DISCUSSION

Acute renal injury in newborn infants continues to be an important factor contributing to morbidity and mortality of critically ill pediatric patients. It is a clinical syndrome of multifactorial origin with numerous variables influencing its evolution and resolution[42,53]. Under normal circumstances the kidneys adapt to various endogenous and exogenous stresses. However, in sick neonates and in stressful conditions like septicemia, the adaptive capacities of the kidney may be overcome leading to renal dysfunction[19,54]. The fatality among septic neonates with AKI was 2.5 times higher. This highlights AKI as an ominous complication in cases of neonatal sepsis, which has to be managed aggressively[19].

The present study was conducted on 100 septic neonates admitted to the NICU at AUCH between September 2012 and April 2013 to determine the occurrence, types and the risk factors associated with development of AKI **.** Of the 100 septic newborns enrolled in this study, 20 suffered from AKI. Renal failure was oliguric in only 25% of the cases. The AKI patients were further differentiated into prerenal failure and intrinsic renal failure [17(85%) and 3(15%) respectively] according to fractional excretion of sodium and renal failure index.[30,32,43] (fig. 5,6,table 9) .

AKI epidemiologic data in neonates are sparse and mostly from single-center studies. Published reports estimate its incidence in critically ill neonates ranging between 8% and 24%, with mortality rates between 10% and 61%[14, 15,16,19,31,38,41,54,55,56]. In a study by Williams et al in USA on septic AKI pediatric fatality decreased over 20 years from 23% to 3% [57]. Earlier studies have focused on perinatal asphyxia as the main cause of AKI[19,20,58]. It is difficult to compare information because of differences in populations examined and criteria used to estimate renal function, particularly with regard to preterm infants with low gestational age[39] . Duzova et al in 2010, reported an incidence of 32% in newborns in Turkey, 24% were septic[28].Another study in same country by Bolat et al found septic AKI neonates to be 19% [55]. Mathur et al in India conducted a case control study on 200 out born neonates with sepsis to evaluate the occurrence of acute renal failure and the factors associated with it. They reported AKI due to neonatal sepsis to be 26%[18]. In same country other studies by Jayashere et al and Pradhan et al documented occurrence of AKI in septic neonates to be 20% and 28% respectively [16,58]. Several studies reported sepsis to be a cause of AKI with an incidence ranging from 15.7% to 57% of studied neonates [14,28,41,42,46].

The prevalence of AKI among the present study septic population is 20%., which was similar to that of developing countries. NICU at the AUCH is a tertiary referral center with a large number of admissions most of them are premature babies . Moreover 90% of AKI cases were preterms (table 10). Such gestational age group are subjected to various comorbidities, which have multifactorial influences on the disease. Sepsis as mentioned before can operate through a variety of mechanisms in producing renal failure[19,42,56] such as shock, DIC, dehydration and may lead to multiple organ failure. Close monitoring to renal functions and U.O.P of the critical admitted cases leads to their early management and prevention of rapid deterioration .

The mean gestational age of the 100 studied cases was 34 weeks; 70% were preterms. Mean birth weight was 1932.6 grams. Most of the cases had early onset sepsis (66 % of the

cases) table (3) . Regarding the maternal data of studied neonates it was noted that 41 mothers had premature rupture of membrane (table 4). Blood culture was positive in 19% of cases (table 5) and pleocytosis was present in 27% (table 6) . In AKI cases it was noted that the mean of BUN in 1ST and 2nd samples were 40.3 and 42.95 respectively. The mean creatinine in 1ST and 2nd samples were 1.59 and 1.73 respectively (table 8). The mean age at presentation of acute renal failure was 4.25 ± 2.12 days.

In the present study, there was no significant statistical difference as regard gender between septic neonates with AKI (group1) and septic neonates without AKI (group 2). However, the total number of males was exceeding that of females, representing 55% and 45% respectively (table 10)**.** A study by Gharehbaghi et al reported that the prevalence of AKI in boys is more than girls (male to female ratio 1.34-3.3:1) in several studies including their own. It assumed that predisposing factors of AKI such as sepsis are more common in boys than girls[41,42]. Azat et al reported a ratio of male to female AKI neonates to be 3.16:1 for same previous reason[56].

