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Effect of Fluid Resuscitation in Patients with ESRD and Sepsis or Septic Shock: An Integrative Review

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Currently, an estimated 1.5 million individuals are diagnosed with sepsis in the United States annually (CDC, 2020). Sepsis is a life-threatening organ dysfunction that is caused by body dysregulation as a response to infection (Rhodes et al., 2016). These infections are usually caused by a bacteria, fungus, or virus with the most common infections being pneumonia, abdominal infections, and kidney infections (Vaughan & Parry, 2016). Sepsis ranks as the 10th leading cause of death in the United States and is estimated to cost 20.3 billion healthcare costs annually (Abou Dagher et al., 2015; O'Brien, 2015). Sepsis accounts for almost 10% of all hospitalizations in the U.S. and remains to be one of the most expensive to treat (Rhee et al., 2017).

New evidence-based guidelines for sepsis management, developed by the Surviving Sepsis Campaign (SSC), lend hope of a comprehensive approach to early recognition and treatment (Rhodes et al., 2016; Dantes & Epstein, 2018; Makic & Bridges, 2018; Lehman & Thiessen, 2015; Nagalingam, 2018). The guidelines recommend a 30ml/kg intravenous (IV) crystalloid fluid bolus administered within the first three hours, obtaining blood cultures, both aerobic and anaerobic, measuring serum lactate levels, broad-spectrum IV antibiotic administration, and administration of vasopressors in treating hypotension and decreased organ perfusion (Vaughan & Parry, 2016; Singer et al., 2016). Initiating this treatment bundle allows clinicians to begin fluid resuscitation while obtaining more specific clinical information (Rhodes et al., 2016; Silva, Goncalves, & Sousa, 2018).

The addition of a comorbidity such as end-stage renal disease (ESRD) or chronic kidney disease (CKD) increases the prevalence and morbidity rates of sepsis by 100-300 times (Abou

Dagher, 2015; Powe et al., 1999). Abou Dagher et al. (2015), found that 11.7% of hemodialysis patients and 9.4% of patients on peritoneal dialysis have experienced at least one episode of infection in the bloodstream and have an in-hospital mortality rate of 40% and a 28 day out of hospital mortality rate of 25%.

Fluid resuscitation using a 30ml/kg IV crystalloid fluid bolus is a mainstay recommended treatment for patients diagnosed with sepsis. However, in patients with ESRD and CKD, this amount of fluid may be too much. The dilemma is these patients often present as fluid overloaded yet are hypotensive from intravascular depletion (Mcgloin, 2015; Marik et al. 2017). Fluid resuscitation in these patients is often limited because fluid overload is associated with increased mortality rates (Truong et al., 2019). The variable fluid status of patients with ESRD decreases compliance in the administration of this treatment (Truong et al., 2019; Jorgensen, 2019). Because of this, a diagnosis of sepsis may be mistreated, and patients may miss out on needed treatment methods.

Background of problem

In patients with ESRD, clinicians are tentative to initiate fluid resuscitation given the chance of negative outcomes associated with fluid overload. Given this, many ESRD patients with sepsis are severely under-resuscitated with fluids and experience a delay in receiving antibiotics (Abou Dagher et al. 2015). There is also controversy surrounding the type of fluid that should be used with patients with ESRD. The mainstay fluid for treatment is 0.9% sodium chloride solution (normal saline). Patient studies have found that this fluid could be harmful to the kidneys and should not be administered in patients with kidney disease (Rochwerg et al. 2015). This tentative treatment leads to decreased patient outcomes and slows the healing process.

The aim of this literature review is to synthesize the studies that explored fluid resuscitation in the management of ESRD patients diagnosed with sepsis. There are retrospective as well as quasi-experimental studies available for review on the treatment of sepsis and the treatment of ESRD patients diagnosed with sepsis. These articles will be analyzed, and a synthesis of research will be developed that focuses on best practice in treating ESRD patients diagnosed with sepsis or septic shock. This integrative review will help to understand the current literature on the problem and enable future research to be performed to improve overall knowledge and practice.

