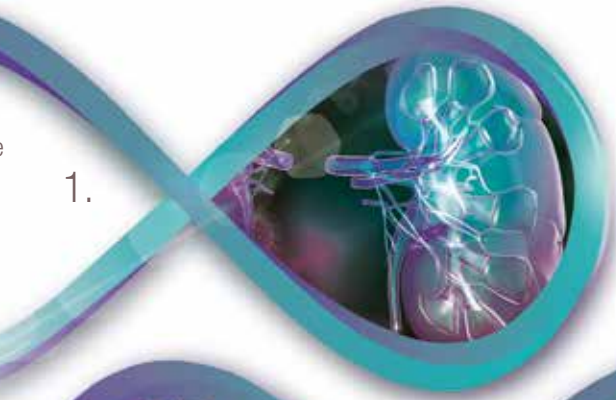
Sepsis and AKI –

Exploring their relationship and therapeutic role of extracorporeal inflammatory mediator removal

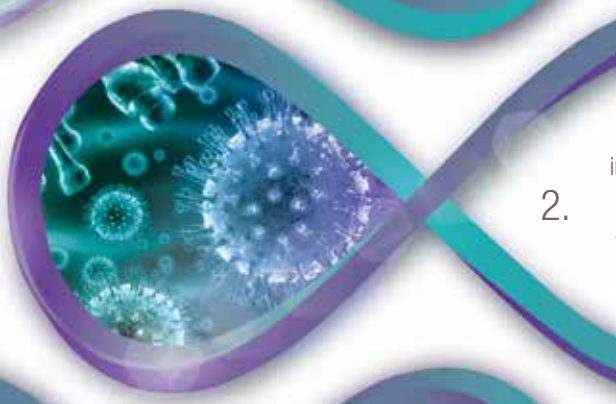
Baxter

Sepsis and AKI in critically ill patients – overview

1. Sepsis is a major contributory factor in the development of acute kidney injury (AKI),[1] and is also a potential consequence of AKI.[2,3]

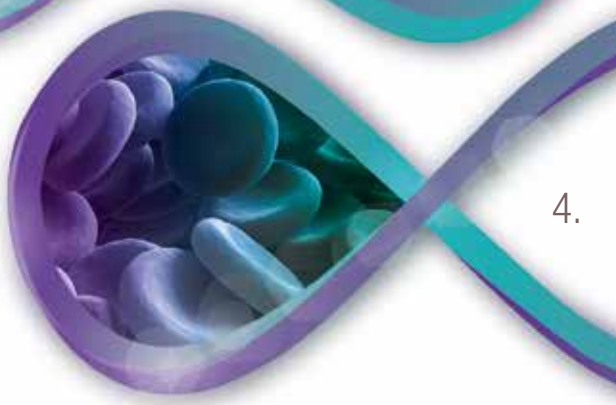


2. For patients with sepsis, elevated inflammatory mediators predict AKI severity,[4] and outcomes are poorer for septic AKI versus non-septic AKI – increased mortality and hospital length of stay[1,5,6]



3. Extracorporeal blood purification (EBP) is traditionally used in patients with sepsis and AKI to support renal function.[7,8] Evolving techniques designed to remove inflammatory mediators are being evaluated but their clinical benefits are yet to be confirmed.[7–10]

4. For patients with sepsis and AKI – who frequently have coagulation abnormalities[8,11–16] – increased bleeding risk must be considered when using anticoagulation to maintain circuit patency during extracorporeal therapies.[8]



Sepsis: what is the scale of the problem?

Sepsis

Life threatening organ dysfunction caused by a dysregulated host response to infection[17]

Septic shock

A subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality[17]

A significant and increasing global burden, affecting millions of people each year[18]

Estimates of incidence range from

149–240

cases per 100,000 population[19–21]

Reported to be **commonly associated with AKI** in the ICU[1]

Associated with high mortality and significant economic burden:

Up to

Overall **mortality** has been reported globally,[19,22] increasing to **more than 50% for patients with septic shock**[19,23]

Approximately

€1–3 k

per day

Mean **daily costs of treating patients with sepsis** have been reported to range between €1090 and €3139 in Europe[24,25]

Approximately

$20 bn

Sepsis resulted in the **highest cost of hospitalization** in the US in 2011[26]

2 X

The **cost of hospitalization for severe AKI** may be more than double that for patients who do not have AKI[27]

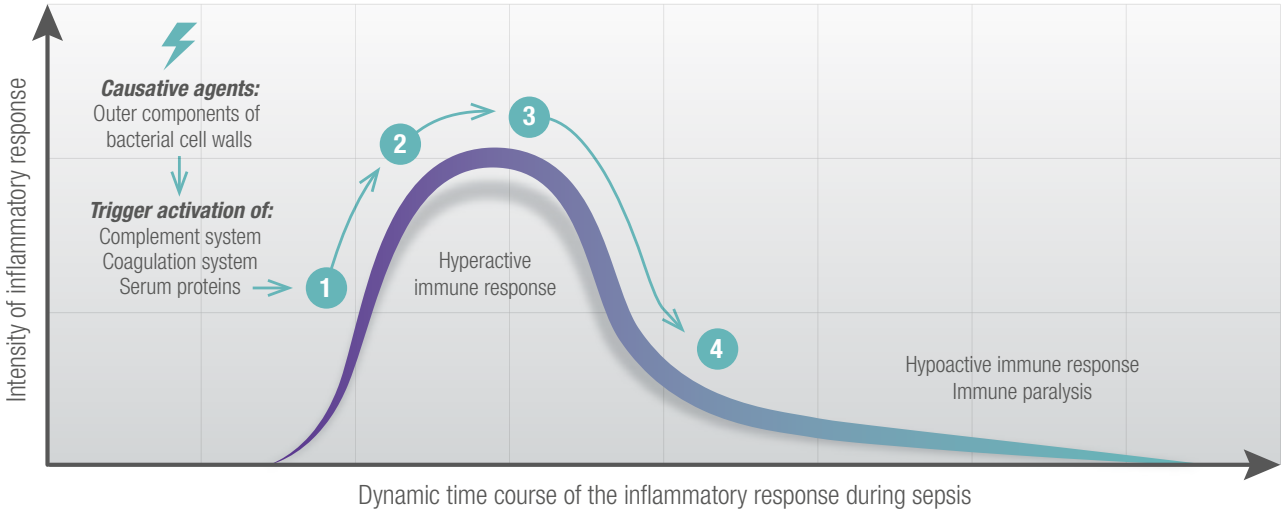
With increasing incidence and healthcare costs, **sepsis is a global medical emergency,**[18] and improving quality of care for patients with sepsis and AKI is a clinical priority for healthcare systems.[28]

