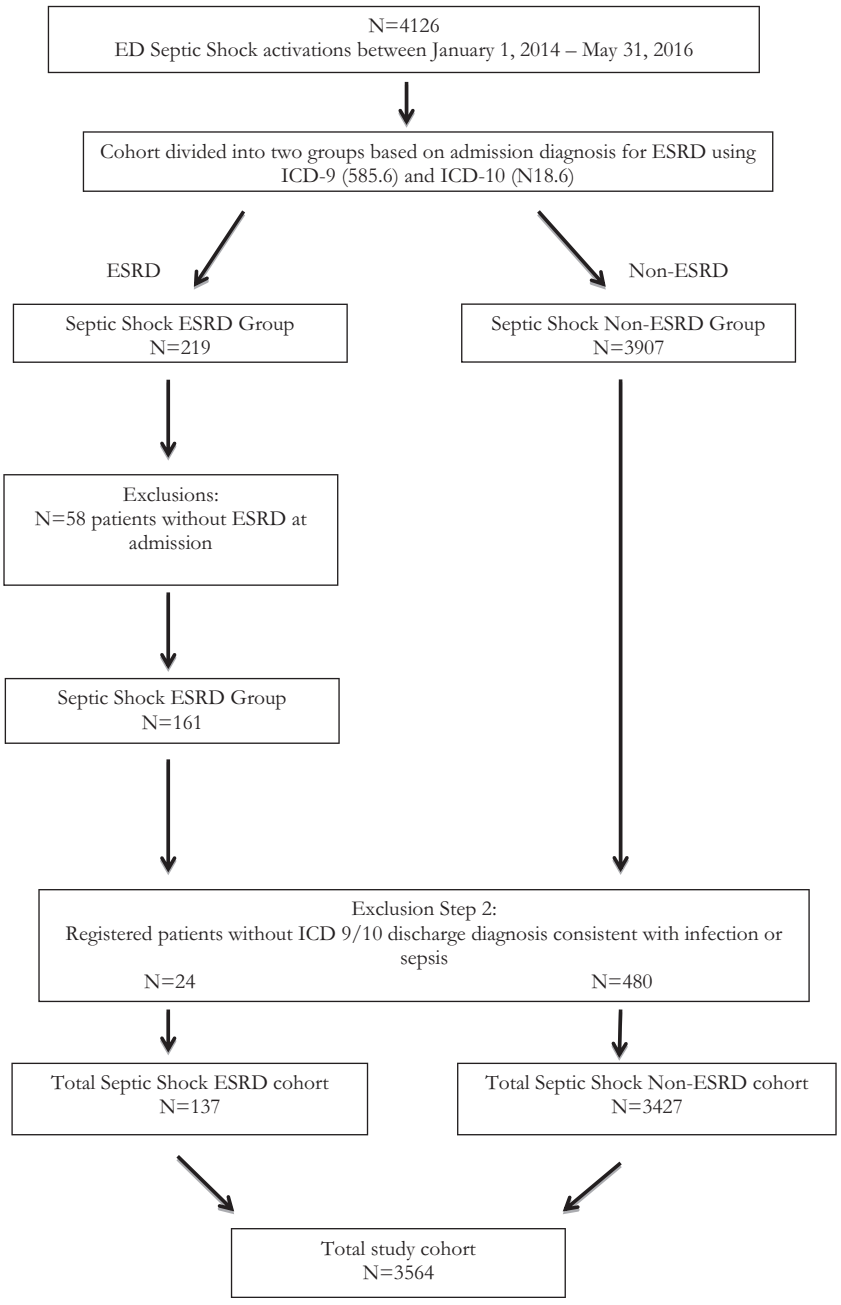

Figure 1. Study cohort selection flow diagram. ED = emergency department; ESRD = end-stage renal disease; ICD = International Classification of Diseases.

Comparison of ESRD Septic Shock Survivors vs. Nonsurvivors

Compared with survivors of ESRD septic shock, nonsurvivors were older (67 ± 9 and 58 ± 14 years, $p < 0.001$) and had higher admission Premier CareScience® Mortality Risk Model score (0.5 ± 0.2 vs. 0.2 ± 0.2, $p < 0.001$) and APACHE IV score (88 ± 30 vs. 67 ± 23, $p = 0.002$). Nonsurvivors had nearly double the incidence of externalized dialysis access catheters (50% vs. 28%, $p = 0.03$) and lower incidence of arteriovenous (AV) fistula or graft (57% vs. 80%, $p = 0.01$) (Table 3).