In the present study, there was no statistical difference between the studied groups regarding mode of delivery (table10). Low birth weight infants category are significantly higher in septic AKI group neonates (55%) than neonates without AKI (table 10). This was in agreement with Mathur et al who reported that low birth weight was an important predictor of AKI in septic neonates[19]. In study by Vachvanichsanong et al 56.5% of AKI had a birth weight < 2500 gm . Low birth weight has been reported as a risk factor of developing impaired renal autoregulation and chronic kidney disease[29] . Pradhan et al reported that LBW and prematurity are risk factors for sepsis in newborn in Indian study[58]. Although 30% of AKI patients in present study were of VLBW , there was no significant difference between the two studied group as regard of this birthweight category. In Bolat et al study, very low birth weight (VLBW) infants (<1500 gm) accounted for 34.5% of the infants with AKI . Their prevalence of AKI was three times higher than that of those infants with birth weight more than 1500 g (20% vs. 7%)[54]. Cataldi et al reported that a very low birth weight infant is at specific risk of AKI.[39,55]. Gheissariei showed that their GFR was less than that of term infants [60].

In our study, there was significant statistical difference as regard preterm gestational age category between group 1 and 2. This was in agreement with by Pradhan et al[58]. Mathur et al reported that AKI was not found to be more common in septic neonates with lower gestational age [19]. On the other hand, Cataldi et al stated that prematurity must be considered one of the main risk factors for AKI development.[39,55]. There are several reasons for premature infants to be at high risk of AKI. First, these infants may suffer from insults during intrauterine life because of infections, intrauterine growth retardation, placental insufficiency or maternal medication. Second, the postnatal course of premature infants is often complicated by hypovolemia, sepsis, hypotension and ischemia. These factors would make preterm infants more vulnerable to renal failure[55]**.** Black and et al stated that preterm birth adversely affects nephrogenesis in developing kidney by decreasing renal size and nephron deficit. This has the potential to not only affect kidney function in the early postnatal period but to also increase the risk of renal disease later in life[61].Therefore, prematurity by itself is an independent risk factor for development of AKI regardless birth weight or gestational age[39,62]. Neonatal sepsis is the most important cause of morbidity and mortality especially among low birth weight (LBW) and preterm babies in developing countries [58]**.**

Fetal programming hypothesis suggests that an adverse intrauterine milieu causes structural, hormonal and metabolic adaptations in the fetus**.** Adverse intrauterine environment may produce renal damage in the neonatal period[39,55]. As regard to variable maternal risk factors in our study, there were no statistical significant difference between both groups (table 10). History of PROM was found in 41% of septic neonates, it was associated with 55% of AKI cases and in 37.5% of non AKI cases (table 4,10) . Also 28% of mothers of septic neonates had history of preeclampsia (table 4), 35% of their neonates developed AKI (table 10). Twenty two percent of studied septic neonates had history of maternal administration of antibiotics (table 4), only 6 neonates of them suffered from AKI (table 10). Non of their mothers received aminoglycosides. Cataldi et al found AKI in newborn infants to be associated with antibiotics taken by the mothers during pregnancy or delivery, confirming the influence of maternal pharmacological treatments on the fetus or newborn[18,64]. It is known that b- lactams and aminoglycosides cross the placenta, and adverse renal effects have been observed in newborn animals [39]. Antibiotic use during pregnancy was reported to have adverse effects on neonatal renal function[39,55]. Iacobelli et al and Bolat et al both reported that neonatal AKI development was associated with pregnancy induced hypertention and antenatal steroids. There was a disagreement on AKI association with PROM as Bolat et al observed that there was a significant correlation between it and AKI development but Iacobelli et al didn't [55,64]. PROM itself is an intrauterine insult[55],which when treated with antibiotics during pregnancy may contribute to exposure of newborns to nephrotoxic agents[39,55]. Pradhan et al found no significant relation to septic AKI and history of PROM[58].