Methods

Aim

The aim of this literature review was to review current studies examining the use of a fluid resuscitation bolus when treating patients diagnosed with sepsis or septic shock that have a history of ESRD. A synthesis of these studies was developed to inform practitioners on the best practice in treating these patients.

Design

The integrative review methodology utilizes the Whittemore and Knafl (2005) approach to the integrative review process. Using this process, a diverse collection of articles was collected, synthesized, and presented. Proceeding through stages, articles were researched, evaluated using the Johns Hopkins Nursing Evidence-Based Practice (JHNEBP) research appraisal tool, analyzed for content and relevant themes, and discussed (Whittemore and Knafl, 2005).

Search Strategy

A comprehensive literature search was conducted using PubMed, CINAHL Plus, Medline Complete, Scopus, and Ebsco Host electronic databases. Key search terms included the terms

sepsis, septic shock, end-stage renal disease (ESRD), chronic kidney disease, fluid resuscitation, and fluid administration. Inclusion criteria for studies included (a) primary research and other integrative reviews that are peer-reviewed and focus on fluid resuscitation in patients with a history of end-stage renal disease or chronic kidney disease that have been diagnosed with sepsis or septic shock; (b) published from 2015 to 2020; (c) written in English; and (d) accessible in full text. Articles were excluded if they were: not primary research or integrative reviews focused on fluid resuscitation in patients with a history of end-stage renal disease or chronic kidney disease that have been diagnosed with sepsis or septic shock, published before 2015, not written in English, and not accessible in full text. Reference lists of relevant articles were used to identify additional articles that met the inclusion criteria. Articles were saved and categorized using Zotero reference management software.

Search Outcome

Based on the search strategy above, the initial search yielded 664 articles with duplicates removed. Of these 664 articles, 627 were excluded following a title search, leaving 37 articles to be assessed further. These 37 articles were further narrowed by reading the abstracts, leaving 15 articles to be read in their entirety. As shown in Figure 1, the full article reviews found 10 articles meeting inclusion criteria and appropriate appraisal level.

Quality appraisal

The 10 articles were analyzed using the JHNEBP research appraisal tool to justify their inclusion in the review. Two of the articles were literature reviews and were appraised as level V evidence with high-quality ratings. The remaining 8 articles were found to be non-experimental retrospective studies. They were appraised as level III evidence with 3 of the articles being of high quality and 5 of them being good quality.

Data reduction

Utilizing the framework of Whittemore & Knafl (2005), information from the articles was coded and categorized. The articles were read and coded utilizing a color-coding strategy. Information between articles relating to the same topic was coded using a specific color to later synthesize. This allowed the identification of major themes across the articles.

Results

Main themes were identified throughout the article analysis. Table 2 delineates the themes that emerge. The three themes included: Timeliness of Fluid Administration, Volume of Fluids Administered and Secondary Outcomes.

Timeliness of Fluid Administration

The evidence-based guidelines developed for the SSC recommend administering 30mL/kg of crystalloid fluids within the first three hours after recognizing the signs and symptoms of sepsis or septic shock (Rhodes et al., 2016; Dumont et al., 2016; Kleinpell, Eitken, & Schorr, 2013). This is a universal recommendation that is set for every patient. While this is the recommendation, it does not always occur in practice; various situations decrease compliance with this recommendation and cause a delay in fluid administration (Moreira & Sinert, 2020; Truong et al., 2019).

Six of the articles had data comparing timeliness of fluid administration between patients with ESRD and patients without ESRD. By analyzing the selected articles, it was found that these delays are more common in patients with ESRD. The study by Kuttab et al. (2019) found that only 18% of the patients with ESRD in their study received the 30mL/kg fluid resuscitation bolus within three hours of presentation. This is mirrored in the study by Rajdev et al. (2020a) that found that only 23.08% of patients with ESRD received >30mL/kg

of fluid resuscitation within the first 6 hours of presentation. This is compared to 60.36% of patients without ESRD receiving >30mL/kg of fluid resuscitation in that same period.

All studies that compared the timeliness of fluid administration between patients with ESRD, and those without ESRD, found disparities between the two groups. The patients with ESRD experienced a consistent delay in the administration of the recommended crystalloid fluid resuscitation bolus (Rajdev et al., 2020a; Kuttab et al., 2019; Lowe et al., 2017; Long, Koyfman, & Lee, 2017; Khan et al., 2020; Truong et al., 2019).

