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Sepsis and Dialysis Disequilibrium Syndrome

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1. Introduction

Dialysis disequilibrium syndrome (DDS) is a central nervous system disorder, usually occurs in patients during hemodialysis (HD) or within 24 hours of HD. DDS was first described by Kennedy *et al.* in 1962.¹¹ If a critically ill patient on HD develops severe sepsis and septic shock with multiple organ failure (MOF), the adverse effect of HD on the brain is likely to be amplified, which may predispose to the DDS.

Severe sepsis and septic shock are the common indications for intensive care therapy admission. Sepsis/ severe sepsis are usually manifested by inadequate organ perfusion/function. Multiple organ dysfunction syndrome (MODS) is the presence of altered organ function, in an acutely ill septic patient whose homeostasis is maintained with the intervention.⁴

Mechanism (Fig1) for the occurrence of MODS is result of imbalance between the pro and anti-inflammatory response and the dominance of pro-inflammatory reaction. This leads to the systemic microvascular thrombosis, hypoxic hypoxia, immunosuppressant and apoptosis.⁹ Which ultimately leads to organ dysfunction/failure in severe sepsis/ septic shock patients

Acute renal failure is one of the common complications of severe sepsis and septic shock. It occurs in 23% of severe sepsis and 51% of septic shock patients and requires hemodialysis. In case of renal failure due to sepsis, the renal vasoconstriction occurs due to the increased sympathetic tone; in contrast to the systemic vasodilatation.¹⁶

Twenty three percent of septic shock patients develop septic encephalopathy.⁸ various anatomical abnormalities are found in these patients of severe sepsis and septic shock with brain involvement, these are collectively termed as the septic encephalopathy. These abnormalities includes proliferation of astrocytes, cerebral infarcts, multiple white matter hemorrhages, central pontine myelinolysis, multiple microabscesses, reduction in cerebral blood flow, cerebral capillary leakage, and malfunctioning of the blood brain barrier.¹⁰

These septic encephalopathy changes can be amplified if patient is having traumatic brain injury, subarachnoid hemorrhage or on hemodialysis.

Critically ill patients frequently require renal replacement therapy and intermittent HD. DDS is an acute neurological manifestation due to cerebral edema that occurs during or after dialysis, these manifestations can be mild, such as nausea and vomiting, or severe, as

seizures, coma, and death.³ Walter *et al.* demonstrated by CT scan of the brain that about 2% of patients who underwent HD developed brain edema.²² In all reported cases of DDS, the patients were conscious and undergoing HD for the first time. Hence DDS was easy to detect and treated promptly. Di-Fresco *et al.* successfully treated a case of DDS.⁵