How are sepsis and AKI related?

Sepsis is a major contributory factor in the development of AKI

- Sepsis is a **systemic inflammatory response**, most commonly to bacterial infection.[29]
- Early in the classically-described time course of sepsis, the production of large amounts of pro-inflammatory mediators triggers a series of reactions that can result in **direct tissue injury** and **coagulopathy**.[29–31]
- This hyperinflammatory response may culminate in a critical **reduction in tissue perfusion**, with potential for multiple organ failure, including **AKI**.[29,30]

FIGURE: Classically-described time course of sepsis leading to acute organ failure[29–31]



1
- Production of large amounts of pro-inflammatory cytokines and chemokines
- ROS production
- Enzyme release

2
- Vasodilation & capillary leakage
- Bacterial killing
- Microvascular clotting
- Tachypnea & tachycardia
- Fever
- Leukocytosis
- Peripheral resistance

3
- Edema
- Critical reduction in tissue perfusion culminating in tissue damage and organ failure

4
- Leukocytopenia
- Shutdown of neutrophil & phagocytic cell function
- Susceptibility to infection

ROS, reactive oxygen species.
Adapted by permission from Macmillan Publishers Ltd: Riedemann NC, et al. Novel strategies for the treatment of sepsis. Nature Medicine; 9:517–24, Copyright 2003.[30]

Between approximately 12% and 64% of patients with sepsis may develop AKI[1,3,32–34]

12% of intensive care unit (ICU) patients with AKI from emerging countries (n = 429) and 27% from developed countries (n = 316) had **sepsis as a cause of AKI** in a prospective observational study[32]

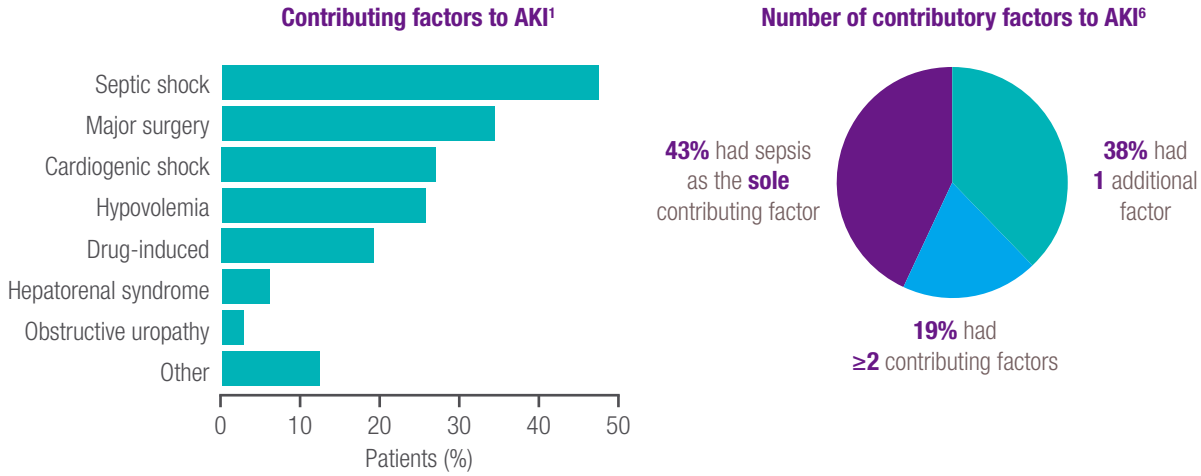
28% of critically ill patients with AKI (n = 611) met septic criteria **prior to being diagnosed with AKI** in a multicenter observational study[3]

48% of ICU patients with AKI (n = 1738) **had sepsis as a contributing factor** in a prospective, multinational, observational study[1]

61% of adults admitted to ICU (n = 390) **developed AKI after onset of septic shock** in a retrospective, observational, cohort study[33]

64% of **adults with septic shock** (n = 4532) **developed AKI within 24 hours** after onset of hypotension in a retrospective, multinational, cohort study[34]

FIGURE: Septic shock – a contributing factor for the development of AKI in 48% of ICU patients and the sole contributing factor in 43% of patients[1,6]



