INTRODUCTION

Neonatal sepsis remains the unconquered frontier of modern neonatal medicine today, despite advances in knowledge, technology and therapeutic armamentarium available[1]. Blood stream infection rates in hospitals (in the developed world) range from 10-25% for all neonates to around 50% in preterm very low birth weight (VLBW) infants[2,3]. Exact figures for the developing world are not known but are considerably higher. World Health Organisation estimates that of the four million neonatal deaths all over the world every year, over 35% are due to infection in the neonatal period ;[4] this translates to approximately two deaths per minute! Whilst most of these deaths take place in the developing world where mortality from sepsis may be as high as 85%, in the developed world neonatal mortality from sepsis has remained around 20% for nearly three decades[1].

Identifying the risk and prognosis factors prevailing in the different geographical contexts has become a crucial issue for optimizing neonatal care [5]. Risk factors implicated in neonatal sepsis reflect the level stress and illness experienced by the fetus at delivery, as well as the hazardous uterine environment surrounding the fetus before delivery[6]. Most of the maternal factors contributing to the risk of neonatal sepsis include prematurity, low birth weight, rectovaginal colonization, prolonged rupture of membranes, maternal intrapartum fever, chorioamnionitis and urinary tract infection. Factors in the postnatal period associated with an increased risk of sepsis or septic shock include male gender, birth weight <1000 grams, meconium staining, hypogammaglobulinemia, intravenous alimentation, central venous catheters, prolonged use of steroids or drugs that decrease gastric acidity, and prolonged duration of mechanical ventilation[7].

Throughout pregnancy and until the membranes rupture, the fetus is relatively protected from the microbial flora of the mother by the chorioamniotic membranes, the placenta, and poorly understood antibacterial factors in amniotic fluid. However, there are many ways that infectious agents can reach the fetus or newborn to cause infection. Procedures disturbing the integrity of the uterine contents, such as amniocentesis, cervical cerculage, transcervical chorionic villus sampling, or percutaneous blood sampling, can permit entry of skin or vaginal organisms, causing amnionitis and secondary fetal infection. Certain bacteria, particularly Treponema pallidum and Listeria monocytogenes, can reach the fetus through the maternal bloodstream despite placental protective mechanisms, causing transplacental infection[8].

Initial colonization of the neonate usually takes place after rupture of the maternal membranes. In most cases, the infant is colonized with the microflora of the birth canal during delivery. However, particularly if the rupture of membranes lasts longer than 24 hours(prolonged rupture of membranes), vaginal bacteria may ascend and in some cases produce inflammation of the fetal membranes, umbilical cord, and placenta. Fetal infection can result from aspiration of infected amniotic fluid. Infection of the mother at the time of birth, particularly genital infection, is the principal pathway of maternal transmission[8,9]. Transplacental hematogenous infection during or shortly before delivery (including the period of separation of the placenta) is possible, although it seems more likely that the infant is infected during passage through the birth canal. Finally, bacteria can be

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introduced after birth from the environment surrounding the baby, either in the nursery or at home[8].

A number of pathogens have been associated with sepsis in the neonatal period. The predominant agents are bacterial, but viruses including herpes simplex and enteroviruses have been associated fulminant neonatal sepsis with high mortality. The Gram-negative infection was associated with 69% of cases of fulminant septic shock. Gram-positive etiologies of sepsis are dominated by group b- Sterptococcus and coagulase-negative staphylococcus (CoNS).Fungi (primarily Candida albicans) may also lead to fulminant neonatal sepsis and predominantly affect ELBW infants[7].

Though the ability of a senior experienced clinician to diagnose sepsis is high, there is still lack of diagnostic certainty at the cot side which is often influenced by the presence or absence of 'risk factors', lack of specific clinical signs and symptoms, differing pathophysiology and crucially the lack of highly sensitive and specific laboratory test[10]. Blood culture remains the 'gold standard' but is often unreliable when intra-partum antibiotics have been administered to the mother. Blood culture also fails to detect bacteraemia in 27%-92% of preterm VLBW infants[11].

The most significant clinical findings for sepsis were presence of tachyapnoea with grunting/chest retraction or apnoea, temperature instability and a capillary refill time of greater than 3 seconds, changes in heart rate or its variability, hypotension and or decreased urine output, persistent metabolic acidosis and hypo or hyperglycaemia. Of the laboratory tests leucopoenia or leucocytosis, C-reactive protein greater than 10 mg/dl and interleukin 8 value of greater than 70 pg/ml were the most important variables. Sepsis was defined as the presence of two or more of clinical features plus one or more of laboratory parameters outlined with or without positive blood culture[5,8,10].

Neonatal sepsis is a life threatening condition with an ominous course and high subsequent fatality. The morbidity and mortality are still on the rise, especially so in developing countries. Meningitis, septic shock, acute tubular necrosis, necrotizing enterocolitis, disseminated intra-vascular coagulation, pneumonia and respiratory failure were common systemic complications observed during hospital stay[12].

ARF is a serious complication for severe systemic infection, as it is also considered a major risk factor for the development of ARF. Development of acute renal failure (ARF) remains a serious prognostic factor for the outcome of high risk neonates[13].