Although there was no difference in ED triage vital signs or infection source between the two groups, ESRD nonsurvivors had higher initial serum lactate (6.3 ± 3.8 vs. 3.7 ± 2.1, $p = 0.001$). They were also more likely to present with lactate ≥ 4 mmol/L (71% vs. 49%, $p = 0.04$). Serial and maximum serum lactate levels were higher in nonsurvivors. Nonsurvivors also exhibited an increase in serum lactate

Table 1. Septic Shock Non-ESRD and ESRD Groups – Baseline Characteristics

Variable	Total Group (n = 3564)	Septic Shock Non-ESRD (n = 3427)	Septic Shock ESRD (n = 137)	*p* Value
Age (year)	64 ± 16.9	65 ± 17	60 ± 13.7	0.0004
Sex (% male)	52 (n = 1837)	52 (n = 1781)	41 (n = 56)	0.01
Body weight (kg)	80 ± 27	80 ± 27	83 ± 24	0.26
BMI (kg/m^2)	28 ± 9	28 ± 9	29 ± 8	0.59
DNR status %, (n)	10 (351)	10 (328)	17 (23)	0.005
Comorbid factors, % (n)				
Diabetes	40 (1419)	39 (1323)	70 (96)	< 0.0001
Hypertension	73 (2589)	73 (2483)	77 (106)	0.20
COPD	28 (988)	27 (939)	36 (49)	0.03
Heart failure	24 (845)	22 (761)	61 (84)	< 0.0001
CKD	22 (800)	19 (663)	–	–
Cirrhosis	11 (395)	11 (379)	12 (16)	0.82
Malignancy	20 (722)	20 (700)	16 (22)	0.21
Dementia	21 (758)	22 (738)	15 (20)	0.05
MRSA positive	7 (259)	7 (244)	11 (15)	0.09
CRE positive	3 (93)	3 (88)	4 (5)	0.43
ED triage vital signs				
Heart rate, beats/min	105 ± 24 (3431)	106 ± 24 (3296)	97 ± 24 (135)	< 0.0001
Temperature, °F	99.0 ± 2.7 (3434)	99.0 ± 2.8 (3301)	98.9 ± 2.2 (133)	0.89
Maximum ED temperature, °F	99.7 ± 2.5 (2972)	99.7 ± 2.5 (2862)	99.7 ± 2.2 (110)	0.92
Mean arterial pressure, mm Hg	74 ± 22 (3301)	74 ± 21.3 (3171)	73 ± 27.9 (130)	0.91
Systolic blood pressure, mm Hg	111 ± 30 (3452)	111 ± 29.5 (3317)	110 ± 31.8 (135)	0.75
Minimum ED systolic blood pressure, mm Hg	86 ± 23 (3248)	86 ± 23 (3124)	87 ± 27.6 (124)	0.89
Shock index	1.0 ± 0.3 (3431)	1.0 ± 0.3 (3296)	0.9 ± 0.3 (135)	0.01
ED lab values				
WBC, 10*3/uL	15.5 ± 10.6 (3446)	15.6 ± 10.7 (3311)	13.9 ± 7.7 (135)	0.01
Initial ED lactate ≥ 4, %	54 (1910)	54 (1837)	53 (73)	0.74
Triage lactate, mmol/L	4.6 ± 3.0 (3421)	4.6 ± 3.0 (3287)	4.3 ± 2.8 (134)	0.23
Maximum lactate, mmol/L	4.8 ± 3.1 (3177)	4.8 ± 3.1 (3054)	4.4 ± 2.7 (123)	0.11
Lactate normalization, %	55 (1453)	55 (1398)	58 (55)	0.57
Premier CareScience Mortality Model Risk Score	0.2 ± 0.2 (n = 3435)	0.2 ± 0.2 (n = 3303)	0.2 ± 0.2 (n = 132)	0.25
APACHE IV score	72 ± 31 (n = 2056)	72 ± 31 (n = 1976)	71 ± 25 (n = 80)	0.66