It is known that prenatal steroids may lead to low birth weight and compromise organogenesis, but its effects on nephrogenesis have not yet been investigated extensively[55]. However Finken et al found that the subjects who were exposed antenataly to betamethasone had a lower glomerular filtration rate[65]. Other studies on infants whom their mothers were treated with dexamethasone had a lower kidney weight and a lower number of glomeruli and alerted tubular transporters [55,66]. On the contrary Black and et al have examined the effect of administration of antenatal steroids on nephrogenesis in the neonatal kidney. They found that although there was acceleration of glomerular maturation, the total number of nephrons was within the normal range and importantly they demonstrated that fetal exposure to maternal glucocorticoids was not the cause of the glomerular abnormalities associated with preterm birth[61]. In the present study 31% of septic neonates had history of exposure of antenatal steroids (table 4), 30% of them developed AKI (table10).

Chorioamnionitis may manifest as either a clinical or subclinical condition. When severe, it can ultimately give rise to the fetal inflammatory response syndrome, which will lead to renal inflammation in chorioamnionitis-exposed infants. This will have deleterious effects on nephrogenesis, and if present at the time of delivery, it will adversely impact on renal function. Following the hemodynamic transition at birth, it may be then that glomerular morphological abnormalities develop in these already compromised kidneys. In this regard, there is recent evidence in fetal sheep to demonstrate that such effect on nephrogenesis, leads to reduction in nephron endowment in exposed fetuses [61]. In the present study only 5 neonates of studied septic cases (5%) (table 4) had history of maternal chorioamnionitis. This low percentage may be because of poor antenatal care, which may lead to underdiagnosis of the problem. Moreover it may pass through a subclinical course. It was noted that only 2 cases (40% of chorioamnionitis cases) have developed AKI (table 10),

this can be explained by that chorioamnionitis –as previously reported – may not be severe enough or renal inflammation was not present at birth among non AKI neonates with history of its exposure.

In our study, percentage of neonates with AKI was significantly higher in patients with early onset sepsis than those with late onset sepsis (table 10), this may be explained by high incidence of EOS especially in preterms with inadequate antenatal care -associated with multiple maternal risk factors- in developing countries, leading to bad general condition of preterms with need of multiple interventions . In a study by Mathur et al the difference was not significant with respect to age of onset of sepsis[19]. Mean age at presentation of AKI in septic neonates was 4.2 ± 2.21 days in our study but in the study by Mathur et al mean age at presentation was 7.14 ± 0.85[19].

In the present work, the newborn infants were studied for potential risk factors for development of AKI such as meningitis, shock, DIC, NEC, PDA, mechanical ventilation and administration of nephrotoxic drugs. The effect of shock and DIC on development of AKI was statistically significant (table 11). These two conditions were also much more common in septic neonates with AKI in a studies by Mathur et al and Pradhan et al [19,58]. It appears that shock and DIC are the two main mechanisms through which sepsis causes AKI in neonates[19,31,42,58,59]. Increased fibrin degradation products (FDP) are frequently found in the serum and urine of patients with AKI. Temporary obstruction of peritubular or capillary vessels by fibrin deposits may therefore be an important factor in initiating the changes of tubular necrosis[19]. Jayashere et al also found septicemic shock to be significantly associated with occurrence of AKI in septicemic neonates . They suggested that an episode of shock due to sepsis causes renal anoxia and ischemia which trigger renal failure[16,68]. In study by Stojanovic et al on acute renal failure in preterm neonates they found that hemodynamic stress is the leading cause in AKI [69]. In a study by Abu helewa . it was found that neonates AKI associated with DIC and shock had high mortality rates[59]. Duzaova et al, Bolat et al, Otukesh et al and Plotz et al also reported same results[28,55,70,71].

In the present work, no statistical significant difference was detected between two groups as regard presence of meningitis in septic neonates (table 11). This was in agreement with Pradhan et al [58] .On the contrary Mathur et al in India found difference between the two groups to be significant with respect to associated meningitis, but meningitis itself did not affect mortality[19]. Kidney is a commonly affected organ during sepsis. The pathophysiology of AKI in sepsis is complex and multifactorial[72] .