Definition of acute renal failure in neonates:

Acute renal failure (ARF) which is now referred to as acute kidney injury (AKI) is defined as the rapid elevation in the concentration of blood urea nitrogen (BUN), creatinine, and other cellular waste products in the blood resulting from diminished glomerular filtration rate (GFR) in the kidney. Frequently, it involves abnormal tubular function, including reduced sodium resorption and increased loss of bicarbonate, as well as diminished excretion of water [14]. The definitions of AKI vary, ranging from a 50% SCr rise to the need for renal replacement therapy. To standardize the definition of AKI in neonates, Askenazi et al proposed a modification for neonates regarding the internationally recognized Acute Kidney Injury Network staging (Table 1), based on rise in SCr from a previous trough level. This definition deals with the challenge unique to neonates of

maternal creatinine concentrations and the physiologic SCr decrease in the first weeks after birth. The definition does not include evaluation of urine output because it is still unclear how to incorporate urine output criteria for AKI definition in children and neonates[15].

Table (1): Proposed AKI Definition in Neonates[15]

Stage of Severity	Criteria
No AKI	No serum creatinine change or rise by <0.3 mg/dL (26.5 mmol/L) from a previous trough SCr value.
Stage 1	Increase in SCr by 0.3 mg/dL (26.5 mmol/L) or by 150%–200% (1.5–2 times) from a previous trough SCr value.
Stage 2	Increase in SCr by 200%–300% (2–3 times) from a previous trough SCr value.
Stage 3	Increase in SCr by 300% (3 times) from a previous trough value or SCr =2.5 mg/dL (221 mmo/L) or receipt of dialysis for AKI.

Incidence of acute renal injury:

The incidence of AKI in the neonatal period is greater than during later childhood, but exact numbers have been difficult to determine accurately because many mild cases characterized by transient oliguria may never be recognized, and cases of nonoliguric failure, even those that are severe, may be undiagnosed [14,16]. That high incidence during neonatal period is also attributed to prolonged survival of seriously ill newborns with improved resuscitation and ventilator support and use of nephrotoxic drugs with increased incidence of gram negative sepsis, and increased survival of premature neonates a higher risk of renal failure due to physiological immaturity of renal function and sudden adaptation to extrauterine life and exogenous stress factors which break down the homeostasis of body function regulated by the placenta in fetal life. In addition to increased awareness of renal failure and importance of monitoring urine output together with serial measurements of blood urea and serum creatinine in neonates, also antenatal diagnosis of renal anomalies by ultrasonograghy [16].

Older studies identified a prevalence as high as 24% of admissions to neonatal intensive care units (NICUs), but more recent analyses have found a prevalence of 3%to 8% [14,17,18], one third are preterms[17]. The incidence of AKI in newborn in developing country was 3.9/1000 livebirth and 34.5/1000 newborn admitted to the neonatal unit[18]. Mathur N. reported in 2006 the incidence of septic neonates with renal failure to be 20%-26% in India[19]. Two thirds of preterm VLBW infants will develop renal function

abnormalities with sepsis, these should be looked for and treated conventionally [10]. With appropriate management, many cases are reversible but longer term problems are still frequently observed 10-50% of babies with AKI may die, with 20% referral to dialysis[17,20].

Functional development of neonatal kidneys:

Maturation during fetal life and after birth is a process involving all organs and functions of the growing human[21]. At birth, the kidney replaces the placenta as the major homeostastic organ, maintaining fluid and electrolyte balance and removing harmful waste products. This transition occurs with changes in renal blood flow (RBF), glomerular filtration rate (GFR), and tubular function. The level of renal function relates more closely to the postnatal age than to the gestational age at birth[22]. Nephrogenesis is completed by the end of 34th week of gestation[21,23]. The kidney of a full-term neonate possesses a full set of nephrons, approximately 850,000 to1,200,000 per kidney. Some events during pregnancy such as growth retardation or nephrotoxic drugs administered to the mother may negatively affect the total number of nephrons present in the neonate[21].

Fetal renal function is characterized by a low glomerular filtration rate (GFR), the result of low mean arterial blood pressure (MAP) with very low renal blood flow (RBF) and high renal vascular resistance (RVR) as well as reduced glomerular filtration area. After birth GFR rises very rapidly from 10-13ml/min/1.73m^2 in preterms and 26-40ml/min/1.73 m^2 in fullterms at birth, to 54-60ml/min/1.73 m2 after 2 weeks in the latter, (Adult levels of GFR (120 ml/min/1.73 m^2) are reached between 1 and 2 years of age)[24,25]. This rate of GFR maturation is markedly diminished in preterm infants. GFR in preterm infants do not reach normal mature levels until 8 years of age[25]. The GFR increase is because of an increase in MAP and glomerular hydraulic pressure, as well as sharp fall in RVR, with redistribution of intra renal blood flow from the juxtamedullary to the superficial cortical nephrons and in addition an increase in the glomerular filtration surface. The GFR of the newborn is, however, still very low both in absolute terms as well as corrected for adult body surface area(1.73 m^2). This is a unique situation confined to the newborn and explains the vulnerability of renal (glomerular) function in early extrauterine life. In order to minimize this vulnerability and to assure that low precarious effective filtration pressure is maintained under most pathophysiological circumstances, a delicate balance of intrarenal vasconstrictive and vasodilator forces is essential[23].

Serum creatinine is elevated in the first days of life reflecting maternal creatinine and a low intrinsic GFR. The lower the gestational age at birth, the higher is the serum creatinine. A tubular creatinine reabsorption in the preterm neonate both with the existence of a slight state of dehydration may partly explain the increase of serum creatinine during the first days of life in those babies[21,25,26]. This latter temporary phenomenon is attributable to backflow of creatinine across leaky immature tubular and vascular structures. With time maturational changes will impose a barrier to creatinine. From that point onwards total body muscle mass, GFR and tubular secretion will determine the plasma creatinine level of the individual[25,26].