ESRD = end-stage renal disease; BMI = body mass index; DNR = do not resuscitate directive; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; MRSA = methicillin-resistant *Staphylococcus aureus*; CRE = carbapenem-resistant enterobacteriaceae; ED = emergency department; WBC = white blood cell; APACHE = Acute Physiology and Chronic Health Evaluation.

between initial presentation and time 3 compared with survivors, who demonstrated a decline in lactate. There was a trend in failure to normalize lactate (< 2 mmol/L) at 6 h in nonsurvivors (40% vs. 63%, $p = 0.06$).

ED treatment variables are reported in Table 4. ESRD nonsurvivors were activated more quickly than survivors after triage presentation (1.3 ± 1.1 vs. 2.0 ± 1.9 h, $p < 0.01$), and received initial antibiotics more rapidly (1.6 ± 1.1 vs. 2.2 ± 1.7 hours, $p = 0.02$). There was no difference

Table 2. Septic Shock Non-ESRD and ESRD Groups – Treatment Variables and Bundle Compliance

Variable	Total group (n = 3564)	Septic Shock Non-ESRD (n = 3427)	Septic Shock + ESRD (n = 137)	*p* Value
Treatment variables, (n)				
Central line placement, %	66 (2355)	66 (2247)	79 (108)	0.001
Vasopressors, %	52 (1865)	52 (1786)	58 (79)	0.20
Mechanical ventilation, %	19 (674)	19 (651)	17 (23)	0.51
Bundle compliance, (n)				
Triage to activation time, h	2.0 ± 5.4 (3564)	2.0 ± 5.5 (3427)	1.9 ± 1.8 (137)	0.44
Bundle compliance at 3 h, %	56 (1979)	56 (1931)	35 (48)	< 0.0001
Fluid goal (> 30 mL/kg) within 3 h, %	66 (2337)	67 (2279)	42 (58)	< 0.0001
IVF in 3 h, mL/kg	38 ± 24	38 ± 24	25 ± 17	< 0.0001
IVF in 6 h, mL/kg	45 ± 28	46 ± 29	29 ± 19	< 0.0001
Time to first antibiotic, h	2.3 ± 4.4 (3522)	2.3 ± 4.5 (3388)	2.1 ± 1.6 (134)	0.13
Antibiotic < 1 h, %	83 (2960)	83 (2850)	80 (110)	0.37
Antibiotic < 3 h, %	90 (3199)	90 (3079)	88 (120)	0.39

ESRD = end-stage renal disease; IVF = intravenous fluid.

