Effect of Septicaemia on Renal Performance in the Neonate

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Abstract

Acute Renal Failure (ARF) and renal impairment may result from insults to the otherwise normal neonatal kidneys in the postnatal period. Neonatal septicaemia is associated with multiorgan dysfunction and is a leading cause for the occurrence of acute renal failure in such infants.

Aim of the Study: 1s to assess the occurrence of ARF complicating neonatal sepsis and effect of associated contributing factors.

Patients and Methods: Over a period of 12 months at the neonatal department of Al Galaa teaching hospital, out of 250 studied cases with neonatal sepsis, ARF complicated 79 (31.6%) of neonates. All cases were assessed for gestational age, birth-weight, sex, AS, and other co-morbidities: nephrotoxic drugs, DIC, shock, maternal drug intake and mechanical ventilation. A full sepsis screen and evaluation of renal functions by estimating the urine output, BUN and Pcr was carried out for all studied babies. ARF was diagnosed if Pcr >1.5mg/dl adjusted for gestational and postnatal age, with or without oliguria, with or without increased BUN >20mg/dl., on two separate occasions 24 hours apart.

Results: Majority of cases of ARF complicating neonatal sepsis were preterm babies between 32-36 weeks gestation, 35 cases (44.3%). Oliguric ARF was found in 16.5% of cases. The mortality rate was 72.2% (57 cases) in ARF compared to 26.3% (45 cases) in sepsis without ARF (p<0.001). Acute renal failure was significantly higher in low-birth-weight (LBW) and extremely low-birth-weight (ELBW) neonates of same gestational age group without ARF (87.4% & 30.3% Vs 65.5% & 17%, p<0.01 & p<0.001 respectively). DIC and shock were significantly higher in ARF complicating neonatal sepsis (p<0.05, p<0.001). Perinatal asphyxia, mechanical ventilation and nephrotoxic drugs did not significantly increase the occurrence of ARF in septic neonates. Recovery from ARF occurred in 43 (54.4%) cases.

Conclusion: ARF complicating neonatal sepsis occurred in 31.6% of our study cases. It was significantly increased in, the lower birth-weight and gestational age neonates, DIC and shock.

Key Words: Sepsis – ARF – Neonates.

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Introduction

ADVANCES in neonatal intensive care has markedly improved the management and survival of the high-risk neonates; however, sepsis remains a leading cause of morbidity and mortality among neonates in these facilities [1]. Although the presence of multiple organ dysfunction and other co-morbidities certainly contributes to the high mortality [2].

Sepsis is characterized by a generalized inflammatory response and activation of the coagulation and fibrinolytic cascades, resulting in endothelial injury [3]. A broad array of humoral mediators are released in the systemic circulation, including cytokines, lipid mediators such as platelet activating factor and arachidonic acid metabolites, endothelin-1, and complement components. Systemic hypotension results in renal ischemia, and contributes significantly to the development of septic ARF. Intra-renal vasoconstriction, owing to an imbalance between vasodilatory and vasoconstrictory substances, results in a decline in renal blood flow (RBF) and abnormalities in intra-renal blood flow distribution that predominantly affect the outer medulla [4]. Inflammatory cells infiltrate the kidney, causing local damage by release of oxygen radicals, proteases, and further production of inflammatory cytokines. Leukocyte-endothelial interactions result in physical congestion of the medullary vasculature and a further decreased regional blood flow. Dysfunction of the coagulation and fibrinolytic cascades contributes to intra-glomerular thrombosis. Tubular injury leads to cell detachment with intratubular obstruction and tubular back-leak. Recovery from ARF requires clearance of necrotic tubular cells and debris, as well as regeneration and repair of the non-fatally injured cells.

ARF occurs in as many as 3.4% to 24% of neonates admitted to neonatal intensive care units.
Acute Renal Failure (ARF) is a complex disorder with clinical manifestations ranging from mild dysfunction to complete anuric renal failure. ARF may be oliguric or non-oliguric, depending upon the severity of the reduction in GFR and the degree of tubular reabsorption. Most often, ARF is recognized because of oliguria, although non-oliguric neonatal ARF is being detected with increasing frequency. Normal urine output is found in approximately one-third of neonates with ARF, although low urine output may occur in the absence of ARF. So, if urine output alone is used to assess renal function, ARF often will be either overlooked or over diagnosed. The mortality of oliguric neonatal renal failure may be as high as 60% in medical ARF and even higher in neonates with congenital heart disease, or with anomalies of the genitourinary system. In contrast, non-oliguric renal failure in neonates has an excellent prognosis [7].

The incidence of intrinsic oliguric ARF in newborn infants admitted to the NICU ranges between 1-6% in retrospective studies and 6-8% in prospective studies [6].

**Aim of the study:**

In the following study, the aim was to evaluate the risk of occurrence of acute renal failure in cases of neonatal septicaemia and to evaluate other contributing factors complicating ARF in these neonates.