Etiology and classification of AKI in neonates:

The underlying causes of ARF generally can be divided into prerenal, renal (intrinsic) and postrenal categories. Flynn drew attention to the variation in the etiology of AKI that was present not only between centers from developing and developed countries, but also between different centers from only developing countries[27]. Socio-economical status, availability of health facilities, and environmental factors may affect the etiology and outcome of AKI[28,29].

● Prerenal:

* Decreased true intravascular volume:

- Perinatal hemorrhage (fetomaternal transfusion, intraventricular heamorrhage, twin to twin transfusion, cord accidents)
- Dehydration
- Third space losses (sepsis, traumatized tissue, necrotizing enterocolitis)
- Gastrointestinal losses
- Hypoalbuminemia

* Decreased effective intravascular volume:

- Congestive heart failure (e.g patent ductus arteriosus, coarctation of aorta)
- Pericarditis, cardiac tamponade
- Hypotention
- Hyperviscosity

* Sepsis

* Hypoxic –ischemia (asphyxia)

* Post cardiac surgery

● Intrinsic Renal:

*Persistant prerenal causes

*Congenital parenchymal renal diseaseDiseases

- Renal agenesis
- Renal dysplasia / hypoplasia
- Autosomal recessive/dominant polycystic kidney disease
- Finnish-type congenital nephrotic syndrome

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* Acute tubular necrosis
  - Perinatal asphyxia
  - Ischemic /hypoxic insults
  -Toxins
  - Drug-induced
    - Aminoglycosides
    - Intravenous contrast media
    - Nonsteroidal anti-inflammatory drugs (eg.indomethacin)
    - Angiotensin-converting enzyme inhibitors (eg.captopril, enalapril)
    - Amphotericin B
* Interstitial nephritis
* Vascular lesions
  - Renal vessels thrombosis
  - Cortical necrosis
  - Disseminated intravascular coagultion
* Infectious causes
  - Sepsis
  - Pyelonephritis
  - Syphilis
  - Toxoplasmosis
* Maternal drug use **(** leading to prenatal injury and vascular damage**)** e.g
  - Angiotensin-converting enzyme inhibitors
  - Angiotension II receptor antagonist
  - Nonsteroidal anti-inflammatory drugs

● Postrenal/Obstructive:

(1) Intrarenal obstruction:

* Obstruction in a kidney (uric acid nephropathy, myoglobinuria, heamoglobinuria)

(2) Extrarenal obstruction:

* Bilateral ureteral obstruction e.g Bilateral fungal bezoar

* Urethral obstruction e.g Posterior urethral valves.

*Neurogenic bladder due to myelomeningocele [14,18,30,31]

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Pathogensis:

* Prerenal failure

Prerenal insufficiency is a functional response of structurally normal kidneys to hypoperfusion. Globally, prerenal insufficiency accounts for approximately 70% of community - acquired cases of acute renal failure and as many as 60% of hospital-acquired cases. Pre-renal injury occurs when blood flow to the kidney is reduced due to true intravascular volume contraction or to decreased effective blood volume[18]. A decrease in circulatory volume evokes a systemic response aimed at normalizing intravascular volume at the expense of the glomerular filtration rate (GFR). (See fig1)