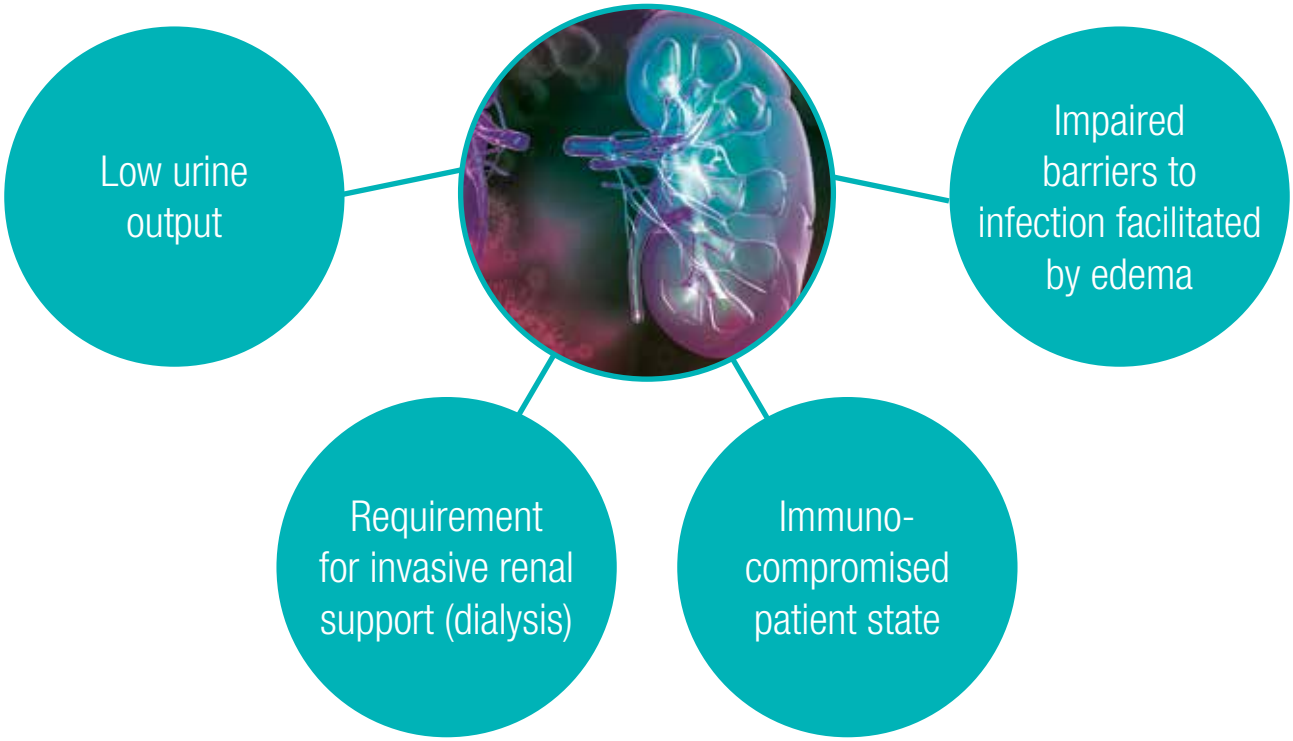
Prospective observational study: The prevalence and etiology of AKI among ICU patients (n = 29,269 in total; n = 1738 with AKI) from 54 hospitals in 23 countries were assessed.
AKI, acute kidney injury; ICU, intensive care unit.

- For patients with sepsis, the effects of the systemic pro-inflammatory response and coagulopathy may culminate in a **critical reduction in tissue perfusion** with potential for AKI and death.[29,30]
- As observed among ICU patients, even when other factors such as major surgery and cardiogenic shock are considered, **septic shock is an important contributory factor** in the development of AKI.[1,6]

Patients with AKI are at risk of developing sepsis

- AKI is characterized by a rapid reduction in renal excretory function, which leads to an accumulation of waste products and other toxic compounds in the blood.[8,35]
- While sepsis is a major contributory factor in the development of AKI, the milieu created by AKI may conversely increase the risk of sepsis.[3]

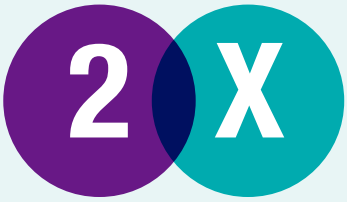
While the precise mechanism by which AKI predisposes patients to sepsis is unclear, a number of contributory factors may be relevant[3]



Observational studies suggest more than 1 in 5 patients with AKI may develop sepsis[2,3]

Of critically ill patients with AKI (n = 611) **developed sepsis** 5 days after AKI diagnosis in a multicenter observational study[3]

Of patients who had been diagnosed with AKI requiring dialysis (n = 2983) subsequently **developed severe sepsis** during their hospitalization in a population-based cohort study[2]



The prevalence of severe sepsis has been reported to be **two-fold greater** in hospitalized patients after diagnosis of dialysis-requiring AKI versus matched controls without AKI[2]

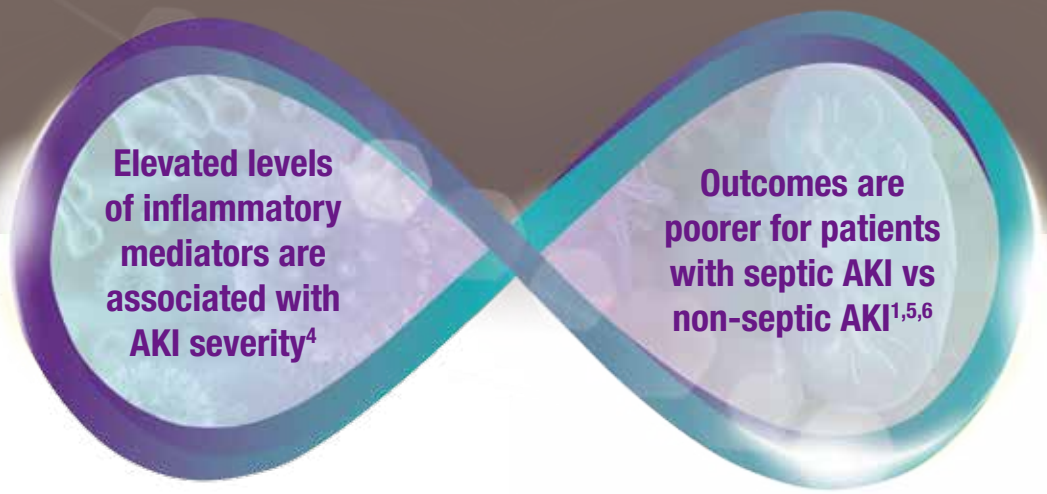
TABLE: Predictors of sepsis following AKI diagnosis may include dialysis, prolonged oliguria, and fluid overload[3]

