CHAPTER 225

Vasoactive Drugs, Renal Function, and Acute Kidney Injury

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OBJECTIVES

This chapter will:

1. Discuss acute kidney injury as a frequent complication in patients with sepsis that is associated with a high risk of mortality.
2. Review our current understanding of the pathophysiology of sepsis-induced acute kidney injury, highlighting the potential role of renal tissue ischemia and hypoxia.
3. Evaluate the renal effects of commonly used vasopressor drugs to restore blood pressure in patients with sepsis, such as norepinephrine, epinephrine, vasopressin, or its analogue terlipressin, dopamine, phenylephrine, and angiotensin II, which may be promising vasopressors for use in sepsis.

Sepsis is the most common cause of acute kidney injury (AKI), accounting for nearly 50% of cases of renal failure in intensive care units (ICUs).[1,2] AKI is also an independent risk factor for death in patients with sepsis, with a mortality rate of up to 50% to 60% depending on its severity.[1] Recent epidemiologic studies indicate that patients who survive AKI are at a greater risk of developing chronic and end-stage kidney disease in later stages of life.[3] These studies demonstrate that all severities of AKI predispose individuals to short- and long-term organ dysfunction, morbidity, and mortality.

Conventionally, sepsis-induced AKI was considered a disease of the renal macrocirculation resulting from global renal ischemia, cellular damage, and acute tubular necrosis.[4] However, accumulating evidence from human[5,6] and experimental animal models of hyperdynamic sepsis[7,8] recently has challenged this paradigm by suggesting that AKI can develop despite maintained or even increased renal blood flow. Furthermore, histologic assessment of postmortem kidneys from patients with septic AKI reported heterogeneous tubular injury with apical vacuolization, but with an absence of tubular necrosis or even extensive apoptosis.[9,10] It is obvious that an understanding of the mechanisms causing reductions in renal function in the face of renal hyperperfusion is vital if we are to develop new therapeutic interventions and improve management of patients.

Renal tissue hypoxia is emerging as a critical mediatory factor in the pathogenesis of multiple forms of AKI arising because of stressors such as cardiothoracic surgery requiring cardiopulmonary bypass, radiocontrast administration, and sepsis.[11–13] An increase in global renal blood flow during sepsis does not preclude the possibility of redistribution of intrarenal blood flow, with some portions of the kidney receiving a more than adequate perfusion at the expense of others experiencing local tissue ischemia and hypoxia. Increased heterogeneity of perfusion in the sublingual circulation in humans, resulting from microcirculatory dysfunction, is a hallmark of sepsis and is associated with a high mortality.[14–16] However, whether heterogeneity of perfusion contributes to the development of septic AKI has received little attention. Recent experimental evidence in conscious sheep with hyperdynamic sepsis and AKI, which closely mimics the human septic phenotype, demonstrated an early onset of tissue ischemia and hypoxia selective to the renal medulla (Fig. 225.1), despite an increase in total renal blood flow and oxygen delivery.[17,18] In turn, hypoxia can lead to inflammation and oxidative stress, which can initiate a vicious cycle leading to cellular injury, further kidney injury, and reduced function.[11] Thus the development and implementation of therapeutic strategies for patients with sepsis should include consideration of their effects on intrarenal oxygenation.

Central hemodynamic support with the use of intravenous fluids and vasopressors remains the mainstay of therapy in patients with septic shock.[19] In critically ill patients, with or at risk of developing AKI, the main therapeutic goals for the use of vasopressors are to improve arterial pressure and maintain renal function. The most commonly used vasopressor drugs in patients with septic shock are norepinephrine, epinephrine, vasopressin or its longer-acting analogue terlipressin, dopamine, and phenylephrine.[19] There is also an increasing level of interest in the potential of angiotensin II as an effective adjunctive therapy for patients with catecholamine-refractory septic shock.[20] Now that we appreciate the harmful effects of renal tissue hypoxia in the pathogenesis of septic AKI, it is imperative to understand how restoring renal function with vasopressors affects regional kidney perfusion and oxygenation.

VASOPRESSOR DRUGS

Norepinephrine

Norepinephrine is the first-choice vasopressor used clinically to restore blood pressure and renal function in patients with septic shock.[19] Norepinephrine is a potent α-adrenergic receptor agonist with low affinity for β-adrenergic receptors.[21,22] Norepinephrine increases arterial pressure by α-adrenergic receptor-mediated vasoconstriction, with a small β-adrenergic receptor-mediated increase in stroke volume, and thus cardiac output.[21,22] The use of norepinephrine in the treatment of septic AKI has been the subject of ongoing debates resulting from the fear of it causing further deterioration in renal function due to renal ischemia.[21–23] Nevertheless, in patients with sepsis norepinephrine therapy has been shown to consistently reverse hypotension and transiently improve renal function,