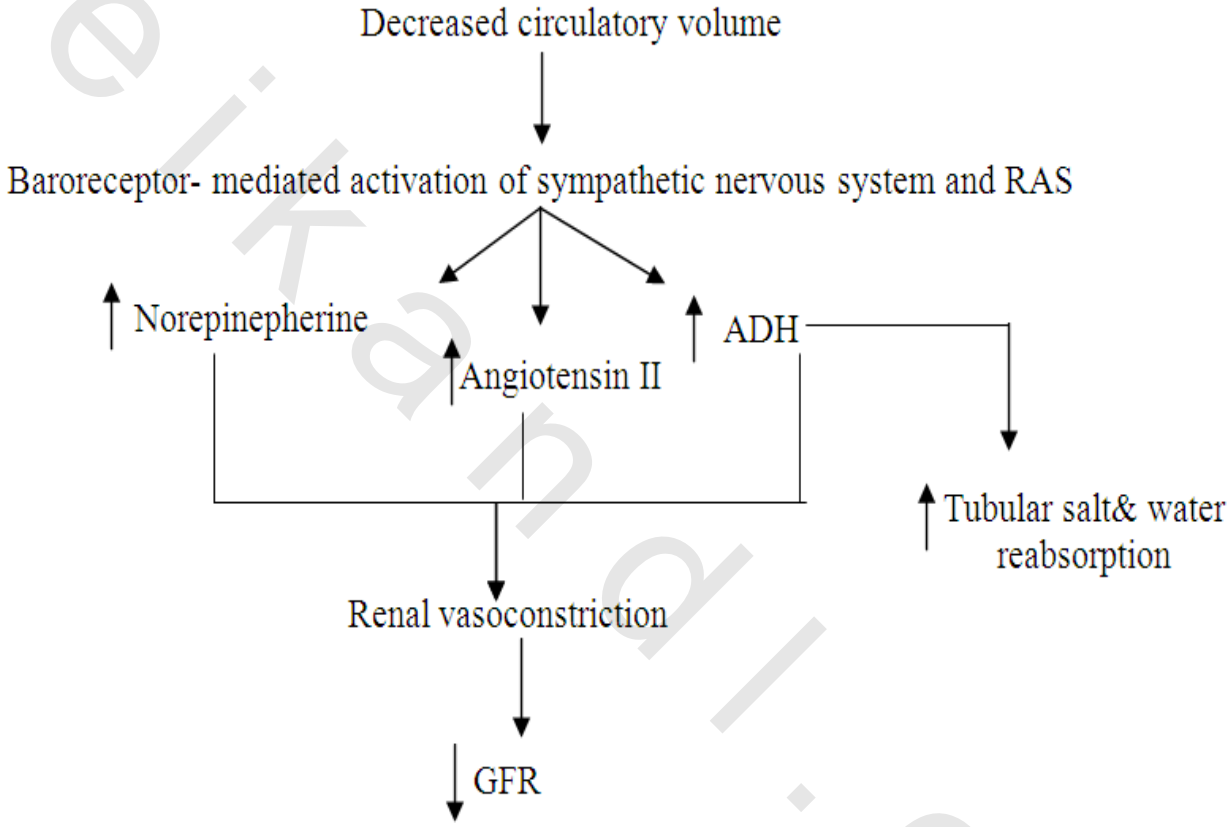

Fig.1: Pathogenesis of prerenal failure[31]

Decreased cardiac volume will initiate a series of neurohormonal response including baroreceptor - mediated activation of the sympathetic nervous system and renin-angiotensin axis and the release of antidiuretic hormone (ADH) leading to increase tubular salt and water reabsorption. This is associated with failure of prostaglandin production. This results in renal vasoconstriction and the resultant reduction in the GFR[30]. The early phase of renal compensation for reduced perfusion includes autoregulatory maintenance of the GFR via afferent arteriolar dilatation (induced by myogenic responses, tubuloglomerular feedback, and prostaglandins) and via efferent vasoconstriction[31].

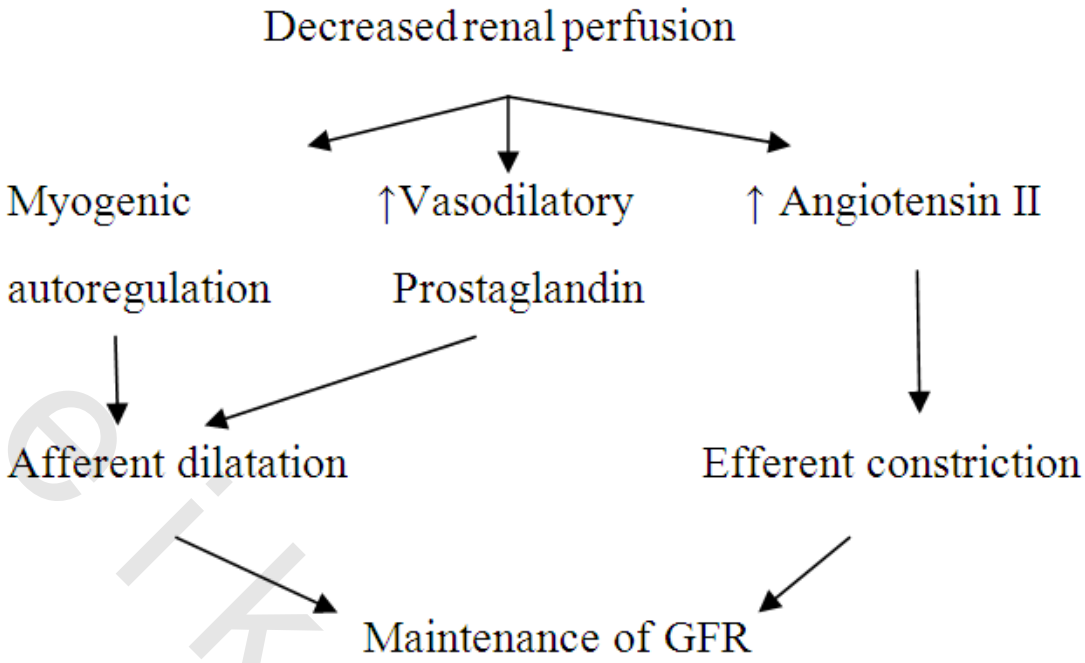

Fig. 2: Compensatory mechanisms for preventing a fall in glomerular filtration rate (GFR) in the presence of prerenal failure.[18,31]

The early phase also includes enhanced tubular reabsorption of salt and water stimulated by the renin-angiotensin-aldosterone system and sympathetic nervous system. Rapid reversibility of oliguria following timely reestablishment of renal perfusion is an important characteristic and is the usual scenario in prerenal insufficiency. However prolonged renal hypoperfusion can result in a deleterious shift from compensation to decompensation. This decompensation phase is characterized by excessive stimulation of the sympathetic and renin-angiotensin systems, with resultant profound renal vasoconstriction and ischemic renal injury[18,31].

* Intrinsic renal failure

Intrinsic renal failure is associated with structural renal damage. This includes acute tubular necrosis (from prolonged ischemia, drugs, or toxins), primary glomerular diseases, or vascular lesions[31].

The pathophysiology of ischemic acute tubular necrosis is well studied. Ischemia leads to altered tubule cell metabolism (eg, depletion of adenosine triphosphate [ATP], release of reactive oxygen species) and cell death, with resultant cell desquamation, cast formation, intratubular obstruction, backleak of tubular fluid, and oliguria[18,31].