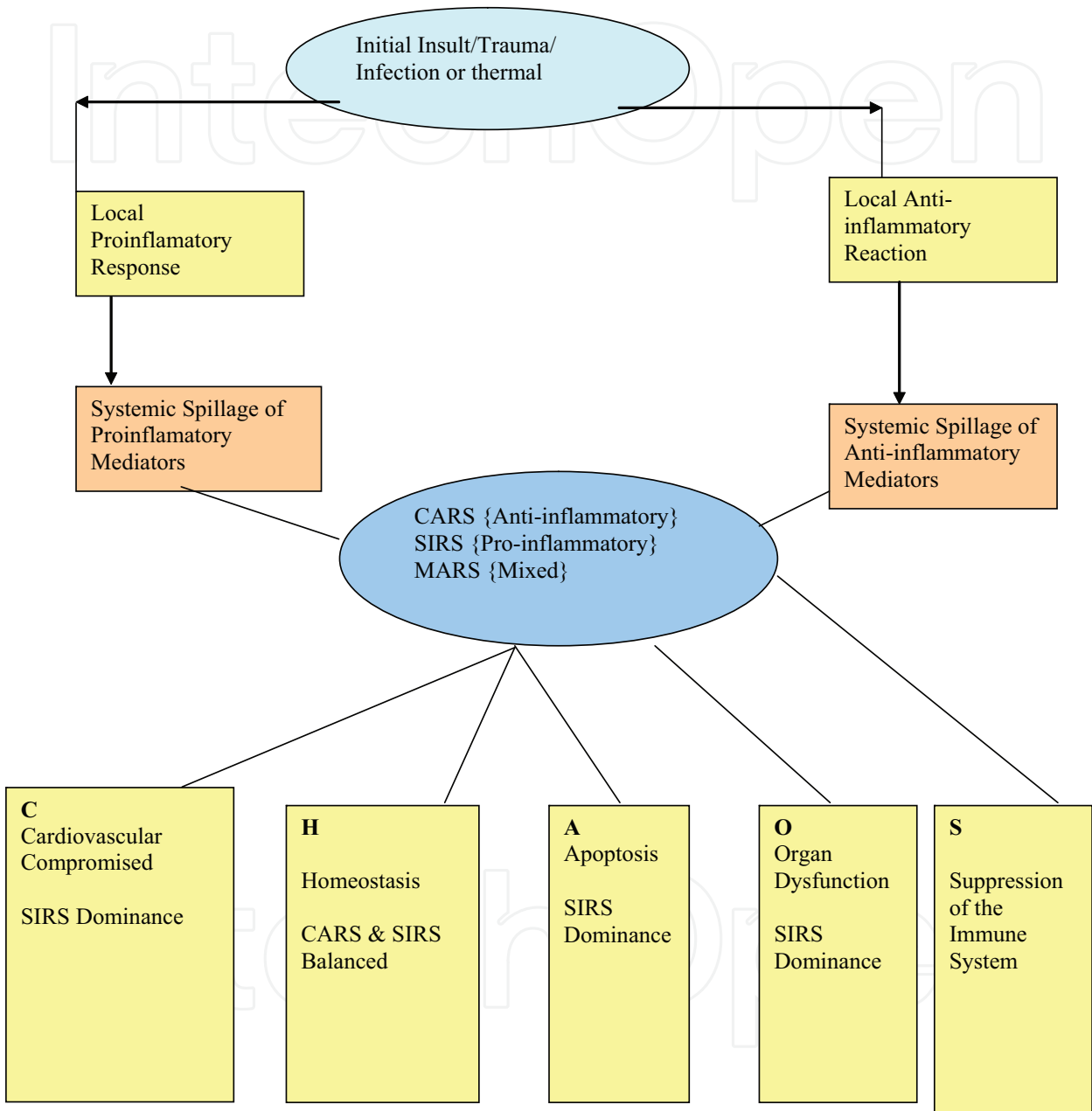


Fig. 1. Mechanism for MODS⁸.

The risk factors for the development of DDS are rapid elevation of pCO₂,¹⁴ head injury,⁷ young age, metabolic acidosis,¹ and severe sepsis.¹⁷ Patients requiring intensive care therapy are different from patients with end-stage renal failure or chronic renal failure, they usually have severe sepsis or septic shock, MOF; and are sedated. Bagshaw *et al.* reported a fatal case of DDS in a patient with sepsis, but this patient was awake and not in septic shock.

He underwent his first episode of aggressive HD resulting in severe and fatal DDS.² If patients are on slow HD for several consecutive days, develops septic shock; and they are supposed to have sepsis-induced changes in the brain.

Severe sepsis and septic shock with polymicrobial bacteremia causes a widespread of immune activation. This may alter the blood-brain permeability and may lead to DDS.²