Predictors of sepsis post-AKI diagnosis	OR	95% CI
Chronic kidney disease	0.40	0.26, 0.63
Steroid therapy	1.93	0.99, 3.74
≥3 days of oliguria	3.40	1.49, 7.76
SOFA score at AKI diagnosis (per point)	1.12	1.04, 1.20
>25% of post-AKI days with cumulative fluid balance >10% of body weight	1.66	1.05, 2.64
Dialysis	1.58	1.01, 2.45
Invasive non-surgical procedure	1.75	1.15, 2.66

Multicenter observational study: Data from critically ill patients (n = 611) with AKI were analyzed for predictors of sepsis.[3]
AKI, acute kidney injury; CI, confidence interval; OR, odds ratio; SOFA, Sequential Organ Failure Assessment.

- For patients with AKI, **multiple factors relating to patient condition and management** may increase the risk of developing sepsis, but these are not yet fully understood.[3]
- Patients with AKI requiring dialysis may be as much as **twice as likely to develop severe sepsis** compared with patients without AKI.[2]

What are the clinical outcomes for patients with sepsis and AKI?



For patients with sepsis, elevated levels of inflammatory mediators may predict AKI severity and be associated with increased mortality

Inflammatory mediators in patients with sepsis

Elevated levels of pro- and anti-inflammatory cytokines[29,30]

Endotoxemia[36,37]

Potential impact on outcomes based on observational studies

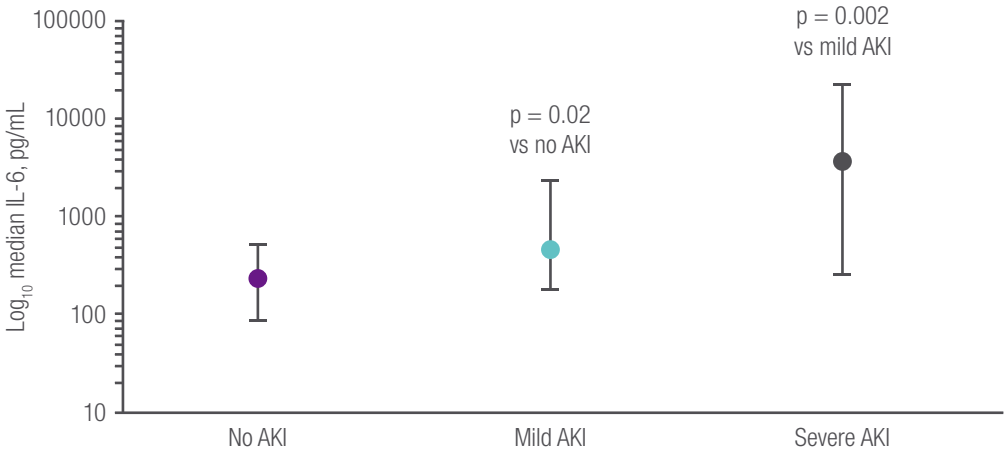
Increased risk of AKI and increased AKI severity[4]

Poorer renal recovery[38]

Increased ICU mortality[36,37]

Increased AKI severity

FIGURE: Elevated levels of IL-6 in patients with sepsis have been observed to be associated with increased AKI severity[4]



Prospective observational study: The association between systemic inflammatory parameters and AKI severity was investigated in patients with severe sepsis and septic shock (n = 176). AKI severity was based on AKIN criteria.[4,39] Data shown are highest values during first 48 hours of the study (median and 25–75th percentile).
AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; IL, interleukin.

Poorer renal recovery

TABLE: Elevated levels of IL-8 and IL-18 may be associated with poorer renal recovery in critically ill patients[38]

	OR (95% CI) for renal recovery	HR (95% CI) for time to renal recovery
Il-6	0.91 (0.81, 1.01)	0.93 (0.86, 1.01)
IL-8	0.74 (0.65, 0.85)***	0.81 (0.73, 0.89)***
IL-10	0.88 (0.77, 1.01)	0.92 (0.83, 1.03)
IL-18	0.82 (0.70, 0.96)*	0.87 (0.78, 0.97)*
MIF	0.86 (0.76, 0.97)*	0.92 (0.85, 1.01)

Prospective cohort study: The association between both plasma pro-inflammatory biomarkers (IL-6, IL-8, IL-18, and MIF) and an anti-inflammatory biomarker (IL-10) on Day 1 and renal recovery at Day 60 (defined as patient alive and independent of dialysis) was evaluated in critically ill patients (including patients with sepsis) receiving renal replacement therapy (n = 817). Multivariable regression analysis suggested statistically significant associations between higher levels of IL-8 and IL-18 with renal outcomes. Renal recovery model, OR <1 indicated association between higher biomarker concentration and likelihood of non-recovery; time-to-renal-recovery model, HR <1 indicated association between higher biomarker concentration and slower recovery. *$p < 0.05$; ***$p < 0.001$.[38]
CI, confidence interval; HR, hazard ratio; IL, interleukin; MIF, macrophage migration inhibitory factor; OR, odds ratio.
Murugan R, et al. Plasma inflammatory and apoptosis markers are associated with dialysis dependence and death among critically ill patients receiving renal replacement therapy. Nephrol Dial Transplant 2014;29:1854–64, by permission of Oxford University Press.