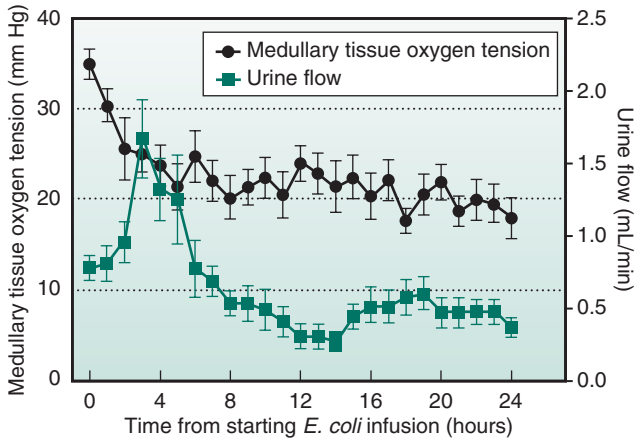

FIGURE 225.1 Time course of changes in medullary tissue oxygen tension and urine flow during the development of septic acute kidney injury in conscious sheep. Each point is the between-animal mean ± SEM of 60-minute averages (n = 13). (Figure modified from Lankadeva et al. *Kidney Int.* 2016;90[1]:100–108.)

as assessed through estimated glomerular filtration rate, with fewer adverse effects than dopamine, vasopressin, epinephrine, and phenylephrine.[24–27] These findings, among others, have provided the clinical basis for the administration of norepinephrine as the first line of therapy for patients with septic shock.

It is now becoming increasingly evident from clinically relevant animal models of sepsis that a preservation of global kidney blood flow and oxygen delivery does not preclude the possibility of localized tissue ischemia and hypoxia.[7,17,18] Indeed, restoration of arterial blood pressure with a clinically relevant dose of norepinephrine (0.4–0.8 μg/kg/min) was shown to exacerbate the underlying renal medullary ischemia and hypoxia in conscious sheep with established septic AKI (Fig. 225.2).[17] Importantly, these effects of norepinephrine occurred in face of preserved global kidney blood flow and oxygen delivery and without measurable changes in whole-kidney oxygen consumption.[17] These findings are not surprising considering the evidence that restoration of systemic hemodynamics with norepinephrine does not improve microcirculatory flow abnormalities in patients with septic shock.[15,16] Experimental evidence in a porcine model of septic shock further demonstrated that resuscitation with norepinephrine has the potential to worsen microcirculatory flow abnormalities in the mesenteric circulation.[28]

The long-term consequences for kidney health of this exaggerated renal medullary ischemia and hypoxia induced by norepinephrine in sepsis are unknown and merit further investigation. However, there is evidence from a meta-analysis that most survivors of septic AKI are predisposed to a greater risk of developing chronic kidney disease in later stages of life.[3] This provides the impetus for using caution when using vasopressors that have the potential to worsen the underlying pathologic and reparative processes that occur during septic AKI. It is also critical to determine if other vasopressors commonly used in the ICU in the treatment of septic AKI have similar effects on regional kidney oxygenation or if these effects are specific to norepinephrine. Such studies may lead to the development of therapies that restore blood pressure while preserving regional kidney oxygenation and thus renal function, which may hold the key to the better management of patients with septic AKI.