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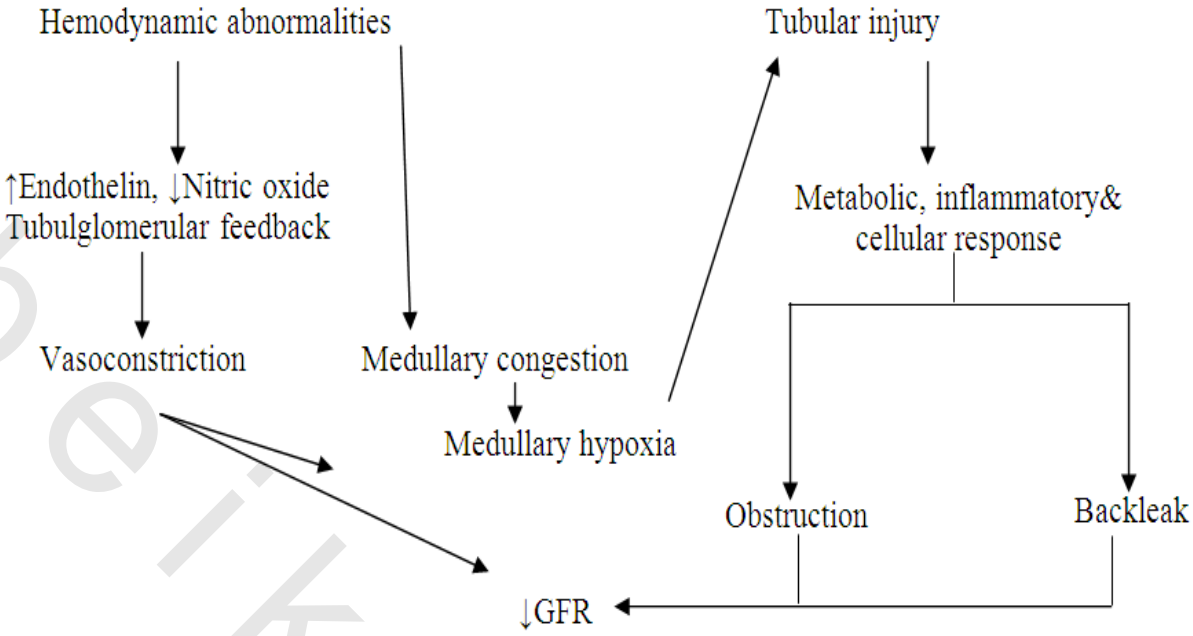

Fig. 3: Mechanisms of intrinsic acute renal failure[18].

Persistant abnormalities in intrarenal blood flow involving the outermedullary region may contribute to the decrease in GFR. The outer medulla is relatively hypoxic even under normal condition, rendering the tubular segments in this region highly susceptible to ischemia. Mediators of both the renal vasoconstriction and persistant reduction in the medullary blood flow include endothelin-1, angiotensin II, PG, adenosine and nitric oxide. An imbalance between the vasodilatory NO and the vasoconstrictory endothelin may also impair medullary blood flow and contribute to tubular cell damage. In the outer medulla, where tubules have higher oxygen requirements, ischemia cause swelling of the tubular and endothelial cells as well as adherence of neutrophils to capillaries and venules. These changes lead to vascular congestion and decrease in blood flow, tipping the tenous balance between oxygenation and energy demand[32].

* Postrenal failure

Postrenal failure is a consequence of the mechanical or functional obstruction of the flow of urine. This form of oliguria and renal insufficiency usually responds to the release of the obstruction[31]. Obstruction of the urinary tract can cause acute kidney injury if the obstruction occurs in a solitary kidney, if it involves the ureters bilaterally, or if there is urethral obstruction. Obstruction can result from congenital malformations such as posterior urethral valves, bilateral ureteropelvic junction obstruction or bilateral obstructive ureteroceles. Acquired urinary tract obstruction can result from passage of kidney stones or, rarely, from tumors[18,33].

Mechanisms of acute renal failure in septic neonates:

Sepsis can operate through a variety of mechanisms in producing renal failure. It can cause renal failure through renal hypoperfusion due to true volume contraction as in hemorrhage and third space losses[17,34] and even by shock like state usually due to gram negative septicemia[14,17,19], direct damage to blood vessels leading to DIC leading to renal ischemia and tubular damage[17]. Also another mechanism is cardiac failure by decreased effective blood volume which occurs when the true blood volume is normal or increased but renal perfusion is decreased[17,35]. Septicemia can also cause transient pyelonephritis and ATN[16,19].

Further more there is possible role of myoglobinuria following renal damage by gram negative bacteria[19]. Haftel et al suggested that myoglobinuric renal failure was associated with anoxia and sepsis. He showed that myoglobin pigment is itself toxic to the kidneys, causing a spectrum of diseases from minimal tubular damage to fulminant severe acute tubular necrosis. The activation renin-angiotensin system, alterations in prostaglandin production, and arginine vasopressin have been associated with renal vasoconstriction in acute myoglobinuric renal failure. Volume depletion and acidosis are necessary for myoglobinuric renal failure to occur[36].

The exact pathophysiology of sepsis-induced AKI is not known, however, it is generally accepted that it has a multi-pronged injury pathway. Data from literature involving mechanisms of acute renal failure in neonates is scarce therefore we used that related to children and adults. This form of AKI has components of: ischemia-reperfusion injury, direct inflammatory injury, coagulation and endothelial cell dysfunction, and apoptosis[37]. It is note worthy that ion channels in tubular epithelium are energy/oxygen dependent thus particularly sensitive to hypotension and hypoxia[10].

In children with multiorgan failure secondary to septicemia, the systemic inflammatory response is thought to contribute to AKI as well as other organ dysfunction by the activation of the inflammatory response, including increased production of cytokines and reactive oxygen molecules, activation of polymorphonuclear leukocytes (PMNs), and increased expression of leukocyte adhesion molecules. Reactive oxygen molecules can be generated by several mechanisms including activated PMNs, which may cause injury by the generation of reactive oxygen molecules including superoxide anion, hydrogen peroxide, hydroxyl radical, hypochlorous acid, and peroxynitrite, or by the release of proteolytic enzymes. Myeloperoxidase from activated PMNs converts hydrogen peroxide to hypochlorous acid, which may react with amine groups to form chloramines ; each of these can oxidize proteins, DNA and lipids resulting in substantial tissue injury[18].