In the present work, no statistical significant difference was found among group 1 and 2 (table 11) as regard presence of PDA in septic neonates as this may be because size of PDA was not significantly wide enough to compromize the circulation, such cases were excluded from the study due to heart failure. Viswanathan et al had similar result to our study and this may be due to their policy of early ligation of PDA [73]. Bolat et al and Catadli et al stated that patent ductus arteriosus may contribute to the development of AKI[39,55]. The presence of PDA and its association with AKI development may be due to the disease itself, but also to its treatment . In fact, a severe PDA causes hypovolaemia with subsequent stimulation of the renin-angiotensin system, predisposing the newborn to renal problems. Consequently, administration of NSAIDs results in decreased renal perfusion and urine output[39].

In our study results, the occurrence of NEC was insignificantly different between group 1 and 2 (table 11) . This was in agreement with Mathur et al[19] and Bolat et al study results [55]. Moreover a study by Abu helewa . found that AKI associated with NEC had high mortality rates[59].This can be noted in cases with PDA specially on indomethacin treatment in preterm infants born <1500 gm who are susceptible to hypoperfusion of vital organs and resultant co morbidities such as NEC and prerenal failure[74].

In the present work, there was no significant difference as regard mechanical ventilation on development of AKI in septic neonates (table 11). In this respect Cuzzolin et al had similar results as the current study[75]. Toth-Heyn et al stated that the therapeutic interventions applied to preterm infants as intubation had been indicated as risk factors for AKI development[23]. Bolat et al and Duzova et al found mechanical ventilation to be significantly associated with AKI in infants[28,55]. Studies by Mortazavi et al and Otukesh et al, revealed that mechanical ventilation is a significant determinant of AKI prognosis in children[42,70].

The pathogenesis of AKI associated with mechanical ventilation can be explained by several possible mechanism. First, is the compromise of renal blood flow by hypercapnia or hypoxemia, which may affect vascular dynamics via activation or inactivation of vasoactive factors such as nitric oxide, angiotensin II, endothelin, and bradykinin . Another possibility is a pulmonary inflammatory reaction in response to barotrauma, with subsequent induction of a systemic inflammatory reaction[55]. The mode of ventilation of the preterm infant also has the potential to impact on the developing kidney, since alterations in airway pressure are reported to lead to significant cardiopulmonary haemodynamic changes, which may subsequently affect renal perfusion[23]. It is likely that changes in renal blood flow will directly influence the growth of the kidney[61].

The effect of umbilical arterial and venous catherization on the development of AKI in septic neonates was insignificant in our study (table 11) . Cuzzolin et al in had similar results as the current study[75]. Toth-Heyn et al and Cataldi et al reported that the therapeutic interventions applied to preterm infants as catheterization has also been indicated as risk factor for AKI development[23,39]. Bolat et al found umbilical venous catheterization to be significantly associated with AKI but not umbilical arterial catheters[55]. Arterial thrombosis in either the renal arteries themselves or in the aorta, may occur spontaneously, but it is strongly associated with placement of an umbilical artery catheter[14]. Occurrence of renal vein thrombosis. is multifactorial diseases which is associated with presence of indwelling venous catheter and sepsis, also genetic predisposition to thromboembolism is a contributing factor[75] .

The effect of metabolic acidosis on the development of AKI in septic neonates was significant in our study (table 9). This was in agreement with Pradhan et al study on septic neonates [58]. Also in study by Duzova et al metabolic acidosis was significantly associated with occurrence of AKI [28]. It is well known that the newborn easily becomes acidotic in stressful situations, this results from impairment of renal net acid excretion[43,54]. Lower ph and concentration of bicarbonate in blood in infants has been attributed to low renal threshold for bicarbonate. Also responsible for this tendency in premature infants is an increased production of organic acids, low phosphate intake and inability of the newborn kidney to establish a steep gradient of hydrogen ions[77]. Consequently newborns are more susceptible to the metabolic insults associated with increased acid load and are unable to

maintain normal homeostasis under stress[54]. Metabolic acidosis is a conjoint finding in both sepsis and renal failure.