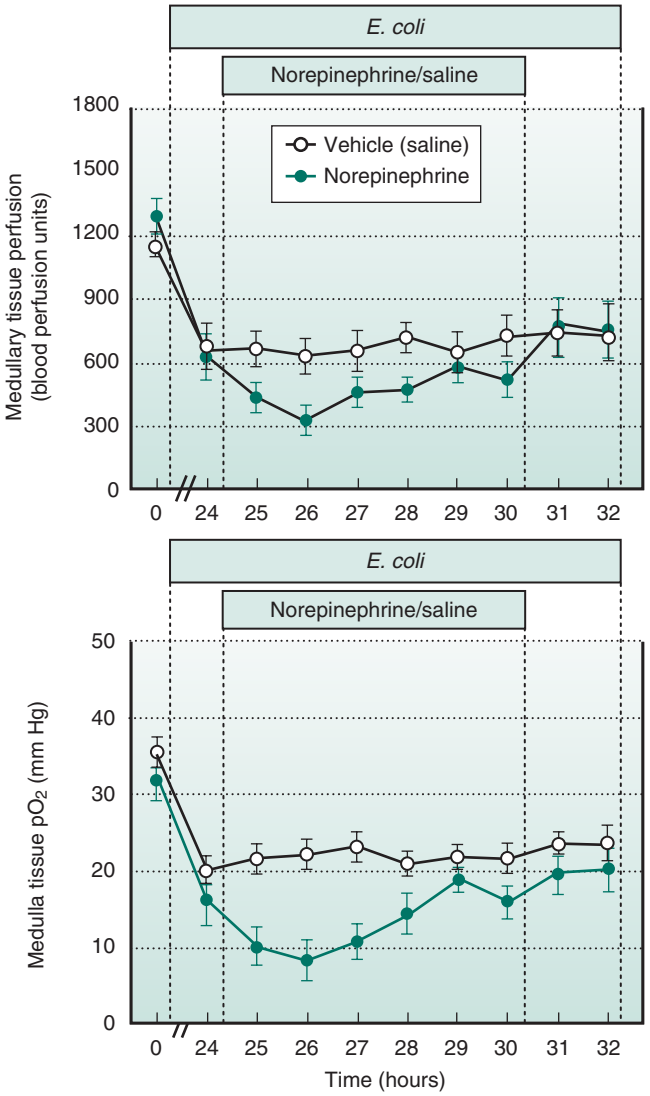

FIGURE 225.2 Renal medullary tissue perfusion and oxygen tension (pO_2) during infusion of *Escherichia coli (E. coli)* from 0 to 32 hours and subsequent treatment of norepinephrine (n = 7) or saline (n = 8) from 24 to 30 hours in conscious sheep. Time 0 is the mean of the 24th hour of the baseline period, and times 24 to 32 hours are means of 1-hour periods. Data are between-animal mean ± SEM. $*p < .05$ represents significant differences between norepinephrine and saline treatment. (Figure modified from Lankadeva et al. *Kidney Int.* 2016;90[1]:100–108.)

Epinephrine

Epinephrine is recommended as the first alternative therapy to norepinephrine to maintain arterial blood pressure in patients with sepsis.[19] Epinephrine is a potent agonist at β- and α-adrenergic receptors that increases arterial blood pressure by increasing cardiac output and systemic vascular resistance.[21,22] The main concern with the use of epinephrine in patients with sepsis is its potential to cause metabolic acidosis and reduce regional blood flow, especially in the splanchnic and renal circulation.[29–32] Randomized clinical trials comparing epinephrine to norepinephrine treatment have been unable to detect differences in the risk of overall mortality.[33] However, there appears to be a common occurrence of transient lactic acidosis, tachycardia,

and arrhythmias in patients with sepsis resuscitated with epinephrine when compared with norepinephrine.[25,31,32] In a porcine model of septic shock, treatment with epinephrine was associated with distribution of blood flow away from the mesenteric circulation, indicative of possible deleterious effects on the gut.[28]

There are limited studies investigating the renal effects of epinephrine, compared with other vasopressor drugs in patients with septic AKI. Thus most evidence on the effects of epinephrine on renal hemodynamics and function comes from experimental animal models of sepsis. In conscious sheep with hyperdynamic sepsis, restoring blood pressure with epinephrine (0.4 μg/kg/min) reduced renal blood flow and increased urine flow with no improvement in creatinine clearance.[34] These observations were similar to those observed in patients with severe hyperdynamic sepsis.[30] In another sheep model of sepsis, epinephrine was shown to have no effect on renal blood flow, but transiently reduce creatinine clearance.[35] The brief improvements in urine flow with epinephrine in sepsis therefore can be attributed to an increase in renal perfusion pressure leading to diuresis, rather than a protective effect on renal hemodynamics and regional perfusion. Whether epinephrine has any adverse outcomes on regional kidney perfusion during sepsis is currently unknown. However, given the inability of epinephrine to improve glomerular filtration rate in sepsis, the risks of using epinephrine certainly seems to outweigh its benefits, at least in the setting of septic AKI.

Vasopressin

The current international consensus guidelines do not recommend the use of vasopressin as a single vasopressor agent for the management of patients with septic shock.[19] Instead, vasopressin is used as a second-line therapy for patients that have become unresponsive to norepinephrine or epinephrine and/or for decreasing the dosage of norepinephrine.[19] This is largely due to the evidence that at higher doses vasopressin (>0.05 IU/min) has the potential to induce myocardial, digital, and mesenteric ischemia.[19,36] Vasopressin increases arterial pressure mainly via stimulating the V_1 receptors located on the vascular smooth muscle cells to induce vasoconstriction.[36] Vasopressin also may increase blood pressure by preventing excessive opening of ATP-sensitive potassium channels in sepsis.[36] Sepsis is characterized by a transient increase in endogenous levels of vasopressin at early stages, which then is followed by a rapid reduction in prolonged shock states.[36] Therefore the potent vasopressor effects of vasopressin, even in patients with catecholamine-resistant septic shock, can be attributed to its relatively low levels in the circulation in sepsis.