Table 3. ESRD Septic Shock Survivors and Nonsurvivors – Baseline Characteristics

Variable	Total Group (n = 137)	Sepsis + ESRD Survivor (n = 109)	Sepsis + ESRD Nonsurvivor (n = 28)	*p* Value
Age (y)	60 ± 13.7	58 ± 14.1	67 ± 9.0	0.0002
Sex (% male)	41 (n = 56)	40 (n = 44)	43 (n = 12)	0.81
Body weight (kg)	83 ± 24	81 ± 25	89 ± 18	0.11
BMI (kg/m2)	29 ± 8	28 ± 8	31 ± 7	0.08
DNR status, % (n)	17 (23)	14 (15)	29 (8)	0.06
Comorbid factors, % (n)				
Diabetes	70 (96)	71 (77)	67 (19)	0.77
Hypertension	77 (106)	75 (82)	86 (24)	0.23
COPD	36 (49)	33 (36)	46 (13)	0.18
Heart failure	61 (84)	58 (63)	75 (21)	0.09
Cirrhosis	12 (16)	10 (11)	18 (5)	0.25
Malignancy	16 (22)	16 (17)	18 (5)	0.77
Dementia	15 (20)	14 (15)	18 (5)	0.58
MRSA positive	11 (15)	11 (11)	14 (4)	0.52
CRE positive	4 (5)	3 (3)	7 (2)	0.26
Dialysis access, % (n)*				
Arteriovenous fistula or graft	75 (102)	79 (86)	57 (16)	0.01
Externalized hemodialysis access	33 (45)	28 (31)	50 (14)	0.03
Peritoneal access	5 (7)	4 (4)	11 (3)	0.13
ED triage vital signs				
Heart rate, beats/min	96 ± 24 (n = 135)	97 ± 24 (n = 107)	94 ± 25 (n = 28)	0.55
Temperature, °F	98.9 ± 2.2 (133)	99.1 ± 2.2 (106)	98.3 ± 1.9 (27)	0.08
Maximum ED temperature, °F	99.7 ± 2.2 (110)	99.8 ± 2.3 (89)	99.3 ± 2.1 (21)	0.35
Mean arterial pressure, mm Hg	73 ± 28 (130)	75 ± 29 (102)	69 ± 23 (28)	0.33
Systolic blood pressure, mm Hg	110 ± 32 (135)	112 ± 34 (107)	102 ± 21 (28)	0.06
Minimum ED systolic blood pressure, mm Hg	87 ± 28 (124)	88 ± 29 (99)	80 ± 20 (25)	0.19
Shock index	0.9 ± 0.3 (135)	0.9 ± 0.3 (107)	1.0 ± 0.3 (28)	0.80
ED lab values				
WBC, 10^{*3}/uL	13.9 ± 7.7 (135)	14.0 ± 7.9 (107)	13.5 ± 6.6 (28)	0.77
Initial ED lactate ≥ 4, %	53 (73)	49 (53)	71 (20)	0.04
Triage lactate, mmol/L	4.3 ± 2.8 (134)	3.7 ± 2.1 (106)	6.3 ± 3.8 (28)	0.001
Maximum lactate, mmol/L	4.4 ± 2.7 (123)	3.9 ± 2.1 (98)	6.2 ± 3.8 (25)	0.007
Lactate normalization, %	58 (55)	63 (47)	40 (8)	0.06
Premier CareScience Mortality Model Risk Score	0.2 ± 0.2 (n = 132)	0.2 ± 0.2 (n = 104)	0.5 ± 0.2	< 0.0001
APACHE IV score	71 ± 25 (n = 80)	67 ± 23 (n = 65)	88 ± 30 (n = 15)	0.002
Infection source, % (n)†				
Unknown	25 (34)	25 (27)	25 (7)	0.98
Pneumonia	21 (29)	21 (23)	21 (6)	0.96
Abdominal	15 (21)	14 (15)	21 (6)	0.31
Skin	12 (16)	12 (13)	11 (3)	0.85
Catheter/HD access site infection	11 (15)	11 (12)	11 (3)	0.96
GU	11 (15)	12 (13)	7 (2)	0.46
Viral	2 (3)	3 (3)	–	–
Bacteremia	18 (24)	17 (19)	18 (5)	0.95
Dialysis access related bacteremia	8 (11)	7 (8)	11 (3)	0.51

ESRD = end-stage renal disease; BMI = body mass index; DNR = do not resuscitate order; COPD = chronic obstructive pulmonary disease; MRSA = methicillin-resistant *Staphylococcus aureus*; CRE = carbapenem-resistant enterobacteriaceae; ED = emergency department; WBC = white blood cell; APACHE = Acute Physiology and Chronic Health Evaluation; HD = hemodialysis; GU = genitourinary.
* Values sum to > 100% if patients had more than one type of dialysis access.
† Values sum to > 100% if patients had more than one identified source of infection.

between 3-h bundle compliance, IVF dose, or IVF resuscitation goal compliance at 3 h. Nonsurvivors required early vasopressors more frequently (79% vs. 52%, $p = 0.01$), and had higher mechanical ventilation requirement (36% vs. 12%, $p = 0.002$). There was no difference in period of ventilation (4.4 ± 4.1 vs. 3.9 ± 3.0 days; $p = 0.75$) or ICU LOS (3.1 ± 3.7 vs. 3.0 ± 2.8 days; $p = 0.95$) between survivors and nonsurvivors. After risk adjustment through logistic regression modeling, the following factors were independently associated with death in ESRD septic shock (area under the curve 0.84): age (odds ratio [OR] 1.06, 95% CI 1.01–1.12), initial SBP (OR 0.98, 95% CI 0.96–0.99), and initial lactate (OR 1.59, 95% CI 1.24–2.03).