How do outcomes for patients with septic AKI compare with non-septic AKI?

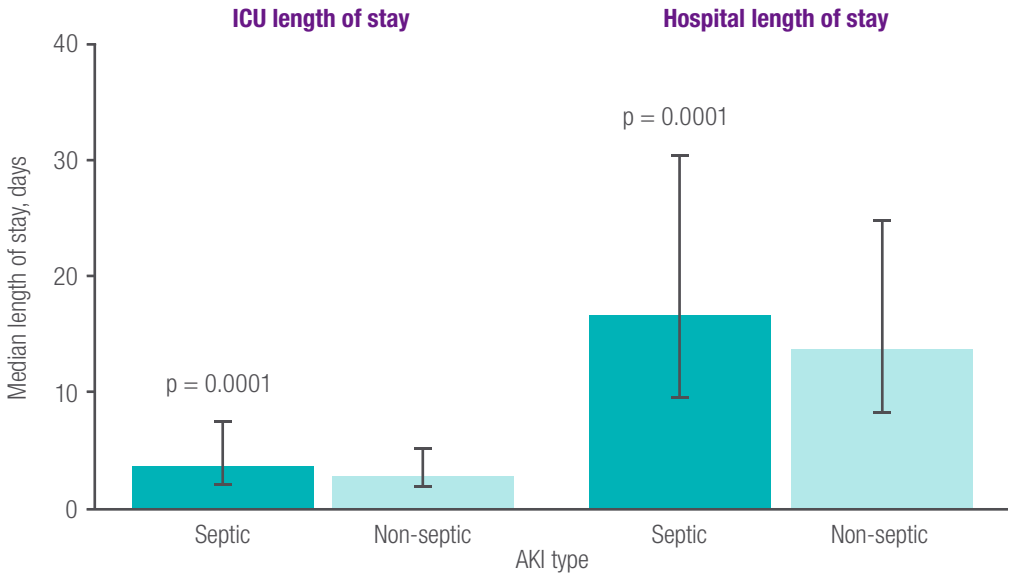
Potential consequences of sepsis for patients with AKI may include **prolonged hospital stay**[5,6] and **increased mortality**.[1,5,6]

Prolonged ICU and hospital stay[5,6]

Length of hospital stay to discharge alive has been observed to be **more than 20% longer**[5,6]

ICU length of stay has been observed to be **more than 35% longer**[5,6]

FIGURE: Length of ICU and hospital stay to discharge alive have been reported to be significantly increased in critically ill adults with septic versus non-septic AKI[5]

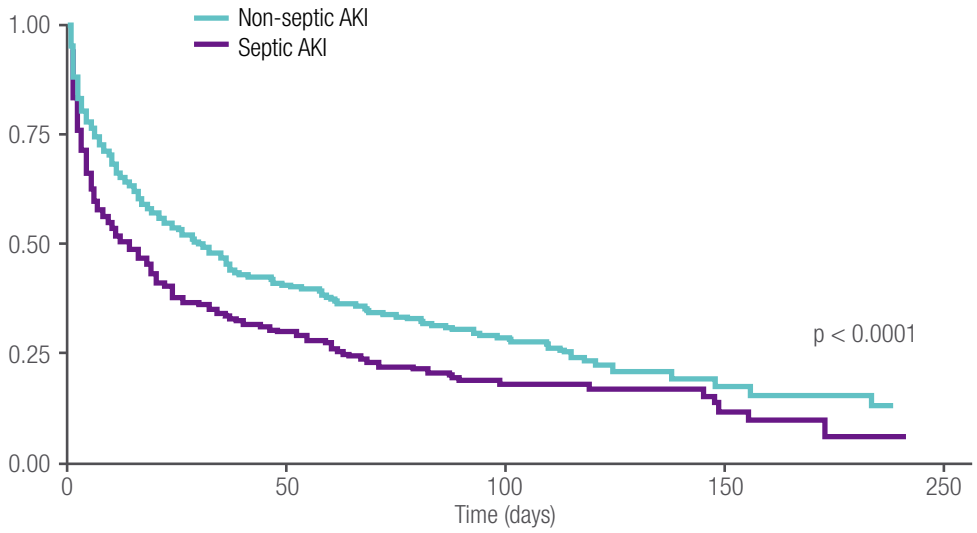


Retrospective observational study: The clinical characteristics of septic (n = 14,039) versus non-septic (n = 29,356) AKI were compared in adult ICU patients in a retrospective analysis of prospectively collected data.[5]
Error bars represent interquartile range. AKI, acute kidney injury; ICU, intensive care unit.

Greater risk of in-hospital and ICU mortality

- Compared with non-septic AKI, findings from observational studies suggest that:
  - In-hospital mortality rates may be more than **35% higher** in patients with septic AKI[5,6]
  - ICU mortality rates may be approximately **47% higher**.[5]
- Septic shock has been observed to be an **independent risk factor** for ICU mortality.[1]