In the Vasopressin and Septic Shock Trial (VASST), treatment with low-dose vasopressin (0.01–0.03 U/min) was not associated with lesser mortality than treatment with norepinephrine (5–15 μg/min).[24] However, subsequent analysis of the VASST trial revealed that vasopressin reduced the progression of renal injury and mortality rate in patients at risk of sepsis-induced AKI.[37] In accordance with these clinical observations, recent experimental studies in conscious healthy sheep reported that infusion of vasopressin preserved intrarenal perfusion and oxygenation, despite a reduction in global kidney blood flow and oxygen delivery.[38] This was in contrast to norepinephrine that resulted in dose-dependent reductions in renal cortical and medullary perfusion and oxygenation despite a preservation in global kidney blood flow and oxygen delivery.[38] These findings provide direct evidence that overall measures of renal blood flow are a poor indicator of regional kidney perfusion and oxygenation under "healthy" and "pathologic" conditions. Also considering the evidence that renal medullary hypoxia may play a critical role in the pathogenesis septic AKI,[11–13] it is feasible that vasopressors that conserve medullary oxygenation may improve or at least prevent a further decline in kidney function. In relation to sepsis, restoration of blood pressure with low-dose vasopressin (0.02 IU/min) significantly improved urine flow and creatinine clearance in sheep with AKI.[39] Moreover, results from the VASST trial reported enhanced improvement in urine flow and glomerular filtration rate with vasopressin, when compared with norepinephrine in patients.[37,40] In collation, there is evidence from clinical and experimental studies that vasopressin (<0.05 IU/min) at lower doses may offer a degree of renoprotection in the setting of sepsis-induced AKI and thus merits future investigation.

Terlipressin

Terlipressin is a synthetic analogue of vasopressin, with a greater selectivity to V_1 receptors and a longer half-life.[41] Terlipressin is the drug of choice for the treatment of hepatorenal syndrome, another pathologic condition characterized by systemic vasodilatation and renal dysfunction[42] (a similar state to septic shock). In patients with hepatorenal syndrome, treatment with terlipressin has been reported to significantly increase creatinine clearance and urine output, with no overt signs of splanchnic, myocardial, or digital ischemia.[43,44] Thus it is not surprising that terlipressin has been considered as a rescue therapy for patients with catecholamine-resistant septic shock to restore blood pressure and improve renal function.[45–47]

Because of its longer half-life, terlipressin often is administered by intermittent high-dose bolus infusion (1 mg every 4-6 hours).[41] However, administration of high-dose bolus infusions of terlipressin can lead to excessive vasoconstriction and reductions in cardiac output and oxygen delivery to vital organs, thereby limiting its clinical applicability in septic shock.[48,49] In conscious sheep with hyperdynamic sepsis, restoring blood pressure with terlipressin (1 mg; bolus) improved renal function but resulted in reductions in cardiac output (approximately 30%), mesenteric blood flow (approximately 40%), and coronary blood flow (approximately 20%).[48] In contrast, continuous low-dose infusion of terlipressin (2 mg over 24 hours) was shown to restore blood pressure and prevent unfavorable effects on cardiac output, compared with septic sheep treated with intermittent high-dose bolus infusions of terlipressin (1 mg every 6 hours).[50] A randomized pilot study demonstrated that administration of a continuous infusion of low-dose terlipressin (1.3 μg/kg/hr) as a first-line therapy for patients with septic shock was effective at maintaining blood pressure and reducing norepinephrine requirements.[51] Further experimental studies are necessary to evaluate the effects of high-dose bolus and low-dose continuous infusions of terlipressin on intrarenal perfusion and oxygenation in clinically relevant models of septic AKI. Such studies could inform major clinical trials in the future to investigate whether terlipressin improves health outcomes in patients with septic AKI compared with standard therapy.

Dopamine

The existing international consensus guidelines for management of septic shock only recommends the use of

dopamine in patients with a low risk of tachyarrhythmias and absolute and relative bradycardia.[19] Dopamine acts on dopaminergic receptors and α-adrenergic and β-adrenergic receptors. At low doses, dopamine (<5 μg/kg/min) is more selective for the dopaminergic (D_1 and D_2) receptors, leading to vasodilation in the renal and mesenteric circulation.[22] At higher doses, dopamine (>10 μg/kg/min) predominantly acts on α-adrenergic receptors to induce vasoconstriction and increase arterial blood pressure.[22] The use of dopamine to resuscitate patients with septic shock has fallen out of favor because of the high risk of tachycardia and cardiac arrhythmia.[21,22] Several clinical trials have provided evidence that norepinephrine is more effective than dopamine in improving systemic hemodynamics and kidney function and enhancing survival in patients with septic shock.[21,22]

Traditionally, it was believed that low-dose dopamine (2 μg/kg/min) was renoprotective in critically ill patients. However, there is now convincing evidence that low-dose dopamine has no beneficial effects on reducing the risk of AKI or the need for renal replacement therapy in patients but may worsen myocardial and visceral perfusion.[52,53] Even at these lower doses, dopamine has been shown to worsen renal perfusion in patients with acute renal failure.[54] It is also feasible that the natriuretic effects of dopamine, mediated at the level of the proximal tubule, would increase solute delivery to the loop of Henle and so increase medullary oxygen consumption and thus exacerbate the underlying medullary hypoxia in the setting of AKI. Therefore the use dopamine in the treatment of patients with sepsis-induced AKI should be abandoned.[19]