ESRD Septic Shock Infection Source and Organisms

Among ESRD patients, the most common category of infection was culture-negative unknown source at 25% (n = 34), followed by pneumonia (21%, n = 29) and bacteremia (18%, n = 24). Of the 137 ESRD patients, 102 (75%) had AV fistulas or AV grafts, 45 (33%) had externalized dialysis access catheters, and 7 (5%) had

Table 4. Septic Shock ESRD Survivors and Nonsurvivors – Treatment Variables and Bundle Compliance

Variable	Total Group (n = 137)	Sepsis + ESRD Survivor (n = 109)	Sepsis + ESRD Nonsurvivor (n = 28)	*p* Value
Treatment variables, (n)				
Central line placement, %	79 (108)	76 (83)	89 (25)	0.12
Vasopressors, %	58 (79)	52 (57)	79 (22)	0.01
Mechanical ventilation, %	17 (23)	12 (13)	36 (10)	0.002
Bundle compliance, (n)				
Triage to activation time, h	1.9 ± 1.8 (137)	2.0 ± 1.9 (109)	1.3 ± 1.1 (28)	0.008
Bundle compliance at 3 h, %	35 (48)	35 (38)	36 (10)	0.93
IVF in 3 h, mL/kg	25 ± 17	24 ± 17	27 ± 15	0.43
IVF in 6 h, mL/kg	29 ± 19	29 ± 20	30 ± 17	0.75
Time to first antibiotic, h	2.1 ± 1.6 (134)	2.2 ± 1.7 (107)	1.6 ± 1.1 (27)	0.02
Antibiotic < 1 h, %	80 (110)	79 (86)	86 (24)	0.41
Antibiotic < 3 h, %	88 (120)	87 (95)	89 (25)	0.76

ESRD = end-stage renal disease; IVF = intravenous fluid.

peritoneal dialysis access catheters. Sixteen patients (12%) had more than one type of dialysis access. Infected dialysis access sites were identified in 11% (n = 15) of cases. Dialysis access-related bacteremia was identified in 11 patients (8%) of ESRD septic shock patients (Table 3).

Causative microorganisms were identified by positive blood, urine, sputum, peritoneal fluid, or surgical cultures in n = 65 of the ESRD septic shock patients. *Staphylococcus aureus* was the causative microorganism for infection in 14 patients (22%), of which 11 (17%) were identified as methicillin-resistant (MRSA). Gram-negative organisms were causative in 29 cases (45%). *Escherichia coli* was the most common pathogen in this group (10 cases; 15% of culture positive infections). The third most common microorganism, *Enterococcus* species, was identified in 7 cases (11%; Table 5).

Regression Analysis to Identify Factors Associated with Fluid Resuscitation

For our entire septic shock study group, a linear regression model with total fluid dose delivered (mL/kg) as the outcome indicated the following factors were independently associated with IVF dose: survival to hospital discharge ($p = 0.05$; coeff: −2.09; 95% CI −4.16 to −0.01), ESRD (Yes/No) ($p < 0.0001$; coeff: −11.48; 95% CI −15.62 to −7.33), body mass index (BMI) group (underweight, normal, overweight, obese, extremely obese) ($p < 0.0001$; coeff: −5.36; 95% CI −6.04 to −4.69), triage SBP ($p = 0.001$; coeff: −0.06; 95% CI −0.10 to −0.02), triage temperature ($p = 0.04$; coeff: 0.30; 95% CI 0.01–0.59), and triage lactate ($p < 0.001$; coeff: 1.15; 95% CI 0.88–1.41). These results suggest that nonsurvivors, patients with ESRD, and those with higher BMI received significantly lower fluid dose than survivors, patients without ESRD, or those with lower BMI. Lower fluid dose in nonsurvivors persisted when we restricted the model confounding variables to ED clinical markers only.