**Patients and Methods**

This randomized controlled prospective case-control study was carried out on the high risk neonates who were admitted to the neonatal intensive care unit at Al Galaa Teaching Maternity Hospital, a central tertiary level neonatal department following the General Organization of Teaching Hospitals and Institutes (GOTHI) in Egypt. All babies admitted to the NICU in the period from February 2009 to January 2010, who were suspected of having neonatal sepsis, whether early-onset (EOS) or late-onset (LOS) were assessed for the presence of acute renal failure. Babies who had neonatal sepsis and complicated by ARF (Group I) are compared to those controls with neonatal sepsis without acute renal failure (Group II). All cases were studied prospectively and selected on the basis of presence of indices of neonatal sepsis using the department guidelines of sepsis screen. All selected cases had a full clinical evaluation including assessment of gestational age, birth weight, sex, AS at birth, maternal medications as non-steroidal anti-inflammatory drugs (NSAIDs) e.g. indomethacin for preterm labour, or receiving antihypertensives ACE inhibitors e.g. captopril, age of onset of sepsis, and the use of nephrotoxic drugs. Assessment of gestational age was done using the Dubowitz scoring system for physical and neurological evaluation [11]. Birth weight was taken using an electronic scale measure for all studied cases on admission to the NICU. All sick and preterm babies (<35 weeks GA) are started on antibiotics, an aminoglycoside (amikacin)+B lactam (usually Ampicillin) from admission according to the guidelines of the department. Babies who received potentially nephrotoxic drugs such as indomethacin for patent ductus arteriosus (PDA) in preterm babies were also evaluated for renal functions. Birth asphyxia was diagnosed if: Intrapartum fetal distress as assessed by the obstetrician, AS
<5 at 5 min of postnatal age, metabolic acidosis during the 1st hour of life.

Venous samples were collected through a peripheral IV line and analyzed for a complete blood count (CBC), CRP, ESR and serum glucose; blood culture was collected from a separate peripheral IV site.

Urine quantification was done either by bag collection, or urethral catheterization in VLBW babies in which urine bag collection is difficult due to small amount of urine in these babies. Catheterization is used if an infant has failed to pass urine by 36-48 hrs of age and is not hypovolemic.

Urine culture was collected through a supra pubic aspirate in girls or a clean catch method in boys.

The CBC samples were collected on EDTA in Advac tube and analyzed on the Cell Dyne 1700 Cell Coulter. The differential count is done with Leishman stain to calculate the immature to total (I:T) ratio. Venous blood samples for CRP are analyzed using semi-quantitative reagent kit (TECO diagnostics). It is considered significant if >8mg/dl. Venous blood samples for ESR estimation are collected on Na citrate Advac tube and analyzed using the Westergren ESR pipette. For blood culture, 1-2ml of venous blood is withdrawn using a complete aseptic technique, into a 10ml of biphasic blood culture medium (Hi Combi Dual Performance Medium-Polypharma Diagnostic), the blood culture bottle is incubated at 37ºC for 7 days and to be examined daily for growth. Any sign of growth will be followed by subculture on blood agar and MacConkey’s agar and identified by gram stain and biochemical reaction.

BUN is done using colourimetric of Spectra Diagnostics (Modified Urease-Berthlot Method) with reference range for neonates -18mg/dl. Creatinine is measured using Kinetic Jaffe method (Vitro Scient Diagnostics) with reference range in neonates.

0.1-1mg/dl. Both BUN and plasma creatinine are evaluated using the Spectrophotometer Remel 4040 V5 of BM Egypt.

Sepsis was diagnosed on the basis of clinical findings and a positive sepsis screen. Clinical signs suggestive of neonatal sepsis were e.g. Colour changes, skin mottling, recurrent apnea, fluctuations in blood glucose concentrations, respiratory distress, temperature instability, poor feeding, abdominal distension, inactivity, lethargy, metabolic acidosis, jaundice, etc.

A sepsis screen was considered positive if two or more of the following were present: Positive CRP >8mg/dl, a rising CRP titre on two consecutive occasions 24 hrs apart, a total leucocytic count <5000/mm or >25000/mm after 48hrs of birth, an immature: Total neutrophil (I:T) ratio of >0.2, ESR >age in days +2mm or >15mm; with or without a positive blood culture on any occasion. If neonatal sepsis was suspected, collection of 24 hours urine was requested, and the amount of urine collected was recorded every eight hours, and adjusted to the daily fluid intake. BUN and Pcr were collected 24 hours after the clinical diagnosis of sepsis and repeated 48 hours later or as needed.

Acute renal failure was diagnosed as a serum creatinine level of >1.5mg/dl, with or without oliguria (oliguria = urine output (UOP) <1ml/kg/hr) with or without a blood urea nitrogen (BUN) >20mg/dl on two separate occasions at least 24 hours apart, Babies were assured to be well hydrated and receiving adequate amount of fluids.