Phenylephrine

Phenylephrine is a selective α_1-adrenergic receptor agonist that increases blood pressure mainly by increasing systemic vascular resistance, without an associated increase in myocardial contractility.[21] Therefore phenylephrine is recommended only for patients experiencing serious arrhythmia with norepinephrine, have a high cardiac output, or as a salvage therapy.[19] Because of its high selectivity for α_1-adrenergic receptors, phenylephrine is believed to reduce perfusion to the splanchnic and renal circulation. However, a randomized clinical trial comparing norepinephrine with phenylephrine as an initial treatment was unable to detect differences in hepatosplanchnic perfusion, gastrointestinal perfusion, or cardiopulmonary performance in patients with septic shock.[55] An advantage of phenylephrine is that, unlike norepinephrine, it does not stimulate β-adrenergic receptors and so does not increase heart rate and myocardial oxygen demand in sepsis. In anesthetized pigs with peritonitis-induced septic shock, administration of norepinephrine redistributed blood flow away from the mesentery (jejunal mucosa and jejuna muscularis) to other regions of the body via β-adrenergic stimulation.[28] In contrast, treatment with phenylephrine did not impair microcirculatory blood flow in the mesentery and even improved blood flow to jejuna mucosa.[28] In accord with these findings, restoration of blood pressure with phenylephrine in ovine hyperdynamic sepsis had negligible effect on mesenteric blood flow and increased renal blood flow.[56] It is conceivable that selective α_1-adrenergic receptor agonists may be beneficial in septic shock, because they restore blood pressure without causing deleterious effects on regional tissue blood flow via β-adrenergic stimulation.

The renal effects of phenylephrine have not been elucidated fully in septic AKI. Clinical trials that used phenylephrine as a replacement therapy to norepinephrine reported reductions in creatinine clearance in patients with septic shock.[26] In contrast, administration of phenylephrine as a first-line therapy in patients with septic AKI was shown to cause similar increases in urine flow and creatinine clearance to treatment with norepinephrine.[55] Therefore the timing of phenylephrine treatment during sepsis may play a pivotal role in achieving favorable effects on kidney function. Collectively, available evidence indicates that phenylephrine does not have major adverse effects on renal and mesenteric hemodynamics and function in sepsis. The positive effects on redistribution of microcirculatory blood flow in the mesenteric circulation during phenylephrine treatment is promising, especially if these effects extend to the renal microcirculation in septic AKI. Therefore administration of phenylephrine as a first-line therapy to treat sepsis-induced AKI merits further investigation, particularly in terms of regional kidney perfusion and oxygenation.

Angiotensin II

In relation to septic shock, there is extensive evidence that excessive levels of catecholamines and their metabolites have many adverse effects.[46] These include deleterious effects on immune function and metabolic efficiency, stimulation of bacterial growth, and increased pulmonary artery pressure causing myocardial injury.[57] This hypothesis was supported by findings from a randomized clinical trial in patients with sepsis treated with norepinephrine or a combination therapy of norepinephrine with esmolol.[58] In this study, β-adrenergic blockade with esmolol significantly reduced the 28-day mortality rates (49.4%) compared with norepinephrine alone (80.5%).[58] Thus vasopressors that do not possess the harmful effects of catecholamines may be beneficial in patients with sepsis. Angiotensin II is one such vasopressor, which acts mainly via the angiotensin type I receptors to cause vasoconstriction and increase blood pressure. Angiotensin II currently is not recommended as a standard vasopressor by the international consensus guidelines for management of septic shock. However, accumulating data from experimental and clinical studies provide evidence that angiotensin II is a safe and effective vasopressor in restoring blood pressure and renal function in septic AKI.

In ovine hyperdynamic sepsis, resuscitation with angiotensin II restored blood pressure, reduced renal blood flow, normalized creatinine clearance, and increased urine flow.[59] Angiotensin II caused these renal changes without major adverse effects on blood flows to other vital organs, blood lactate, or biochemical variables.[59] In a pilot study, angiotensin II also was shown to effectively restore blood pressure and double renal function in patients with catecholamine-resistant septic shock.[20] It has been proposed that this potent renal action of angiotensin II in sepsis is due to its ability to preferentially increase resistance in the efferent compared with the afferent arteriole, thus increasing glomerular perfusion pressure and filtration rate.[60] This concept also may explain the results from the VASST trial that vasopressin, another vasoconstrictor with a preferential effect on the efferent arteriole, improved renal function more than norepinephrine.[37]

Studies using animal models of septic shock provide evidence that adrenergic vasopressors (norepinephrine and epinephrine) that have β-adrenergic receptor activity exacerbate microcirculatory abnormalities.[28] These findings have relevance to the pathophysiology of septic AKI, given that norepinephrine was shown to exacerbate the

underlying medullary ischemia and hypoxia (Fig. 225.2).[17] In contrast to norepinephrine, infusion of angiotensin II did not reduce renal cortical or medullary perfusion in "healthy" conscious sheep,[38] and further studies are required to determine the effect of angiotensin II on intrarenal perfusion and oxygenation in sepsis. Collectively, the use of vasopressors that are either highly selective to α_1-adrenergic receptors, or at least lack β-adrenergic receptor actions, may prove beneficial in the treatment of septic AKI. Therefore angiotensin II has promise as an alternative first-line therapy to norepinephrine or as an adjunctive therapy in patients with sepsis-induced AKI. A randomized, double-blinded, multicenter, Phase III clinical trial is currently underway to test the efficacy of angiotensin II in maintaining blood pressure in approximately 300 patients with catecholamine-resistant septic shock.