An elevated plasma concentration of endotoxin (lipopolysaccharide ; LPS) is often found in the systemic circulation during sepsis, regardless of the type of the infecting microorganism, possibly as a result of the translocation of LPS originating from the resident Gram-negative flora of the gut. During the inexorable downward spiral of sepsis, LPS, then cytokines, and consequently nitric oxide (NO) are released[37].

Adding to the translocation of intestinal-derived LPS that occurs during any form of sepsis, the multiplication and destruction of Gram-negative bacteria results in the release of LPS into the bloodstream and its rapid dissemination throughout the component lipid body.

LPS binds with the LPS-binding protein (LBP) through the biologically active A of LPS. The LBP-LPS complex binds to the co-receptor CD14, which leads to interactions with the cell surface Toll-like receptor 4-MD-2 complex on monocytes, macrophages and neutrophils, but this complex also binds to other cells, including renal tubular epithelial cells. These cells are then stimulated to produce cytokines through a myeloid differentiation primary response gene (MyD88)-dependent and an MyD88-independent pathway. The initiation of septic AKI is dependant mainly on MyD88b[37].

The proinflammatory cytokines induced upon LPS exposure, which include tumor necrosis factor (TNF)- α, interleukin (IL)-1, and interferon (IFN)- β, bind to their specific receptors on different cell types. In the kidney, this takes the form of TNF receptor 1 on glomerular endothelial cells and TNF receptor 2 on renal tubular epithelial cells. After a chain of reactions there is transcription of the inducible NO synthase (iNOS) gene, and the translation of iNOS mRNA, and the subsequent assembly of iNOS protein, which culminates in the formation of NO[37].

The production of large amounts of NO during sepsis is responsible for systemic vasodilatation, which results in septic shock. The resultant arterial volume depletion is sensed by baroreceptors, which triggers increased sympathetic activity and angiotensin production. The end result is intrarenal vasoconstriction with sodium and water retention and a reduction in glomerular filtration rate (GFR)[37].

On the other hand, recent animal models of hyper- dynamic sepsis (increased cardiac output along with a decreased blood pressure) reveal that sepsis-induced AKI can occur despite renal hyper- perfusion and intrarenal vasodilatation. An intact renal blood flow does not assure adequate perfusion to microvascular beds, as shown by the reduction in cortical microvascular perfusion that occurs during systemic inflammation[37].

Neither systemic nor intrarenal hemodynamic instability is the sole incriminating factor in sepsis-induced AKI. In fact, hemodynamic factors do not seem to be very significant, as hypotension does not correlate with AKI in critically ill patients with severe sepsis. Further, the conjecture of direct toxic effects of LPS to renal proximal tubular cells in vivo is substantiated by findings from in vitro studies showing that lipid A of LPS is responsible for NO mediated oxidant injury. The production of both cytokines and oxygen free radicals in systemic inflammation might also contribute to renal tubular injury. Thus one may conclude that although the pathogenesis of sepsis-induced AKI is multi- factorial and has not completely been delineated, NO is felt to be a key player in this process. [37]

Risk factors for occurrence of ARF in NICU:

The cause of AKI in neonates is multifactorial, and usually there is one or more associated contributing factors with neonatal AKI [19]. Acute kidney injury (AKI), caused by the physiological and haemodynamic stressors is imposed by the hostile extrauterine environment[38]. Risk factors evaluated for occurrence of AKI included gestational age[39], weight, sepsis, low Apgar score, birth asphyxia, nephrotoxic drugs, congestive heart failure, DIC, and shock [17,19,38,40,41,42]. In addition therapeutic interventions such as endotracheal intubation at birth, catheterization, the placement of arterial and venous catheters and duration of their insertion, phototherapy, and oxygen supplementation can contribute to AKI occurrence. Moreover, patent ductus arteriosus (PDA) was diagnosed in

a significantly greater percentage of preterm infants with AKI [38]. Respiratory distress syndrome is considered one of the main causes of pre-renal failure, as it reduces glomerular filtration rate and renal plasma flow [39,42]. Antenatal maternal usage of NASID can cause neonatal AKI[17].

There are also increasing evidence that certain genetic polymorphisms can predispose to AKI[17]. The cytokine genotypes influence the extent of renal inflammatory processes and the long term effect of renal hypo perfusion[13]. Some of these infants have been found to have polymorphisms of tumor necrosis factor alpha and interleukins-1b, -6, or -10. The risk of AKI is not increased among those who have a single polymorphism, but it is among the babies who have more than one. It is postulated that this group of infants is more likely to develop AKI following infection because the multiple polymorphisms result in an exaggerated inflammatory response[13,17].

Diagnosis:

1. Antenatal

Ultrasonography to diagnose parenchymal or obstructive renal lesions (as bilateral multicystic dyplastic kidneys and lower urinary tract obstructive uropathy)[17].

2. Postnatal

(a) Clinical:

Assessment of AKI begins with history and physical examination, which represent the first step in identifying clinical conditions that may predispose or lead to the condition. In the neonate, most renal failure is due, at least initially, to prerenal factors, and early identification of these factors can prevent progression of renal injury[14].