Further results in our study reviled that, the effect of nephrotoxic drug exposure (aminoglycosides, vancomycin, indomethacin) on development of AKI in septic neonates was insignificant (table 11). Mortazavi et al had similar results as regard the three drugs[42]. Concurrently Mathur et al, had same results concerning effect of aminoglycosides and vancomycin on septic neonates and that they were not associated with increased mortality[19]. Bolat et al stated that no significant difference was found between AKI and non AKI groups regarding the exposure to aminoglycosides and vancomycin, despite that the duration of nephrotoxic antibiotic exposure was found to be longer in infants with AKI[55].

Neonatal status may itself be a risk factor for drug-induced nephrotoxicity**.** Concurrent pathophysiological mechanisms often act in union such as reduction of renal perfusion, direct tubular toxicity, immunomediated toxicity, interference with fluids and electrolytes[78]. Sepsis is a risk factor for development of drug induced nephrotoxicity as decreased effective or absolute circulating blood volume results from sequestration of fluid into third-space compartments[79]. The proximal tubule is generally to be regarded as the target structure for renal damage. Anatomical, physiological and biochemical differences within the nephron may explain the damaging effects of some drugs[78,80].

Most cases of renal failure in infants and children are due to intrinsic renal disease, but in newborns, 60% to 90% of cases are prerenal in origin[14,41] The neonatal kidney is particularly vulnerable to the effects of hypoperfusion since the renal vascular resistance and plasma renin activity are high. Consequently, renal blood flow is proportionately more reduced in neonates[16,19,42].

In the present work the septic patients suffering from acute kidney injury patients were differentiated into 17(85%) with prerenal failure and 3(15%) with renal failure (fig.4,5) according to fractional excretion of sodium (FENa) and renal failure index (table 9) [32,41,43] . There was no cases of post renal causes as they were excluded from the study**.** The AKI cases were predominantly affected due to inadequate renal perfusion. They had variable signs of hypothermia, hypotension, dehydration, shock and majority had history of inadequate antenatal care**.** Immediate and aggressive management of pre renal azotemia often leads to rapid improvement of renal function and urinary output[41,56].

In studies on AKI cases due to heterogeneous causes including sepsis Iacob et al had similar results as the majority of their studied newborn cases were prerenal [80] . Viswanathan et al studied AKI in extremely LBW and reported that pre-renal mechanisms account for 85% of AKI and that intrinsic renal and post-renal failures are less frequent in neonates, accounting for 11 and 3%, respectively [73]. Bolat et al study results were prerenal failure 48.8%, renal failure 46.4% and postrenal 4.8%[55]. In studies in Iran evaluating causes of AKI in neonates by Gharehbaghi et al and Mortazavi et al the prevalence of intrinsic renal failure was higher than prerenal (43.5% vs 49.5%) and (52% versus 42.4%) respectively, that was considered different from other studies[32,42]. Gharehbaghi et al stated that is may be due to delayed hospitalization and management which may cause aggravation of renal injury. Mortazavi et al also added that inadequate supportive care during transportation of neonates with presence of hypothermia,

inadequate feeding and hypoxia may cause acute injury to the kidneys in a neonate who is referred for any other reason[42].

In the present study, non oliguric renal failure was the predominant form as its incidence in septic neonates with AKI was 75% (fig 6). This was in agreement with Pradhan et al, Jayashere et al and Mathur et al. who reported nonoliguric AKI to be 78%,83%, 85% in their studied septic neonates with AKI respectively [16,19,59] . Studies by Wasiu et al and Honda et al stated that septicemia may be accompanied by non oliguric AKI[81,82] . Stapleton et al and Loza et al found nonoliguric acute renal failure in newborns due to miscellaneous causes to be 97% and 78% respectively [31,83], and stated that there is underestimation of the incidence of renal failure because the nonoliguric form of AKI is seldom recognized[31].