Volume of Fluids Administered

Like the findings on timeliness, the volume of fluids administered to patients with ESRD was also found to be lacking. Eight of the articles consistently found that patients with ESRD received a total volume of fluids that was less than the recommended amount (Rajdev et al., 2020a; Lowe et al. 2018; Khan et al., 2020; Truong et al., 2019; Long, Koyfman, & Lee, 2017; Rosa et al., 2017; Abou Dagher et al., 2015; Kuttab et al., 2019). When assessing the volume of fluids administered within six hours after patient presentation, Abou Dagher et al. (2015) found that patients with ESRD were administered an average of 0.58 liters of fluid. These findings were further investigated at the 24-hour mark following patient presentation with similar results. The patients with ESRD were administered an average of 1.27 liters of crystalloid fluid within this period. These findings are again continued in the study performed by Lowe et al. (2018) as they found that only 42% of ESRD patients with a diagnosis of sepsis were receiving 30mL/kg of crystalloid fluid within three hours. This same study found that 67% of patients without ESRD with a diagnosis of sepsis were meeting the SSC recommendation and receiving the proper amount of fluid within three hours.

In the literature reviews performed by Rosa et al. (2017) and Long et al. (2017), they found that fluid resuscitation should be performed with the same measurement and goals as patients without ESRD. They continued to find that these goals were not being met as the patients with ESRD were being under-resuscitated due to physician decision. While patients without ESRD were more commonly administered the recommended amount of fluids, patients with ESRD were not due to fear of fluid volume overload and pulmonary complications. Truong et al. (2019) found that providers are making individualized decisions regarding fluid resuscitation based on specific patient characteristics, such as a diagnosis of ESRD. For reasons such as these, it was found that patients with ESRD were not receiving the recommended amount of fluids and were often found to be hypovolemic with increased periods of hypotension (Truong et al., 2019; Abou Dagher et al., 2015; Rajdev et al., 2020a).

Secondary Outcomes

The third theme addresses the secondary outcomes of fluid resuscitation. The secondary outcomes of fluid resuscitation were attributed to several factors and are described in four subthemes: In-hospital Mortality, ICU LOS, Mechanical Ventilation Rates, and Need for Urgent Dialysis. Seven of the selected articles addressed at least one of the secondary outcomes.

In-hospital Mortality

Mortality rates were addressed in six articles. Four of the articles found that there was no significant difference in mortality rates between patients with ESRD that received 30mL/kg of fluids versus patients that did not (Khan et al., 2020; Neyra et al., 2017; Rajdev et al., 2020b; Truong et al., 2019). In addition to these findings, two articles found that patients with ESRD who received the recommended amount of fluids experienced decreased mortality

rates when compared to those who did not (Kuttab et al., 2019; Rajdev et al., 2020a). These results show that the administration of a 30mL/kg fluid resuscitation bolus to patients with ESRD did not increase the overall in-hospital mortality, and in some cases, led to decreased mortality rates.

ICU LOS

ICU LOS was assessed in four articles. Like the mortality rate findings, the administration of a 30mL/kg fluid resuscitation bolus to patients with ESRD was not correlated with increased ICU LOS. Three of the articles found no significant difference between those who received the recommended amount of fluids and those who did not (Lowe et al., 2017; Rajdev et al., 2020a; Rajdev et al., 2020b). Kuttab et al., (2019) had findings like their findings on mortality rate. They found that patients who received the recommended amount of fluids experienced a decreased ICU LOS.

Mechanical Ventilation

Five of the articles discussed findings related to rates of mechanical ventilation. Overall, the findings found that the administration of a 30mL/kg fluid resuscitation bolus to patients with ESRD did not increase the rates of mechanical ventilation. In four of the studies, no significant difference in ventilation rates was found between patients that received the fluids and patients that did not (Khan et al., 2020; Lowe et al., 2017; Rajdev et al., 2020a; Rajdev et al., 2020b). Once again similar to other findings, Kuttab et al. (2019) found that the administration of the recommended amount of fluids was associated with decreased rates of mechanical ventilation in patients with ESRD.