Overall, there are 2 main theories for the development of DDS. The first theory, also called the reverse osmotic shift, relates to the acute removal of urea, which occurs comparatively slower across the blood-brain barrier than in plasma, thus generating a reverse osmotic gradient. This might promote the movement of water to the brain and cause brain edema.²⁰ This reverse osmotic shift in DDS has been demonstrated in experimental animals. Silver *et al.* demonstrated that rats undergoing rapid HD, urea nitrogen levels were lowered from 72 to 34 mmol in 90 min. This change was associated with a 6% increase in brain water. Surprisingly, neither undialysed nor dialysed rats with urea bath developed cerebral edema.¹⁸ The second theory suggests that increased osmolarity of the extracellular fluid leads to adoptive accumulation of intracellular osmolytes in the brain. This decreases the cerebral cell dehydration and causes paradoxical reduction in the cerebral pH, resulting in brain edema during or after HD.⁶ Recently, experimental studies helped in demonstrating the molecular basis for the development of DDS; the water and urea movement across the plasma membrane is facilitated by specific channels, called, aquaporins and urea transporters (UT), respectively. In the absence of these channels, water and urea diffusion through the cell membrane is slow. Also, because of the less number of UT, the urea exit from the astrocytes may be delayed, while rapid removal of extracellular urea during fast HD can lead to water entry into the cells, subsequently causing brain edema.²¹ The aim of treatment of DDS is to reduce brain edema and to avoid its complication. Only one case of DDS has been reported in the literature, which was successfully treated using mannitol and hyperventilation.⁵ Ideal management of DDS is prevention. The following methods have been tried to prevent DDS: Doorenbos *et al.* used urea to keep blood urea levels constant during HD and succeeded in avoiding DDS.⁶ Another way is a gentle initiation of HD and gradual correction of biochemical abnormalities with slow and less efficient HD.¹² When aggressive HD is indicated, phenytoin may be used to prevent the development of DDS.¹⁵

If the patient has fluid overload, he can be shifted to hemofiltration and a short period of HD, or he can be started on peritoneal dialysis. So far, DDS is not reported with peritoneal dialysis.¹ To our knowledge, there are 2 reported cases of DDS occurring after more than 1 week of daily HD. Both these patients had septic shock, but were stable with inotropic and ventilatory support.¹³ Their follow-up CT of brain and radiography of chest was without any major pathology. Both patients suffered neurologic deterioration during or 1 hour after the HD session and an emergency CT of brain showed severe brain edema with brain herniation (Fig2). Authors made the DDS diagnosis because the neurologic deterioration and herniation occurred during or within a few hours of the HD session, and after excluding other risk factors for hypotension and fatality as per advanced cardiac life support guidelines.¹³ Severe sepsis and septic shock affects brain by reducing the blood flow to the brain and also causing capillary leakage and dysfunction of the blood-brain barrier. These effects are due to either toxic mediators or the indirect effect of hypoperfusion,

hyperthermia, and increased intracranial pressure.¹⁹ These effects will also be amplified if the patient is having a brain injury.¹⁹ Patients on regular daily HD are likely to have brain edema, if they also develop septic shock, the effects on the brain may be amplified and leading to DDS.