CONCLUSION

Currently, there is insufficient clinical evidence to support the use of one vasopressor agent over another to protect the kidney of patients with septic AKI. A major limitation in the field has been that the majority of experimental studies have relied on global measures of kidney blood flow and oxygen delivery as an accurate predictor of kidney function and health. It is evident that heterogeneity of perfusion is a hallmark of septic AKI and monitoring global kidney blood flow and oxygenation are poor predictors of abnormalities in regional perfusion and oxygenation. Thus future studies should rather focus on the renal microcirculation as a potential therapeutic target. The renal medulla appears to be particularly susceptible to ischemia and hypoxia in multiple forms of AKI, including septic shock. AKI develops within the first 24 hours of sepsis in 64% of patients.[61] There is evolving evidence that therapies to preserve renal medullary tissue perfusion and oxygenation during the early stages of sepsis may be an effective strategy to ameliorate AKI and improve management of critically ill patients.

Key Points

1. Septic acute kidney injury can develop as a result of microcirculatory dysfunction in the face of preserved or increased total renal blood flow and oxygen delivery.
2. In sepsis, heterogeneity of perfusion renders the renal medulla particularly susceptible to development of ischemia and hypoxia, which may in turn play a critical role in the pathogenesis of AKI.
3. Vasopressors (norepinephrine, epinephrine, and dopamine) that stimulate α-adrenergic and β-adrenergic receptors may exacerbate the underlying microcirculatory flow abnormalities in septic AKI.
4. Treatment with vasopressors that are highly selective for α_1-adrenergic receptors (phenylephrine) or are nonadrenergic (vasopressin, terlipressin, angiotensin II) may preserve intrarenal oxygenation and offer a safe alternative in the treatment of septic AKI.
5. Development of treatment strategies that optimize regional kidney perfusion and oxygenation may be the solution to preventing the progression of kidney injury in sepsis.

Key References

12. Evans RG, Ince C, Joles JA, et al. Haemodynamic influences on kidney oxygenation: clinical implications of integrative physiology. *Clin Exp Pharmacol Physiol*. 2013;40:106-122.
17. Lankadeva YR, Kosaka J, Evans RG, et al. Intrarenal and urinary oxygenation during norepinephrine resuscitation in ovine septic acute kidney injury. *Kidney Int*. 2016;90:100-108.
18. Calzavacca P, Evans RG, Bailey M, et al. Cortical and medullary tissue perfusion and oxygenation in experimental septic acute kidney injury. *Crit Care Med*. 2015;43:e431-e439.
37. Gordon AC, Russell JA, Walley KR, et al. The effects of vasopressin on acute kidney injury in septic shock. *Intensive Care Med*. 2010;36:83-91.
59. Wan L, Langenberg C, Bellomo R, et al. Angiotensin II in experimental hyperdynamic sepsis. *Crit Care*. 2009;13:R190.

A complete reference list can be found online at ExpertConsult.com.