Need for Urgent Dialysis

Five of the articles discussed findings related to patients with ESRD requiring urgent dialysis as a result of fluid overload. Fluid overload is a leading concern that physicians have regarding patients with ESRD. Given the decreased kidney function, patients with ESRD receiving increased volumes of fluid over an extended period have been found to have an increased need for urgent dialysis and experienced negative patient outcomes (Neyra et al., 2017). While fluid administration over an extended period of time was correlated with an increased need fur urgent dialysis, the five articles found no significant difference in rates of urgent dialysis in patients with ESRD who received a 30mL/kg fluid resuscitation bolus within six hours of presentation compared to those who did not (Khan et al., 2020; Kuttab et al., 2019; Neyra et al., 2017; Rajdev et al., 2020a; Rajdev et al., 2020b). These findings suggest that patients with ESRD presenting with sepsis or septic shock are often hypovolemic and can tolerate the increased fluid volumes with no significant differences in negative outcomes.

Discussion

Strengths and limitations

Given the limited research performed on this specific topic, this integrative review has strength in that it synthesizes current and relevant studies. All studies were performed within the past five years and discussed information pertinent to this topic. Limitations include sample size, study design, and limited ways to limit confounding variables. The studies identified contained non-experimental, retrospective studies and other literature reviews. Given the variables being studied, nothing was being manipulated leaving the findings being observational. While many of the studies expressed limitations in sample size, study design,

and confounding variables, they were included because of the limited research that has currently been performed on this patient population.

Implications

These studies shed light on the treatment of patients with ESRD with a diagnosis of sepsis or septic shock. As discussed above, the recommended treatment guidelines for sepsis and septic shock do not vary based on patient-specific characteristics. It has been found that patients with ESRD have consistently been under resuscitated due to physician hesitance to initiate aggressive fluid resuscitation in a timely manner (Rajdev et al., 2020a; Lowe et al., 2018; Khan et al., 2020; Truong et al., 2019; Long, Koyfman, & Lee, 2017; Rosa et al., 2017; Abou Dagher et al., 2015, Kuttab et al., 2019).

The findings of this integrative review indicate that the administration of a 30mL/kg fluid resuscitation bolus to patients with ESRD within six hours of presentation is not harmful when treating sepsis or septic shock. The findings also suggest that this fluid resuscitation could improve patient outcomes given some findings suggesting decreased mortality rates, ICU LOS, and rates of mechanical ventilation.

When analyzing articles for theme 1: Timeliness of Fluid Administration,

it was consistently found that patients with ESRD and a diagnosis of sepsis experience decreased timeliness of fluid administration. This data shows that there is area for improvement in meeting compliance with the SSC guidelines of administering the fluids within three hours of patient presentation (Rhodes et al., 2016).

Theme 2: Volume of Fluids Administered, also showed that patients with ESRD also received lower volumes of fluids when compared to patients without ESRD. This again shows a decreased compliance with the SSC guidelines. While the reasons behind this are not

explicitly stated, the studies do suggest that it is safe for these patients to receive aggressive fluid therapy and receive the 30mL/kg fluid resuscitation bolus.

Lastly, Theme 3: Secondary Outcomes assessed, provide data promoting the safety of fluid administration in these patients. Overall, the studies found no significant differences in mortality rates, ICU LOS, rates of mechanical ventilation, and rates of urgent dialysis. These findings suggest that the risk of fluid overload commonly associated with patients with ESRD is minimal and that fluid resuscitation should continue in the same manner and with the same goals as when treating patients without ESRD (Rosa et al., 2017).

Conclusion

The use of aggressive fluid therapy in patients with ESRD has been found to be controversial. Providers are having to choose between the risk of aggressive fluid therapy and the risk of worsening sepsis or septic shock. Having the comorbidity of ESRD regularly changes treatment plans as evidenced by the above studies. The importance of these studies is that it can influence the treatment plans of an entire group of people. While the number of included articles was small, they included findings that can help guide the treatment of patients with ESRD presenting with sepsis or septic shock. This information can help guide the clinical decision making of not only physicians, but also that of acute care nurse practitioners and advanced practice registered nurses (APRNs).