On the other hand, other studies reported AKI in neonates to be predominantly oliguric [19,42] . Such studies evaluated AKI due to variable causes, as perinatal asphyxia, which was not included in our study that may be responsible for a higher frequency of oliguria**.** Although the mechanisms involved in the higher urine flow rates in nonoliguric acute renal failure are not clear, the causes of nonoliguric AKI were similar to those of oliguric AKI. Four mechanisms have been implicated; decreased renal blood flow, reduced glomerular capillary ultrafiltration, tubular obstruction by cast and cellular debris and back leakage of filtrate across damaged tubular epithelia. Little is known, however, as to what determines oliguric or nonoliguric AKI. Progressive azotemia occurred in nonoliguric patients despite liberal daily urine volumes, owing to the impaired glomerular filtration rate and renal concentrating capacity of nonoliguric patients[82,84,85]. Prompt management of coexisting conditions by maintenance of renal perfusion may lead to less severe reduction in GFR and better preservation of tubular function and may account for lower incidence of oliguria in the present study. As studies have shown that renal vasodilator drugs, potent diuretics and volume expansion can convert oliguric into nonoliguric failure, provided, they are administerd early in course of disease[19,46,82] . Degree of oliguria doesn't necessarily correlate with the severity of injury. Moreover AKI can occur without affection of urine output and classifying AKI as oliguric or nonoliguric has a prognostic value rather than a diagnostic indication [46]. Nonoliguric AKI has a better prognosis due to a more gentle renal injury and better-preserved fluid and electrolyte homeostasis[69].

In briefing AKI among septic neonates in our NICU necessitates early recognition of risk factors and rapid effective treatment of co-morbid conditions which will reduce mortality and morbidity in NICU. Further wide scale studies are needed to continue focusing on such serious problem.

SUMMARY

Sepsis is a severe and dysregulated inflammatory response to infection characterized by end organ dysfunction distant from the primary site of infection. Development of acute kidney injury during sepsis increases patient morbidity and mortality of critically ill pediatric patients. It is a clinical syndrome of multifactorial origin with numerous variables influencing its evolution and resolution. Recovery of kidney function is frequently possible if diagnosed early and treatment of causative factors instituted is the key of successful management of this condition in neonates.

The aim of this study was to determine the occurrence, types of acute kidney injury in septic neonates and identify the potential risk factors associated with its development as meningitis, shock, DIC, NEC, PDA, mechanical ventilation and administration of nephrotoxic drugs.

To achieve this goal, 100 septic newborn infants admitted to the neonatal intensive care unit at Alexandria University Maternity Hospital from September 2012 to April 2013 were included in the study. Patients were included in study if they had 2 or more clinical signs of sepsis and at least one laboratory finding suggestive of sepsis. Patients were diagnosed with acute kidney injury if blood urea nitrogen >20mg/dl and /or serum creatinine >1.5mg/dl on 2 separate occasions at least 24 hours apart.

All newborn infants enrolled in this study were subjected to thorough history taking, full physical examination, and biochemical markers to detect sepsis and acute kidney injury. Differentiation between prerenal and intrinsic renal disease has been done using fractional excretion of sodium (FENa), and renal failure index (RFI). Abdominal ultrasonography was only done when anomalies and obstructive uropathy was suspected.

Prevalence of AKI among the studied septic neonates was 20%. They were differentiated into 17(85%) with prerenal failure and 3(15%) with renal failure according to fractional excretion of sodium (FENa) and renal failure index (RFI). Nonoliguric renal failure was predominant constituting 75% of cases, with oliguria being only in 25% of the cases. The mean gestational age of the study population was 34 week and seventy percent of the studied group were preterms. Most of the cases had early onset sepsis. Mean age for development of AKI was 4.25 days. The most important risk factors for development of acute kidney injury in septic neonates were prematurity, low birth weight, shock, DIC and metabolic acidosis.

Wide scaled epidemiological studies to better understand the exact incidence and short and long term outcomes of AKI among septic neonates are greatly needed.

CONCLUSION

- The prevelance of AKI among septic neonates study in NICU at AUCH is 20% , most of them are preterms.
- Early onset sepsis is of high prevelance among AKI group of neonates.
- Prematurity and low birth weight are important risk factors for the development of AKI in septic neonates.
- Shock , DIC and metabolic acidosis were significantly associated with AKI.
- Non oliguric renal failure was the predominant type among the studied septic neonates.
- Prerenal type of AKI was the most common type among the septic renal failure cases.