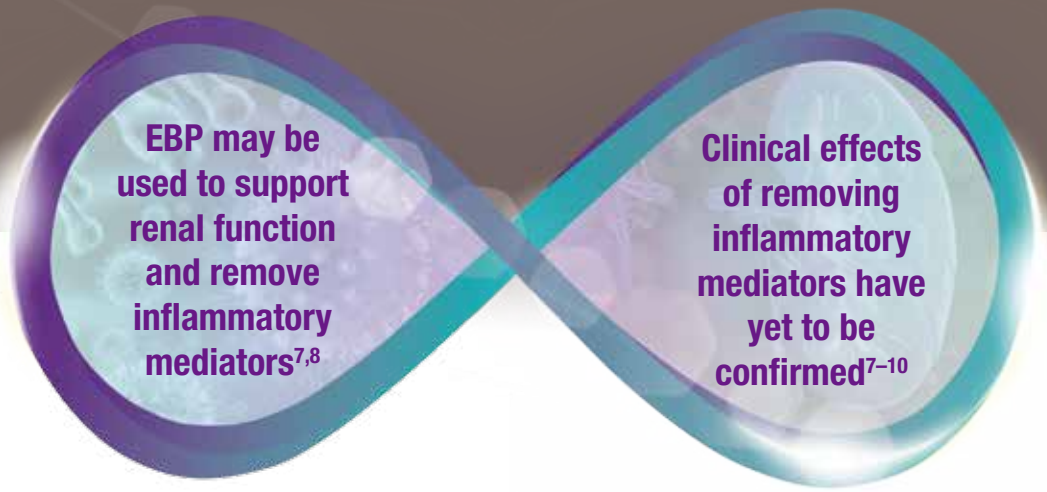
FIGURE: Survival has been observed to be significantly lower in patients with septic AKI versus non-septic AKI[6]



Retrospective observational study: The clinical characteristics of septic versus non-septic AKI were compared in critically ill patients (n = 1753) in a prospective cohort study. Kaplan-Meier survival curves demonstrated reduced survival in patients with septic vs non-septic AKI; median (range) survival was 14 (11–17) days vs 31 (26–36) days, respectively ($p < 0.001$).[6]
p value derived from log rank test.
AKI, acute kidney injury.

- For patients with sepsis, endotoxemia may be associated with increased mortality[36] and elevated levels of specific cytokines with poor renal outcomes.[38]
- In septic versus non-septic AKI patients, more than 35% greater in-hospital case fatality rates, and more than 35% longer ICU stays have been observed.[5,6]

Can EBP therapies remove inflammatory mediators from the blood?



A number of EBP techniques are available to remove undesirable substances from the blood

- EBP techniques employ three clearance mechanisms:[7,40]

Diffusion	Convection	Adsorption
Transport of small molecular weight solutes across membrane generated by concentration gradient	Passive flow of middle molecular weight solutes across membrane driven by pressure gradient	Solutes bound by variety of non-selective or selective forces

- **Traditional approach:** techniques based on **diffusion and convection** have been used to remove excess fluid and waste products in order to **support renal function** in patients with AKI, including those with sepsis and AKI.[7,8]
- **Evolving approach:** techniques based on convection and adsorption have been designed to **remove inflammatory mediators**.[7,8]

TABLE: Examples of available EBP techniques and their therapeutic aims[7,41]

Technique	Mechanisms	Support renal function	Remove inflammatory mediators
IHD	Diffusion	✔	
SLED	Diffusion	✔	
CVVHD	Diffusion	✔	
HDF	Diffusion Convection	✔	
CVVH	Convection Adsorption[a]	✔	✔[a]
CVVHDF	Diffusion Convection Adsorption[a]	✔	✔[a]
HCOM	Diffusion	✔	✔[b]
HVHF	Convection	✔	✔[b]
Hemoadsorption/ hemoperfusion	Adsorption[b]		✔
CPFA	Adsorption		✔

[a]With specific membranes that have adsorptive capacity; [b]Non-selective or selective removal of inflammatory mediators. CFPA, coupled plasma filtration adsorption; CVVHD, continuous veno-venous hemodialysis; CVVH, continuous veno-venous hemofiltration; CVVHDF, continuous veno-venous hemodiafiltration; HCOM, high cut-off membrane; HDF, intermittent hemodiafiltration; HVHF, high-volume hemofiltration; IHD, intermittent hemodialysis; SLED, sustained low efficacy dialysis.

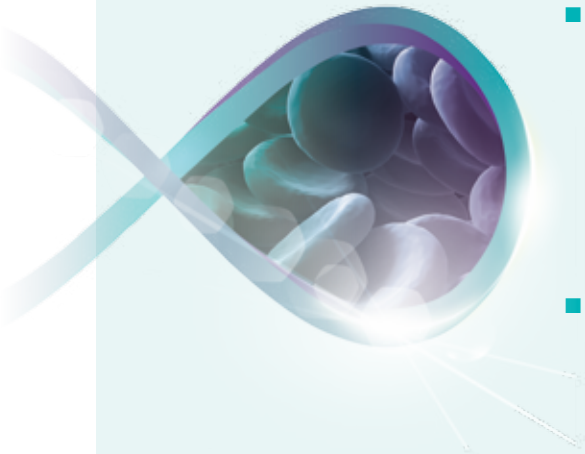
A number of available EBP techniques have emerged in recent years that have capacity to remove inflammatory mediators from the blood, with the aim of attenuating the systemic inflammatory response.[7,41]

Extracorporeal removal of inflammatory mediators – what are the potential clinical applications and considerations for patients with septic AKI?

The potential clinical benefits of removing inflammatory mediators for patients with sepsis, including sepsis complicated by AKI, are being evaluated

- A meta-analysis of randomized studies (1996–2012) has reported **inconsistent effects of EBP techniques** in patients with **sepsis**:
  - Hemoperfusion with polymyxin-B and plasma exchange were associated with decreased mortality[10]
  - Hemofiltration alone did not decrease mortality.[10]
- A more recent randomized controlled trial also found **no benefit of high volume hemofiltration alone on mortality** in patients with **septic shock and AKI**.[9]
- Continuous renal replacement therapy (CRRT) membranes with adsorptive properties have emerged in recent years.
  - Some small observational studies suggest potential for **adsorptive membranes** to improve **mortality**,[42,43] **organ function**,[44–47] **and hemodynamic stability**[45–47] in some patients with **sepsis and AKI**.
  - However, at present, **no products are licensed for this specific indication**.