It has also been made obvious that additional research needs to be conducted. Given the one size fits all SSC recommendation, further research needs to be performed exploring the treatment methods of patients of ESRD presenting with sepsis and septic shock. While this integrative review found themes relating to the timeliness of fluid administration, volume of fluids administered, and secondary outcomes, research needs to be performed to identify the

barriers leading to these shortcomings described. Increased research pertaining to the treatment of these patients can help millions. Studies with increased sample sizes would also increase the generalizability of the results and lead to more concrete findings.

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Figure 1 PRISMA flow diagram

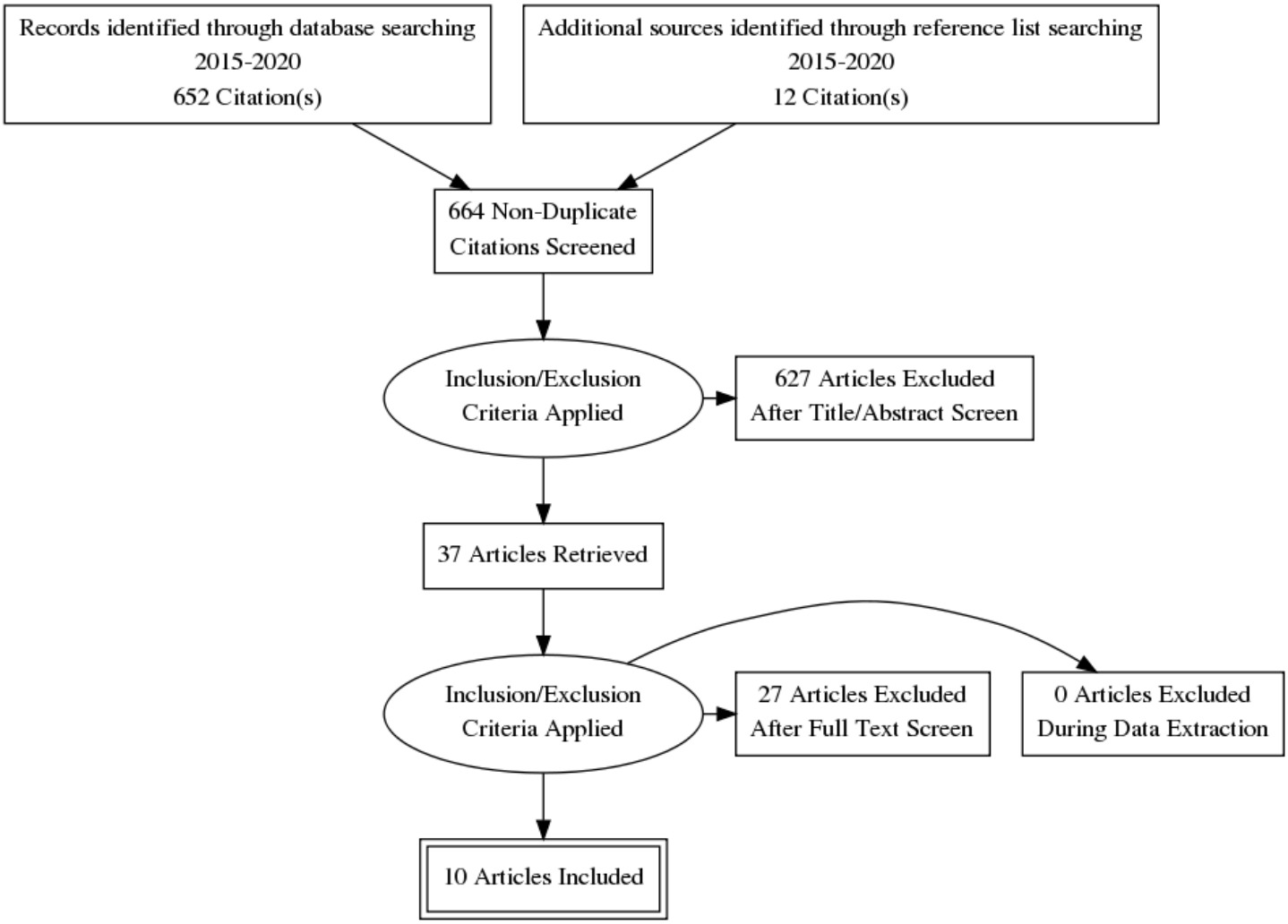

Table 1: Summary of articles

Author & Date	Research Design	Sample, Sample Size, & setting	Study findings that help answer the EBP question	Limitations	Evidence Level & Quality
Dagher, A. et al. (2015)	Retrospective chart review	90 patients who presented to a tertiary hospital with ESRD and had a discharge diagnosis of sepsis, septic shock, or bacteremia	ESRD patients are severely under resuscitated with a delay in fluid administration. The mean amount of intravenous (IV) fluids administered within the first 6 hours was 0.58±0.827 liters. These patients should be resuscitated with IV fluids as excess fluid can later be removed once sepsis has been treated.	Retrospective study Performed at a single tertiary hospital Some patients did not have repeat vital signs charted Serum lactate levels were not drawn on all septic patients Small sample size with no control group to compare mortality rates	Level III Good quality
Khan, R. et al (2020)	Retrospective cohort study	208 patients admitted to a medical ICU with a diagnosis of sepsis with a comorbidity of heart failure, ESRD, or cirrhosis	No statistically significant differences were detected in the intubation rates in patients with sepsis and heart failure, ESRD, or cirrhosis who received a 30mL/kg fluid resuscitation bolus when compared to those who were not. Suggest guideline-based early fluid resuscitation should not be omitted in patients with heart failure, ESRD, and cirrhosis for concern of respiratory failure.	Retrospective study Difficult to determine why patients did not receive the recommended volume of fluids Did not stratify the comorbidities of heart failure, ESRD, and cirrhosis according to disease severity. Only crystalloid fluids were considered when measuring the total volume administered	Level III Good quality