Oliguria is usually present but is not necessary for the diagnosis, non-oliguric AKI occurs but is infrequently diagnosed. The most common clinical sign in AKI is edema, due to a continuation of fluid intake in the presence of unrecognized oliguria. Edema is not a feature of non-oliguric AKI, and polyuria and natriuresis may occasionally lead to salt depletion and dehydration[40]. The diagnosis of pre-renal failure is confirmed by an improvement in urine flow and renal function in response to fluid repletion, provided there is no clinical evidence of circulatory overload, a fluid challenge of isotonic saline 10 ml/kg should be given intravenously over 1 hr, failure to respond confirms ATN as the diagnosis[40].

(b) Biochemical:

AKI is commonly detected in the absence of specific physical signs by the finding of typical biochemical abnormalities during the investigation of an ill infant[40].

(1) Blood studies:

They should include a complete blood count with red cell morphology, coagulation studies, chemistry panel (including sodium, potassium, bicarbonate, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total protein, albumin), and arterial blood gas[30].

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Table (2): Typical changes in plasma biochemical values in acute renal failure[39]

Substance	Direction of change from normal
* **Creatinine**	Increase
* **BUN**	Increase
* **Sodium**	Decrease
* **Potassium**	Increase
* **Uric Acid**	Increase
* **Calcium**	Decrease
* **Inorganic phosphate**	Increase
* **Chloride**	Increase or decrease
* **Hydrogen ion**	Increase
* **Bicarbonate**	Decrease

(2) Urinary studies:

Urinalysis, urine culture, random urinary protein / creatinine ratio, urine osmolality and urine-to-plasma creatinine ratio[30].

(3) Urinary indices:

Urinary sodium concentration, fractional excretion of sodium (FENa) and renal failure index (RFI) can be useful in differentiating between prerenal and intrinsic renal disease. FENa measurements, however, should be used with caution in very preterm infants because of the variability of their values in the first 5 days after birth[30].

The FENa and RFI can be calculated by the following equations[30,32,43] :

$$\text{FENa (\%)} = \frac{(\text{urine sodium} / \text{plasma sodium})}{(\text{urine creatinine} / \text{plasma creatinine})} \times 100$$

RFI= urine sodium / (urine/plasma creatinine ratio)

* Diagnostic indices in neonatal acute renal failure[30,43].

	Prerenal	**Intrinsic renal**
Urine sodium (mEq/L)(mmol/L)	31±19(<30)	63±35(>60)
Urine protein / creatinine ratio	29±16	10±4
Fraction excretion of Na (%)	< 2.5	> 2.5
RFI	< 3	> 3

Very preterm babies (<32 weeks) have a high urinary sodium concentration and excretion rate even in health. In this subgroup, suitable cut off points for diagnosis of ATN are a RFI of over 8 or a FENa of > 6%[40].

(4) Novel early biomarkers of acute kidney injury:

Numerous resources have been expended to improve our understanding of the pathophysiology, to test definitions and classification systems, and to develop non-invasive urinary biomarkers of AKI. Because of the many shortfalls of using changes in SCr to diagnose AKI [43], biomarkers are currently being explored to differentiate between different causes of established AKI, to detect AKI early, and to prognosticate outcomes. Currently, the most promising early non-invasive biomarkers of AKI are serum and urinary neutrophil gelatinase-associated lipocalin(NGAL), urinary interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), and serum cystatin C which are elevated in neonates undergoing cardiopulmonary bypass surgery and in a heterogeneous critically ill pediatric population but not in those with sepsis[20].

Neutrophil Gelatinase-Associated Lipocalin:

The exact physiologic role played in the kidney by NGAL (also called lipocalin - 2 or siderocalin), a 25-kD protein, remains a mystery. One possibility, however, is that it is involved in renal morphogenesis, such as induction of repair and reepithelialization[45]. It was originally isolated from specific neutrophil granules and was later located in the bone marrow cells, lungs, proximal renal tubules and colonic epithelium. It is generally expressed in very low concentration but increase in the presence of epithelial injury or inflammation[46].

The expression of the NGAL messenger ribonucleic acid (mRNA) and protein in the kidney has been shown to be significantly increased in the kidney tubules of patients with ischemic, septic, nephrotoxic and even following contrast administration or post-transplantation AKI, as well as within 2-6 hours post–cardiopulmonary bypass surgery and at frequent intervals for 24 hours post–cardiopulmonary bypass surgery in children [45,46].

Interleukin-18:

Is a candidate biomarker for renal parenchymal injury. The cytokine IL-18 is formed in the proximal tubules and detected in the urine[45]. It is markedly elevated in patients with established AKI but not in subjects with urinary tract infection, chronic kidney disease, nephrotic syndrome, or prerenal azotemia. Urinary IL-18 was found to be significantly upregulated before the increase in serum creatinine in patients with acute respiratory distress syndrome who develop AKI[45]. Furthermore plasma IL-18 levels are known to be increased in various pathophysiologic states, such as inflammatory arthritis, inflammatory bowel disease, systemic lupus erythetnatosus, psoriasis, hepatitis and multiple sclerosis. The relationship between plasma and urine IL-18 remains largely unexplored [46].

Kidney Injury Molecule 1:

Is upregulated in post–ischemic injury in the proximal tubule. Urinary KIM-1 has been suggested as another biomarker for the diagnosis of ischemic ATN. It has been suggested that high urinary KIM-1 levels may be an independent predictor (versus

creatinine clearance, proteinuria, or donor age) for graft loss in post–renal transplantation patients[45,47].