The increased risk of bleeding is an important consideration for critically ill patients with sepsis and AKI undergoing any EBP therapies where anticoagulation is required to maintain circuit patency



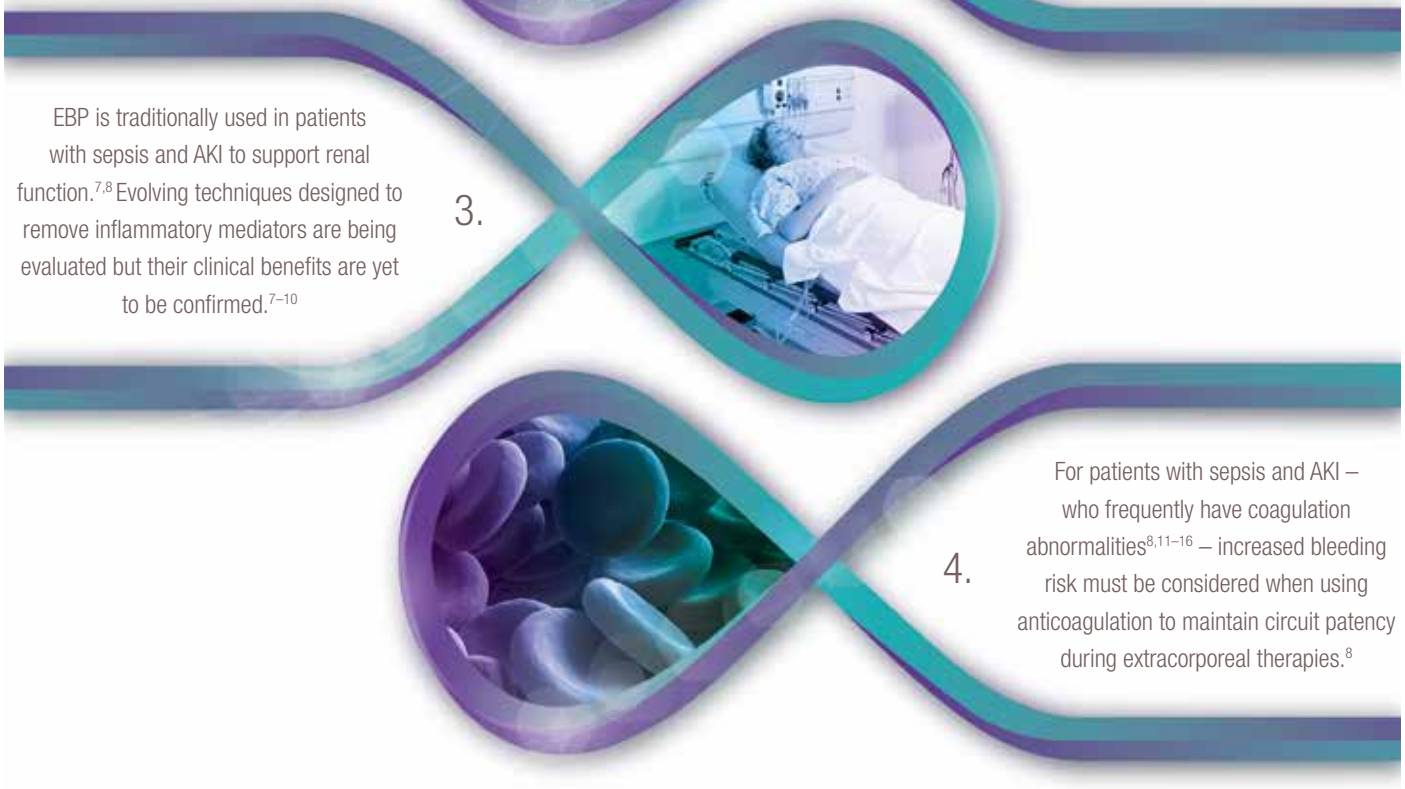
- **Most extracorporeal circuits require anticoagulation to prevent clotting:**[8,41]
  - Susceptibility to clotting arises from contact between blood and the foreign surfaces of the circuit[41]
  - For patients, circuit clotting results in blood loss and reduced dose delivery.[8,48]
- **Coagulation abnormalities are common among the critically ill** and present a **challenge for systemic anticoagulation** therapy during EBP:
  - **Prolonged coagulation** times occur in **14–28% of ICU patients**[11,12]
  - **Low levels of coagulation inhibitors** have been observed in **90% of patients with sepsis**[11,13]
  - **Thrombocytopenia** occurs in more than **40% of critically ill patients**[14–16] and there is a correlation between **sepsis severity** and **thrombocytopenia**.[11]
- The emergence of **CRRT membranes with added properties designed to reduce thrombogenicity** at a local level[44] warrant further investigation.

Sepsis and AKI in critically ill patients

1. Sepsis is a major contributory factor in the development of AKI,[1] and is also a potential consequence of AKI.[2,3]

2. For patients with sepsis, elevated inflammatory mediators predict AKI severity,[4] and outcomes are poorer for septic AKI versus non-septic AKI – increased mortality and hospital length of stay[1,5,6]

3. EBP is traditionally used in patients with sepsis and AKI to support renal function.[7,8] Evolving techniques designed to remove inflammatory mediators are being evaluated but their clinical benefits are yet to be confirmed.[7–10]