Kuttab, H. et al. (2019)	Retrospective cohort study	1,032 treated for sepsis in the emergency department of a tertiary care center between January 1, 2014, to April 30, 2015, and from February 1, 2016, to May 31, 2017.	Patients who did not receive a 30mL/kg fluid resuscitation bolus within 3 hours experienced a higher rate of in-hospital mortality, delayed hypotension, and increased ICU length of stay (LOS). ESRD was identified as a factor that decreased the odds of receiving a 30mL/kg fluid resuscitation bolus. 101 patients were identified as having ESRD. 19 received the recommended volume of fluid while 82 did not	Retrospective study Differences in severity of illness Study relies on accurate data from practitioners Utilize ICD codes that may differ from more recent analyses	Level III Good quality

Table 1 (continued)

Author & Date	Research Design	Sample, Sample Size, & setting	Study findings that help answer the EBP question	Limitations	Evidence Level & Quality
Long, B., Koyfman, A., & Lee, C. (2017)	Literature review	N/A	Found that patients with ESRD receive a fluid resuscitation bolus volume of 0.58L within the first 6 hours of treatment According to current guidelines, these patients should be receiving 30mL/kg in intravenous fluids. If excess fluid is identified, it can later be removed.	Limited patient-specific information provided. Literature review	Level V High quality
Lowe, K. et al. (2017)	Retrospective chart review	3,564 patients enrolled in an emergency department septic shock treatment pathway between January 2014 and May 2016. Of these 137 had a comorbidity of ESRD.	ESRD status is independently associated with lower fluid doses and compliance with the 30mL/kg fluid resuscitation goal within 3 hours. ESRD patients were 2.8 times less likely to meet the 30mL/kg fluid resuscitation goal when compared to patients without ESRD.	Retrospective study Only a small portion of the same had culture confirmation of infection Relatively small portion of ESRD patients in relation to the entire sample size	Level III High quality
Neyra, J. et al. (2017)	Retrospective cohort study	2,632 patients admitted to an urban academic medical center ICU with severe sepsis or septic shock; 1211 of which with CKD	Higher cumulative fluid balance at 72 hours of ICU admission was independently associated with hospital mortality regardless of CKD presence. Patients with CKD may have greater interstitial system adaptation to fluid overload. The compliance of the interstitial system can tolerate up to 4.5L of excess total body fluid before edema becomes evident on physical assessment. This may demonstrate chronic fluid overload adaptation.	Data pertaining to fluid administration prior to ICU admission was not available. Possible over-classification of CKD due to determination of GFV values Confounding variables could not be completely eliminated	Level III High quality