This result was supported by logistic regression analysis of factors associated with the dichotomous outcome of ≥ 30 mL/kg fluid goal met, where significant factors were: triage temperature ($p < 0.0001$, OR 1.06, 95% CI 1.03–1.09), triage SBP ($p = 0.0002$, OR 0.95, 95% CI 0.93–0.98), triage lactate ($p < 0.0001$, OR 1.13, 95% CI 1.10–1.17), BMI grouping ($p < 0.0001$, OR 0.48, 95% CI 0.33–0.70; 0.36, 95% CI 0.25–0.52; 0.28, 95% CI 0.19–0.40; 0.18, 95% CI 0.12–0.27) for normal, overweight, obese, and extremely obese groups, respectively, relative to the underweight group, and ESRD (Yes/No) ($p < 0.0001$; OR 0.36, 95% CI 0.25–0.51). Thus, ESRD persisted as a factor independently associated with lower fluid administration, as measured by both total fluid dose delivered and ≥ 30-mL/kg fluid goal compliance, after controlling for relevant clinical and demographic factors.

Table 5. Septic Shock ESRD Causative Microorganisms

Causative Microorganisms, % (n)	(n = 65)
Staphylococcus aureus	21.5 (14)
Methicillin resistant	16.9 (11)
Methicillin sensitive	4.6 (3)
Escherichia coli	15.4 (10)
Enterococcus species	10.8 (7)
Klebsiella pneumonia	9.2 (6)
Clostridium difficile	7.7 (5)
Staphylococcus coagulase negative	6.2 (4)
Pseudomonas aeruginosa	6.2 (4)
Streptococcus species	6.2 (4)
Streptococcus viridans	3.1 (2)
Streptococcus pyogenes	1.5 (1)
Streptococcus agalactiae	1.5 (1)
Serratia marcescens	4.6 (3)
Enterobacter cloacae	3.1 (2)
Proteus mirabilis	3.1 (2)
Carbapenem-resistant enterobacteriaceae (CRE)	1.5 (1)
Corynebacterium sp	1.5 (1)
Stenotrophomonas	1.5 (1)
Bacillus cereus/thuringiensis group	1.5 (1)

DISCUSSION

ESRD patients represent a small, but important, subset of patients with ED septic shock. Specifically, ESRD is a unique comorbid factor in approximately 1 in 25 ED septic shock patients. Independent of ESRD, these patients are more complicated, as exemplified by higher rates of comorbid disease. We demonstrated a nonsignificant trend toward increased mortality. More importantly, despite presenting with similar infections and physiologic indicators, we recognized an important difference in the early fluid management of ESRD septic shock patients compared with patients without this factor. Our investigation provides insight into dialysis-dependent ESRD septic shock in the context of limited current data on this population.

Infection is the second leading cause of death in patients with ESRD (2). Although the United States Renal Data System registry indicates that hospitalizations for ESRD patients due to infection decreased over the past 10 years, it remains a common admission diagnosis for hemodialysis-dependent patients presenting to the ED (3). Epidemiologic data on this specific subgroup are limited. An international surveillance investigation of hospitalized adults with septic shock identified 7.7% of patients on chronic dialysis (4). Our 3.8% prevalence of ESRD in ED septic shock patients is lower, but represents another contemporary measure of this important comorbid factor across a metropolitan health care system. It is also important to note that although not specifically excluded, ESRD patients may have been unrepresented in recent early goal-directed therapy sepsis trials, with < 3.4% of enrollees described as having coexisting renal disease (5). Appreciation of similar septic shock survival compared with the general population also serves as a reminder to avoid therapeutic nihilism in the ESRD population (4).

Few former studies investigate early septic shock management of ESRD patients. Despite similar presenting physiologic variables and shock markers within our cohort groups, ESRD patients received significantly less fluid resuscitation compared with non-ESRD septic shock patients. ESRD was independently associated with reduced fluid administration upon controlling for other factors, including illness severity. The difference in early fluid administration was potentially clinically important at 11 mL/kg in the first 3 h of resuscitation. Stated another way, ESRD patients were 2.8 times less likely to meet the 30-mL/kg fluid goal. Furthermore, nonsurvivors received similar early IVF doses compared with the entire ESRD group. This similarity in treatment occurred despite earlier recognition, faster antibiotic administration, and in the context of relative hyperlactatemia, which is recognized as a marker of more severe disease. As such, timeliness of treatment does not seem to be a plausible explanation for differential resuscitation.