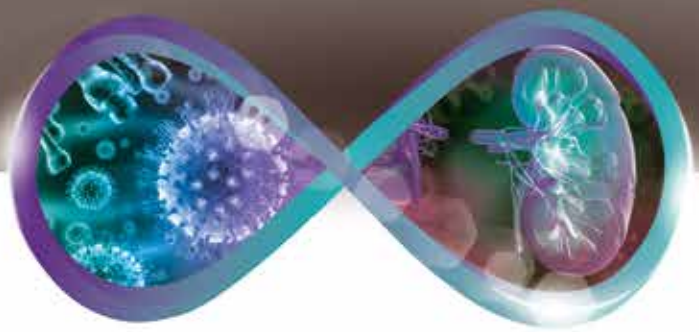
4. For patients with sepsis and AKI – who frequently have coagulation abnormalities[8,11–16] – increased bleeding risk must be considered when using anticoagulation to maintain circuit patency during extracorporeal therapies.[8]

References

1. Uchino S, et al. JAMA 2005;294:813–8.
2. Lai TS, et al. Crit Care 2013;17:R231.
3. Mehta RL, et al. Intensive Care Med 2011;37:241–8.
4. Payen D, et al. PLoS One 2012;7:e35838.
5. Bagshaw SM, et al. Crit Care 2008;12:R47.
6. Bagshaw SM, et al. Clin J Am Soc Nephrol 2007;2:431–9.
7. Panagiotou A, et al. J Intensive Care Med 2013;28:281–95.
8. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. Kidney Int, Suppl 2012;2:1–138.
9. Joannes-Boyau O, et al. Intensive Care Med 2013;39:1535–46.
10. Zhou F, et al. Crit Care Med 2013;41:2209–20.
11. Levi M, Opal SM. Critical Care 2006;10:222.
12. MacLeod JB, et al. J Trauma 2003;55:39–44.
13. Bernard GR, et al. N Engl J Med 2001;344:699–709.
14. Venkata C, et al. J Intensive Care 2013;1:9.
15. Strauss R, et al. Crit Care Med 2002;30:1765–71.
16. Vanderschueren S, et al. Crit Care Med 2000;28:1871–6.
17. Singer M, et al. JAMA 2016;315:801–10.
18. World Sepsis Day fact sheet 1.4, 2013. Available at: https://bcpsqc.ca//documents/2013/09/2014_WSD_FactSheet_English.pdf.
19. Jawad I, et al. J Global Health 2012;2:010404.
20. Flaatten H. Critical Care 2004;8:R180–4.
21. Martin GS, et al. N Engl J Med 2003;348:1546–54.
22. Vincent JL, et al. Lancet Respir Med 2014;2:380–6.
23. Vincent JL, et al. Crit Care Med 2006;34:344–53.
24. Moerer O, et al. Crit Care 2007;11:R69.
25. Jacobson S, et al. Acta Anaesthesiol Scand 2004;48:960–7.
26. Torio CMA, Andrews RMA. National inpatient hospital costs: the most expensive conditions by payer, 2011. HCUP statistical brief #160. Agency for Healthcare Research and Quality, Rockville, MD., 2013. Available at: https://www.hcup-us.ahrq.gov/reports/statbriefs/sb160.jsp.

References

27. Dasta JF, et al. Nephrol Dial Transplant 2008;23:1970–4.
28. NHS England. The forward view into action: planning for 2015/16, 2015. Available at: https://www.england.nhs.uk/wp-content/uploads/2014/12/forward-view-plning.pdf.
29. Maggio P, Carvalho C. Sepsis and septic shock, 2013. Available at: http://www.merckmanuals.com/professional/critical-care-medicine/sepsis-and-septic-shock/sepsis-and-septic-shock.
30. Riedemann NC, et al. Nat Med 2003;9:517–24.
31. Hotchkiss RS, et al. Nat Med 2009;15:496–7.
32. Bouchard J, et al. Clin J Am Soc Nephrol 2015;10:1324–31.
33. Plataki M, et al. Clin J Am Soc Nephrol 2011;6:1744–51.
34. Bagshaw SM, et al. Intensive Care Med 2009;35:871–81.
35. McMillan JI. Acute Kidney Injury (AKI), 2013. Available at: http://www.merckmanuals.com/professional/genitourinary-disorders/acute-kidney-injury/acute-kidney-injury-aki.
36. Marshall JC, et al. J Infect Dis 2004;190:527–34.
37. Adamik B, et al. Medicine 2015;94:e1085.
38. Murugan R, et al. Nephrol Dial Transplant 2014;29:1854–64.
39. Bagshaw SM, et al. Nephrol Dial Transplant 2008;23:1569–74.
40. McMillan JI. Overview of renal replacement therapy, 2014. Available at: http://www.msdmanuals.com/en-gb/professional/genitourinary-disorders/renal-replacement-therapy/overview-of-renal-replacement-therapy.
41. Lim CC, Tan HK. Proc Singapore Healthcare 2012;21:109–19.
42. Quinto BM, et al. Cytokine 2015;71:255–60.
43. Turani F, et al. Abstract presented at the 36th International Symposium on Intensive Care and Emergency Medicine, Brussels, Belgium, March 15–18, 2016. P196.
44. Shum HP, et al. Hong Kong Med J 2013;19:491–7.
45. Caravetta P, et al. Abstract presented at the 18th International Conference on Continuous Renal Replacement Therapies, San Diego, CA, United States, February 12–15, 2013: 53.
46. Candidi F, et al. Abstract presented at the 27th Annual Meeting of the European Association of Cardiothoracic Anaesthesiologists, Amsterdam, The Netherlands, May 23–25, 2012: O-56.
47. Turani F, et al. Abstract presented at the 33rd International Symposium on Intensive Care and Emergency Medicine, Brussels, Belgium, March 19–22, 2013: P63.
48. Claure-Del Granado R, et al. Clin J Am Soc Nephrol 2011;6:467–75.



Note: findings from single-arm and observational studies referred to in this brochure have not yet been confirmed in randomized controlled trials. Some data are preliminary and have not been peer reviewed.

EUMP/MG146/16-0002 May 2016

Baxter