Table 1 (continued)

Author & Date	Research Design	Sample, Sample Size, & setting	Study findings that help answer the EBP question	Limitations	Evidence Level & Quality
Rajdev, K. et al. (2020a)	Retrospective case-control chart review	215 adult patients admitted to a hospital with a discharge diagnosis of sepsis or septic shock.	There was no significant difference in hospital LOS, ICU admission and LOS, need for urgent dialysis, intubation rates, and in-hospital mortality between the two case groups. There was no significant difference in secondary outcomes in the two subgroups of patients. The potential complication of fluid overload was not found between subgroup 1 and subgroup 2, with subgroup 2 receiving 43.4mL/kg of intravenous fluid within the first 6 hours.	Single-center retrospective study Only fluids were not studied, not other volume expanders or blood products APACHE scores were not recorded to measure severity of illness There was an inability to show any significant differences between the two subgroups due to small sample size	Level III Good quality
Rajdev, K. et al. (2020b)	Retrospective chart review	104 adult patients who had a hospital discharge diagnosis of sepsis, septic shock, ESRD and/or HD	There were no significant differences in duration of mechanical ventilation, in-hospital mortality, need for urgent dialysis, or hospital LOS in those who received <20mL/kg of fluids IV and those who received >20mL/kg of fluids IV. Patients who received <20mL/kg of fluids IV did not have worse outcomes than those who received aggressive fluid resuscitation.	Single-center retrospective study Small sample population Only fluids were studied, not other volume expanders or blood products Did not evaluate APACHE scores to measure severity of illness	Level III Good quality
Rosa, S., Samoni, S., Villa, G, & Ronco, C. (2017)	Literature Review	N/A	Volume resuscitation in patients diagnosed with sepsis on long term renal replacement therapy (LT-RRT) should proceed with the same volumes and goals as those not on LT-RRT.	Limited patient-specific information presented	Level V High quality
Truong, T. et al (2019)	Retrospective observational study	1,027 patients admitted to a community hospital with a diagnosis of sepsis between January 2015 and June 2016	Non-compliance with the recommended fluid resuscitation of 30mL/kg was increased in patients with ESRD with only 42.3% receiving the recommended total volume	Retrospective observational study Unmeasured confounding variables May have received lower total volumes of fluids due to lower severity of illness Unable to identify exact reasons regarding clinical decision making Identified no overall association of fluid compliance with mortality	Level III High quality

Table 2: Themes and sub-themes

Themes identified	Subthemes identified	Empirical sources
1) Timeliness of fluid administration (6)		Rajdev et al. (2020a), Kuttab et al. (2019), Lowe et al. (2017), Long, Koyfman, & Lee (2017), Khan et al. (2020), Truong et al. (2019)
2) Volume of fluids administered (8)		Rajdev et al. (2020a), Lowe et al. (2018), Khan et al. (2020), Truong et al. (2019), Long, Koyfman, & Lee (2017), Rosa et al. (2017), Abou Dagher et al. (2015), Kuttab et al. (2019).
3) Secondary outcomes (7)	a) In-hospital mortality (6)	Khan et al. (2020), Kuttab et al. (2019), Neyra et al. (2017), Rajdev et al. (2020a), Rajdev et al. (2020b), Truong et al. (2019)
	b) ICU LOS (4)	Kuttab et al. (2019), Lowe et al. (2017), Rajdev et al. (2020a), Rajdev et al. (2020b)
	c) Mechanical ventilation (5)	Khan et al. (2020), Kuttab et al. (2019), Lowe et al. (2017), Rajdev et al. (2020a), Rajdev et al. (2020b)
	d) Need for urgent dialysis (5)	Khan et al. (2020), Kuttab et al. (2019), Neyra et al. (2017) Rajdev et al. (2020a), Rajdev et al. (2020b)