Failure to complete at least 30 mL/kg IVF within the first 3 h of care, which is endorsed by our clinical pathway, the Surviving Sepsis Campaign guideline, and the Centers for Medicare and Medicaid Services, may have several explanations (6). Clinical determination of intravascular volume status and fluid responsiveness is imperfect. As such, providers may assume volume overload or fluid intolerance in dialysis-dependent patients. The absence of urine output as an endpoint of early resuscitation may also impact resuscitation decisions. In the absence of physiologic justification to support lower-volume resuscitation requirements in ESRD patients with acute septic shock, we believe it highlights a potential systematic bias in the resuscitation of these patients. As another example, despite guideline endorsement and growing evidence that early initiation of intravenous fluid is associated with improved outcome in sepsis, chronic renal failure patients also experience delayed fluid initiation (7,8). The corollary is that this signal may serve as an opportunity for improved management and outcomes in this group. Liu described a large multicenter ED initiative to standardize 30-mL/kg IVF for hemodynamically stable severe sepsis patients (9). Bundle implementation and hospital mortality improved in the intervention group, with outcome improvement primarily associated with increased early fluid administration in patients with chronic kidney disease and heart failure. The compilation of these findings highlight treatment differences that question the most appropriate early fluid strategy for ESRD septic shock. Recognizing that early fluid resuscitation is associated with outcome, an early IVF dosing trial or early fluid therapy guided by markers of fluid responsiveness represent important research opportunities in this target group (10,11).

Prompt infection source control is a cornerstone for the management of septic shock. Few studies have investigated infection sources in ESRD septic shock. Our data illustrate a wide range of infection sources and agents. Pneumonia remained the leading source of identified infection in our cohort, which is consistent with the general population (1,12). Two previous retrospective studies identified dialysis access site infections, pneumonia, peritonitis, ischemic bowel, and cellulitis as the most common sources of sepsis (2,4). Dialysis access-related infection is commonly assumed in these patients but was confirmed in only 10%, with the majority having confirmed bacteremia. Our finding of *S. aureus* and *E. coli* as prominent causative microorganisms is consistent with previous work (2,4).

Early identification of sepsis remains a challenge. Approximately 1 in 8 ED-activated patients (12% non-ESRD and 11% of ESRD cases) did not carry an infection-related discharge diagnosis, which is consistent with prior investigations on the frequency of sepsis mimics

(13). Although not discriminatory in the ESRD and non-ESRD patients, presenting variables emphasize some important points about ED septic shock. Fever was absent in the majority of patients; approximately 1 in 4 patients was febrile at triage across the entire cohort. Deceptively normal initial blood pressure and heart rate were common. In contrast, elevated shock index was a notable measure to promote early identification of high-risk patients (14).

Once infection is suspected, complicated disease is similarly difficult to identify in the early course of illness. Within the ESRD group, ED hemodynamic variables did not strongly differentiate survivors from nonsurvivors, which agrees with previous studies (2,4). In contrast, hyperlactatemia was a strong independent marker of adverse outcome. To our knowledge, this is the first study confirming the utility of early blood lactate measures to identify mortality risk in infected ESRD patients (15). Our sub-analysis also revealed a trend toward failed lactate clearance in response to resuscitation, which is previously reported as a marker of worse outcome in septic shock (16).

Limitations

Our study design includes some important limitations. Patients enrolled and managed in our regional health care system may not be consistent with other regions, limiting the generalizability of our results. ED clinical suspicion for septic shock was reconciled with discharge diagnoses to confirm infection as the primary patient condition, but only a portion of our study group had culture confirmation. Recognizing that our retrospective design is associated with potential biases and inaccuracies in data, we utilized a dedicated registry of patients managed in a standardized treatment pathway in an attempt to minimize the impact of these issues. Our study design also included a single investigator using a standard data collection tool to perform chart abstraction. Lastly, the relatively small proportion of ESRD patients and deaths in this group may have influenced our ability to clarify important differences in patient variables and outcome.

CONCLUSIONS

ESRD patients comprise a small but important portion of patients with ED septic shock. Although presentation clinical profiles are similar to patients without ESRD, ESRD status is independently associated with lower early fluid resuscitation dose and lower compliance with the 30-mL/kg IVF goal. Initial lactate and early lactate kinetics are markers for mortality in ESRD septic shock. Additional research to guide early fluid resuscitation is warranted in this complicated population.