References

1. Bagshaw SM, Uchino S, Bellomo R, et al. Septic acute kidney injury in critically ill patients: Clinical characteristics and outcomes. *Clin J Am Soc Nephrol*. 2007;2:431-439.
2. Bagshaw SM, George C, Bellomo R, et al. Early acute kidney injury and sepsis: a multicentre evaluation. *Crit Care*. 2008;12:R47.
3. Coca SG, Yusuf B, Shlipak MG, et al. Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. *A J Kidney Dis*. 2009;53:961-973.
4. Schrier RW, Wang W. Acute renal failure and sepsis. *N Engl J Med*. 2004;351:159-169.
5. Rector F, Goyal S, Rosenberg I, et al. Sepsis: a mechanism for vasodilation in the kidney. *Ann Surg*. 1973;178:222-226.
6. Brenner M, Schaer GL, Mallory DL, et al. Detection of renal blood flow abnormalities in septic and critically ill patients using a newly designed indwelling thermodilution renal vein catheter. *Chest*. 1990;98:170-179.
7. Chvojka J, Sykora R, Krouzecky A, et al. Renal haemodynamic, microcirculatory, metabolic and histopathological responses to peritonitis-induced septic shock in pigs. *Crit Care*. 2008;12:R164.
8. Langenberg C, Wan L, Egi M, et al. Renal blood flow in experimental septic acute renal failure. *Kidney Int*. 2006;69:1996-2002.
9. Takasu O, Gaut JP, Watanabe E, et al. Mechanisms of cardiac and renal dysfunction in patients dying of sepsis. *Am J Respir Crit Care Med*. 2013;187:509-517.
10. Lerolle N, Nochy D, Guérot E, et al. Histopathology of septic shock induced acute kidney injury: apoptosis and leukocytic infiltration. *Intensive Care Med*. 2010;36:471-478.
11. Heyman SN, Evans RG, Rosen S, et al. Cellular adaptive changes in AKI: mitigating renal hypoxic injury. *Nephrol Dial Transplant*. 2012;27:1721-1728.
12. Evans RG, Ince C, Joles JA, et al. Haemodynamic influences on kidney oxygenation: clinical implications of integrative physiology. *Clin Exp Pharmacol Physiol*. 2013;40:106-122.
13. Brezis M, Rosen S. Hypoxia of the renal medulla — its implications for disease. *N Engl J Med*. 1995;332:647-655.
14. Kanoore Edul V, Dubin A, Ince C. The microcirculation as a therapeutic target in the treatment of sepsis and shock. *Semin Respir Crit Care Med*. 2011;32:558-568.
15. Dubin A, Pozo MO, Casabella CA, et al. Increasing arterial blood pressure with norepinephrine does not improve microcirculatory blood flow: a prospective study. *Crit Care*. 2009;13:R92.
16. De Backer D, Donadello K, Sakr Y, et al. Microcirculatory alterations in patients with severe sepsis: impact of time of assessment and relationship with outcome*. *Crit Care Med*. 2013;41:791-799.
17. Lankadeva YR, Kosaka J, Evans RG, et al. Intrarenal and urinary oxygenation during norepinephrine resuscitation in ovine septic acute kidney injury. *Kidney Int*. 2016;90:100-108.
18. Calzavacca P, Evans RG, Bailey M, et al. Cortical and medullary tissue perfusion and oxygenation in experimental septic acute kidney injury. *Crit Care Med*. 2015;43:e431-e439.
19. Dellinger RP, Levy M, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med*. 2013;39:165-228.
20. Chawla LS, Busse L, Brasha-Mitchell E, et al. Intravenous angiotensin II for the treatment of high-output shock (ATHOS trial): a pilot study. *Crit Care*. 2014;18:534.
21. Pollard S, Edwin SB, Alaniz C. Vasopressor and inotropic management of patients with septic shock. *P T*. 2015;40:438-450.
22. Hollenberg SM. Vasopressor support in septic shock*. *Chest*. 2007;132:1678-1687.
23. Bellomo R, Wan L, May C. Vasoactive drugs and acute kidney injury. *Crit Care Med*. 2008;36:S179-S186.
24. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med*. 2008;358:877-887.
25. Myburgh JA, Higgins A, Jovanovska A, et al. A comparison of epinephrine and norepinephrine in critically ill patients. *Intensive Care Med*. 2008;34:2226-2234.
26. Morelli A, Lange M, Ertmer C, et al. Short-term effects of phenylephrine on systemic and regional hemodynamics in patients with septic shock: a crossover pilot study. *Shock*. 2008;29:446-451.
27. De Backer D, Aldecoa C, Njimi H, et al. Dopamine versus norepinephrine in the treatment of septic shock: A meta-analysis*. *Crit Care Med*. 2012;40:725-730.
28. Krejci V, Hiltebrand LB, Sigurdsson GH. Effects of epinephrine, norepinephrine, and phenylephrine on microcirculatory blood flow in the gastrointestinal tract in sepsis*. *Crit Care Med*. 2006;34:1456-1463.
29. De Backer D, Creteur J, Silva E, et al. Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: which is best?*. *Crit Care Med*. 2003;31:1659-1667.
30. Day NPJ, Phu NH, Mai NTH, et al. Effects of dopamine and epinephrine infusions on renal hemodynamics in severe malaria and severe sepsis. *Crit Care Med*. 2000;28:1353-1362.
31. Levy B, Perez P, Perny J, et al. Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study*. *Crit Care Med*. 2011;39:450-455.
32. Day NPJ, Phu NH, Bethell DP, et al. The effects of dopamine and adrenaline infusions on acid-base balance and systemic haemodynamics in severe infection. *Lancet*. 1996;348:219-223.
33. Annane D, Vignon P, Renault A, et al. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. *Lancet*. 2007;370:676-684.
34. Di Giantomasso D, Bellomo R, May CN. The haemodynamic and metabolic effects of epinephrine in experimental hyperdynamic septic shock. *Intensive Care Med*. 2005;31:454-462.
35. Bersten A, Rutten A. Renovascular interaction of epinephrine, dopamine, and intraperitoneal sepsis. *Crit Care Med*. 1995;23:537-544.
36. Russell JA. Bench-to-bedside review: Vasopressin in the management of septic shock. *Crit Care*. 2011;15:226.
37. Gordon AC, Russell JA, Walley KR, et al. The effects of vasopressin on acute kidney injury in septic shock. *Intensive Care Med*. 2010;36:83-91.
38. Calzavacca P, Evans R, Bailey M, et al. Variable responses of regional renal oxygenation and perfusion to vasoactive agents in awake sheep. *Am J Physiol Regul Integr Comp Physiol*. 2015;309:R1226-R1233.
39. Di Giantomasso D, Morimatsu H, Bellomo R, et al. Effect of low-dose vasopressin infusion on vital organ blood flow in the conscious normal and septic sheep. *Anaesth Intensive Care*. 2006;34:427-433.
40. Di Giantomasso D, May CN, Bellomo R. Norepinephrine and vital organ blood flow during experimental hyperdynamic sepsis. *Intensive Care Med*. 2003;29:1774-1781.
41. Morelli A, Ertmer C, Pietropaoli P, et al. Terlipressin: a promising vasoactive agent in hemodynamic support of septic shock. *Expert Opin Pharmacother*. 2009;10:2569-2575.
42. Rajekar H, Chawla Y. Terlipressin in hepatorenal syndrome: evidence for present indications. *J Gastroenterol Hepatol*. 2011;26:109-114.
43. Uriz J, Ginès P, Cárdenas A, et al. Terlipressin plus albumin infusion: an effective and safe therapy of hepatorenal syndrome. *J Hepatol*. 2000;33:43-48.
44. Hadengue A, Gadano A, Moreau R, et al. Beneficial effects of the 2-day administration of terlipressin in patients with cirrhosis and hepatorenal syndrome. *J Hepatol*. 1998;29:565-570.
45. Albanèse J, Leone M, Delmas A, et al. Terlipressin or norepinephrine in hyperdynamic septic shock: a prospective, randomized study. *Crit Care Med*. 2005;33:1897-1902.
46. Morelli A, Rocco M, Conti G, et al. Effects of terlipressin on systemic and regional haemodynamics in catecholamine-treated hyperkinetic septic shock. *Intensive Care Med*. 2004;30:597-604.
47. O'Brien A, Clapp L, Singer M. Terlipressin for norepinephrine-resistant septic shock. *Lancet*. 2002;359:1209-1210.
48. Ishikawa K, Wan L, Calzavacca P, et al. The effects of terlipressin on regional hemodynamics and kidney function in experimental hyperdynamic sepsis. *PLoS ONE*. 2012;7:e29693.
49. Westphal M, Stubbe H, Sielenkämper A, et al. Terlipressin dose response in healthy and endotoxemic sheep: impact on cardiopulmonary performance and global oxygen transport. *Intensive Care Med*. 2003;29:301-308.
50. Lange M, Morelli A, Ertmer C, et al. Continuous versus bolus infusion of terlipressin in ovine endotoxemia. *Shock*. 2007;28:623-629.