Cystatin C:

Cystatin C is a 13-kD cysteine protease inhibitor that has gained popularity as an alternative to serum creatinine in the measurement of renal function and the glomerular filtration rate (GFR). In contrast to the 3 previously discussed biomarkers, however, serum cystatin C levels are usually noted when the tissue injury has led to significant changes in the kidney's filtration function or capability[45].

(c) Imaging:

Differentiating between intrinsic renal and postrenal disease in neonates is achieved best through renal ultrasonography and voiding cystourethrography. Ultrasonography with Doppler interrogation can provide information regarding the presence or absence of kidneys, size, presence or absence of hydronephrosis, bladder distention, and blood flow to the kidneys. Voiding cystourethrography can identify lesions of the lower urinary tract that cause obstruction, such as posterior urethral valves[30].

Management of acute renal failure in neonates:

In the setting of prerenal renal failure, the underlying condition should be treated and volume resuscitation implemented to restore renal perfusion. In postrenal disease, obstruction may be relieved by primary surgical repair or via temporary drainage with an indwelling catheter. After the diagnosis of intrinsic renal failure is determined, attention is directed to management of the complications that accompany AKI[30].

A) Conservative management:

1. Urine output:

Trying to maintain urine output in established renal failure with medical therapy has to be balanced with the risk of using agents that are with neurological risk (eg. Mannitol) or directly nephrotoxic (eg. frusemide)[17]. Neonates who have hypotension and fail to respond to volume resuscitation often require inotropic and systemic vasoactive support. The use of "renal" dose dopamine (1 to 3 mcg/kg per minute) to improve renal perfusion following an ischemic insult is a very common practice in intensive care units. Dopamine increases renal blood flow by promoting vasodilatation and improves urine output by promoting natriuresis[30].

2. Fluid balance:

Meticulous attention to fluid balance is essential. Hypovolemia should be urgently corrected with isotonic or colloid according to clinical assesement of circulating volume. Maintenance fluid is then calculated as insensible water loss plus urine output, and is adjusted according to clinical assesement of the patient[40].

3. Nutrition:

Attention to nutrition is essential in AKI management to prevent excessive tissue break, formula that has a low renal solute load and low phosphorus (similac PM 60/40) should be used. If oral feedings are not tolerated, nutrition should be administered intravenously with a goal of providing a minimum of 50 kcal/kg per day and 1 to 2 g/kg per day of protein.[30].

4. Drugs:

The majorty of the drugs used in a neonatal intensive care unit will need adjustment of dose and frequency, depending on the calculated GFR eg. vancomycin[17].

5. Electrolytes:

* Hyperkalemia: Remove potassium from any parentral nutrition solution. Temporary interventions must be done as follows [30,40].

Intervention	Dose	Mechanism
Sodium bicarbonate	1 mEq/kg IV over 10 to 30 min	Shifts potassium into cells
Calcium gluconate (10%)	0.5 to 1.0 mL/kg IV over 5 to 10 min	Stabilizes cardiac membrane potential
Insulin/Glucose	Glucose 0.5 g/kg; insulin 0.1 U/kg IV over 30 min	Stimulates cellular uptake of potassium
Furosemide	1 to 2 mg/kg IV	Increases urinary excretion of potassium

- Double volume exchange and peritoneal dialysis are potentially life saving options through enhancing potassium excretion.

* Calcium-Phosphorus Perturbations:

Hyperphosphatemia and hypocalcemia can develop in neonates who have AKI. Treatment of hyperphosphatemia consists of dietary phosphorus restriction, using low-phosphorus formulas as well as the addition of phosphorus binders such as calcium carbonate to the formula to bind phosphorus and prevent gastrointestinal absorption. Symptomatic hypocalcemia should be corrected using intravenous 10% calcium gluconate at a dose of 0.5 to 1 mL/kg in10-15 minutes[30].

* Acid-Base Balance:

Metabolic acidosis is encountered commonly in neonatal AKI because the kidney excretes net acids generated by intermediary metabolism. When neonates exhibit severe acidosis, defined by a plasma bicarbonate concentration of 12 mEq/L (12 mmol/L) or less or plasma pH below 7.20, acidosis should be corrected by the administration of intravenous or oral sodium bicarbonate [17,30,40]. If correction cannot be achieved dialysis must be considered[40].

B) Renal Replacement Therapy

When conservative measures fail to control the complications of AKI, renal replacement therapy is indicated. Indications for initiation of acute renal replacement therapy include severe metabolic acidosis, electrolyte abnormalities (such as hyperkalemia), intoxications, fluid overload, and symptomatic uremia. The various methods of available renal replacement therapy include peritoneal dialysis, hemodialysis, and hemofiltration with or without dialysis. Although the use of hemofiltration is increasing and peritoneal dialysis is decreasing in the pediatric population, the preferred method of dialysis in the neonatal period continues to be peritoneal dialysis[17,30,40].

Outcome:

The major determinants of outcome include the presence of comorbidities and other organ failure as well as the underlying cause of the AKI [14].

The filtration rate of single nephrons and the number of nephrons present determine total GFR. When the number of nephrons is diminished, single-nephron GFR increases as the kidney works to compensate. This compensatory hypertrophy causes the glomeruli to function under increased intracapillary hydraulic pressure, which, over time, causes damage to the capillary walls. This abnormal process leads to progressive glomerulosclerosis, proteinuria, hypertension and chronic kidney disease [20].

The mortality rate of neonatal AKI ranges from 14% to73%. Reversible insults, such as drug toxicity, and cases of nonoliguric failure have good prognosis for survival and recovery[14,31]. Renal tubular dysfunction with growth failure and rickets have been described in children who have recovered from neonatal renal failure [31].

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