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REFERENCES

1. Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. Virulence 2013;5:4–11.
2. Dagher GA, Harmouche E, Jabbour E, et al. Sepsis in hemodialysis patients. BMC Emerg Med 2015;15:30.
3. United States Renal Data System. Annual data report. Chapter 5. Hospitalization. Available at: https://www.usrds.org/adr.aspx. Accessed March 18, 2017.
4. Clark E, Kumar A, Langote A, et al. Septic shock in chronic dialysis patients: clinical characteristics, antimicrobial therapy and mortality. Intensive Care Med 2015;42:222–32.
5. PRISM Investigators, Rowan KM, Angus DC, et al. Early, goal-directed therapy for septic shock – a patient-level meta-analysis. N Engl J Med 2017;376:2223–34.
6. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. Crit Care Med 2016;45:486–552.
7. Leisman DE, Goldman C, Doerfler ME, et al. Patterns and outcomes associated with timeliness of initial crystalloid resuscitation in a prospective sepsis and septic shock cohort. Crit Care Med 2017;45:1596–606.
8. Leisman D, Wie B, Doerfler M, et al. Association of fluid resuscitation initiation within 30 minutes of severe sepsis and septic shock recognition with reduced mortality and length of stay. Ann Emerg Med 2016;68:298–311.
9. Liu VX, Morehouse JW, Marelich GP, et al. Multicenter implementation of a treatment bundle for patients with sepsis and intermediate lactate values. Am J Respir Crit Care Med 2016;193:1264–70.
10. Monnet X, Marik P, Teboul J-L. Passive leg raising for predicting fluid responsiveness: a systematic review and meta-analysis. Intensive Care Med 2016;42:1935–47.
11. Marik P, Bellomo R. A rational approach to fluid therapy in sepsis. Surv Anesthesiol 2016;60:232–3.
12. Novosad SA, Sapiano MR, Grigg C, et al. Vital signs: epidemiology of sepsis: prevalence of health care factors and opportunities for prevention. MMWR Morb Mortal Wkly Rep 2016;65:864–9.
13. Heffner AC, Horton JM, Marchick MR, et al. Etiology of illness in patients with severe sepsis admitted to the hospital from the emergency department. Clin Infect Dis 2010;50:814–20.
14. Tseng J, Nugent K. Utility of the shock index in patients with sepsis. Am J Med Sci 2015;349:531–5.
15. Howell MD, Donnino M, Clardy P, et al. Occult hypoperfusion and mortality in patients with suspected infection. Intensive Care Med 2007;33:1892–9.
16. Puskarich MA, Trzeciak S, Shapiro NI, et al. Whole blood lactate kinetics in patients undergoing quantitative resuscitation for severe sepsis and septic shock. Chest 2013;143:1548–53.

ARTICLE SUMMARY

1. Why is this topic important?

Infection is a common reason for hospitalization and remains the second leading cause of death in patients with end-stage renal disease (ESRD). Prior investigations of septic shock in ESRD patients are limited.

2. What does this study attempt to show?

We aimed to compare clinical variables and outcomes of ESRD and non-ESRD patients diagnosed with ED septic shock to understand their presentation, infection source, treatments, and outcomes. We also compared ESRD septic shock survivors and nonsurvivors.

3. What are the key findings?

a. Mortality rate of ESRD patients with septic shock was similar to those without ESRD.
b. ESRD patients with acute septic shock received less early fluid resuscitation compared with non-ESRD patients, and were 2.8 times less likely to meet the guideline-recommended 30-mL/kg fluid goal compared with ESRD patients. ESRD status was independently associated with reduced fluid dose, even when controlling for severity of illness. These findings highlight a potential bias in the resuscitation of ESRD patients that deserves more investigation.
c. Pneumonia and dialysis access-related infections remained the leading sources of identified infections in the ESRD septic shock group. A quarter of our infection sources remained unidentified.
d. Hyperlactatemia was independently associated with adverse outcome, which confirms the utility of lactate as an important risk-stratification tool in infected ESRD patients.

4. How is patient care impacted?

The difference in early management of ESRD septic shock patients should prompt scrutiny and reconsideration of the initial care of these patients. Lactate is an important risk-stratification tool to identify mortality risk in infected ESRD patients.