51. Morelli A, Ertmer C, Rehberg S, et al. Continuous terlipressin versus vasopressin infusion in septic shock (TERLIVAP): a randomized, controlled pilot study. *Crit Care*. 2009;13:1-14.
52. Bellomo R, Chapman M, Finfer S, et al. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. *Lancet*. 2000;356: 2139-2143.
53. Friedrich JO, Adhikari N, Herridge MS, et al. Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. *Ann Intern Med*. 2005;142:510-524.
54. Lauschke A, Teichgräber U, Frei U, et al. 'Low-dose' dopamine worsens renal perfusion in patients with acute renal failure. *Kidney Int*. 2006;69:1669-1674.
55. Morelli A, Ertmer C, Rehberg S, et al. Phenylephrine versus norepinephrine for initial hemodynamic support of patients with septic shock: a randomized, controlled trial. *Crit Care*. 2008;12:R143.
56. Morimatsu H, Ishikawa K, May C, et al. The systemic and regional hemodynamic effects of phenylephrine in sheep under normal conditions and during early hyperdynamic sepsis. *Anesth Analg*. 2012;115:330-342.
57. Dünser MW, Hasibeder WR. Sympathetic overstimulation during critical illness: adverse effects of adrenergic stress. *J Intensive Care Med*. 2009;24:293-316.
58. Morelli A, Ertmer C, Westphal M, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. *JAMA*. 2013;310:1683-1691.
59. Wan L, Langenberg C, Bellomo R, et al. Angiotensin II in experimental hyperdynamic sepsis. *Crit Care*. 2009;13:R190.
60. May CN, Calzavacca P, Ishikawa K, et al. Novel targets for sepsis-induced kidney injury: the glomerular arterioles and the sympathetic nervous system. *Exp Physiol*. 2012;97:1168-1177.
61. Bagshaw SM, Lapinsky S, Dial S, et al. Acute kidney injury in septic shock: clinical outcomes and impact of duration of hypotension prior to initiation of antimicrobial therapy. *Intensive Care Med*. 2009;35:871-881.