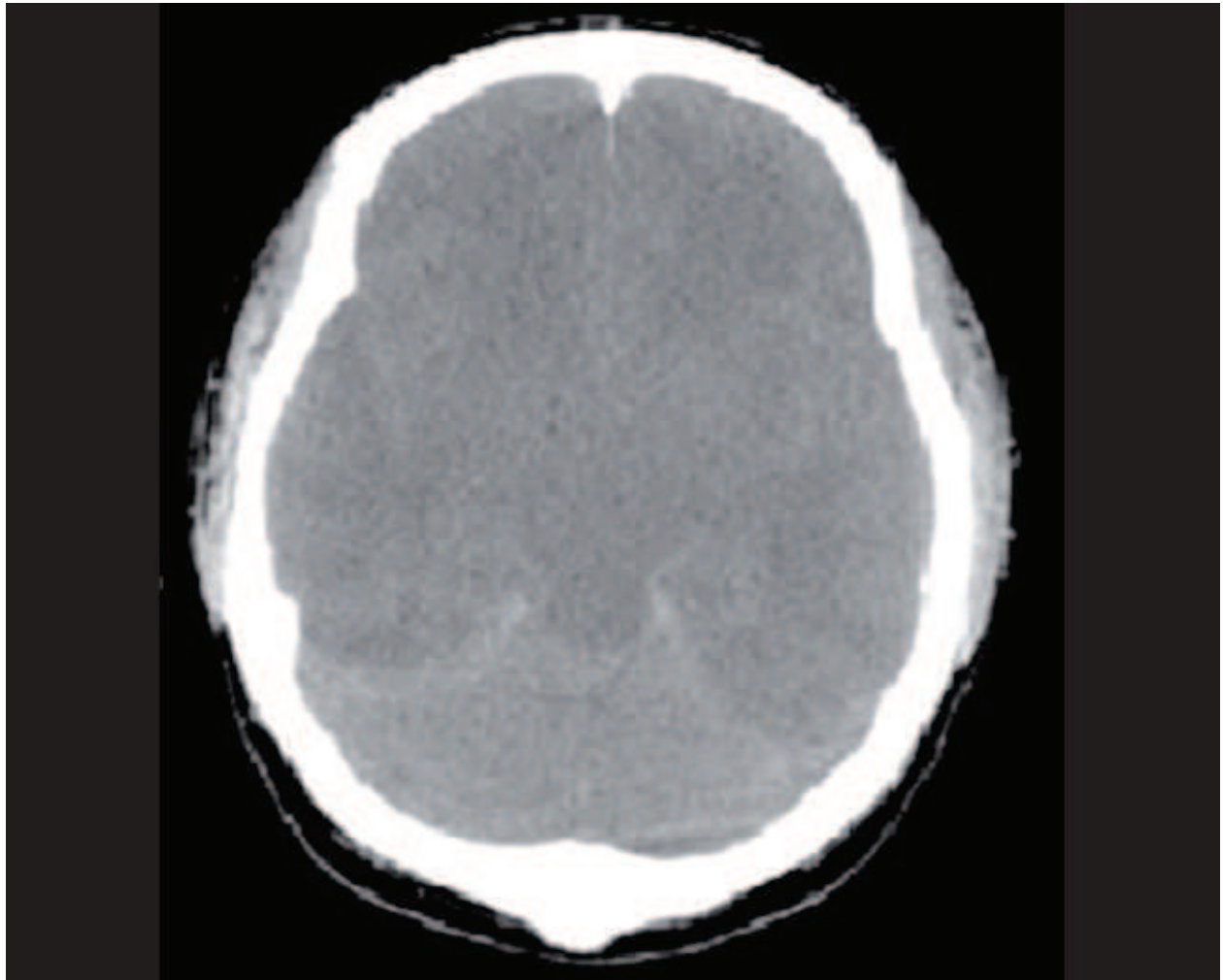


Fig. 2. Diffuse and severe brain edema in DDS

2. Conclusion

If a patient on HD develops severe sepsis or septic shock, DDS can occur even after repeated sessions of HD. DDS may contribute to the sudden deterioration and death in these septic patients. The acute care physicians, intensivists, and nephrologists should be aware of the risks of DDS and act accordingly.

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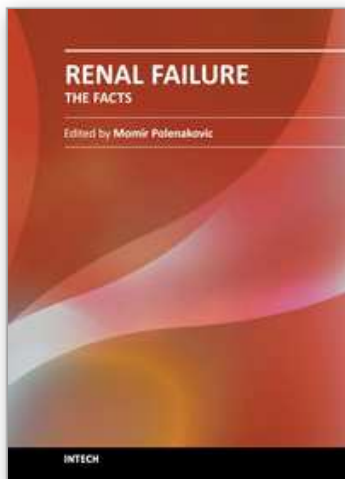
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Renal Failure - The Facts

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The book "Renal Failure - The Facts" consists of some facts about diagnosis, etiopathogenesis and treatment of acute and chronic renal failure. Acute, as well as chronic renal failure is a great medical problem and their treatment is a burden for the budget of each government. The purpose of the chapters is to present some important issues of diagnosis and causes of AKI, as well as caused by snakes and arthropods, after cardiac surgery, as well as some therapeutic achievements in AKI. Well presented are the psychological condition in patients on haemodialysis, as well as the treatment of diabetic uremics. The book is aimed at clinicians with a special interest in nephrology, but it should also prove to be a valuable resource for any generalists who encounter a nephrological problem in their day-to-day practice.

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