Exclusion criteria:

- Babies with major congenital malformations or presence of urogenital malformation.

Ethical aspects:

A written consent was taken from the parents of babies included in the study. The clinical condition of each studied case was explained to the parent before the consent was signed as well as the procedures done for each individual case. The parents were informed that the management of their neonate is running according to the guidelines of management of such cases in the department. Babies of parents who refused to sign were excluded from the study. The protocol of the research was submitted to the ethical scientific committee of the hospital and that of the General Organization Of Teaching Hospitals and Institutes, for approval.

Statistical analysis:

The results were collected, analyzed and evaluated using the student t-test and the Mann Whitney test. The data was expressed as mean ± standard deviation (SD) or number (percent). Statistical significance was considered at a p-value <0.05.

Results

Two hundred and fifty babies with neonatal sepsis were included in the study. 79 cases with ARF (31.6%) in Group (I) and 171 cases without ARF acting as controls (68.1%) Group (II).
Table (1) shows the demographic data of both studied groups. The mean (±SD) gestational age for both groups was 33.6±4.4 in group (I) compared to 36.7±3.7 in group (II). The mean birth weight was significantly lower in cases with ARF compared to cases of neonatal sepsis without ARF (2050±412 grams Vs 2620±580 grams respectively).

The overall male to female ratio in the study group was 1.29:1; 1.54:1 in group (I) compared to 1.4:1 in group (II).

Table (1): Demographic data of studied groups.

<table>
<thead>
<tr>
<th></th>
<th>Group (I)</th>
<th>Group (II)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count (n)</td>
<td>17 (68.4%)</td>
<td>79 (31.6%)</td>
<td></td>
</tr>
<tr>
<td>Gestational age (weeks) mean±SD</td>
<td>33.6±4.4</td>
<td>36.7±3.7</td>
<td>NS</td>
</tr>
<tr>
<td>Birth weight (Grams) mean±SD</td>
<td>2050±412</td>
<td>2620±580</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>LBW (&lt;2500 grams) n (%)</td>
<td>69 (87.4%)</td>
<td>112 (65.5%)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>ELBW (&lt;1000 grams) n (%)</td>
<td>24 (30.3%)</td>
<td>29 (17%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Sex (male/female ratio)</td>
<td>1.54:1</td>
<td>1.4:1</td>
<td>NS</td>
</tr>
</tbody>
</table>

Acute renal failure was significantly higher in low-birth-weight (LBW) and extremely low-birth-weight (ELBW) neonates of same gestational age group without ARF (87.4% & 30.3% Vs 65.5% & 17% respectively; p<0.01 & p<0.001).

Based on gestational age, out of seventy nine cases of sepsis with ARF, 12 cases >36w (15.2%), 35 cases 32-36w (44.3%) and 32 cases ≤31w (40.5%), versus 49 (28.7%), 82 (48%) & 40 (23.3%) respectively in cases without ARF. It was deduced that ARF complicated neonatal sepsis in 19.7% of neonates with GA >36 weeks, in 29.9% of cases between 32-36 weeks gestation and in 44.4% of cases ≤31 weeks gestation Table (2).

Table (2): Distribution of gestational age among the two groups.

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>Group (I) N (%)</th>
<th>Group (II) N (%)</th>
<th>Total N (%)</th>
<th>% With ARF</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;36 wks</td>
<td>12 (15.2%)</td>
<td>49 (28.7%)</td>
<td>61 (24.4%)</td>
<td>19.7%</td>
</tr>
<tr>
<td>32-36 wks</td>
<td>35 (44.3%)</td>
<td>82 (48%)</td>
<td>117 (46.8%)</td>
<td>29.9%</td>
</tr>
<tr>
<td>≤31 wks</td>
<td>32 (40.5%)</td>
<td>40 (23.3%)</td>
<td>72 (28.8%)</td>
<td>44.4%</td>
</tr>
</tbody>
</table>

Sepsis was confirmed by positive blood culture in 58 cases (23.2%), 36 cases (62.1%) with early-onset (EOS) and 22 cases (37.9%) with late-onset (LOS), while clinically supported positive sepsis screen cases accounted for 76.8% (192 cases).

Acute Renal Failure was diagnosed in 31.6% (79 cases) of neonates with sepsis, 48 (60.7%) males and 31 (39.3%) females. The male to female ratio of ARF with neonatal sepsis was 1.54:1.

Oliguric ARF was found in 16.5% (13 cases) in our study group.

The mean (±SD) age of diagnosis of ARF was 2.3±0.6 days and a mean duration of recovery from ARF of 6.8±2.04 days. Recovery from ARF occurred in 39.2% (n=31) of cases; the recovery rate for different gestations was 75% (9 cases) in >36 wks gestation, 45.7% (16 cases) between 32 & 36 weeks and 18.7% (6 cases) in <32 weeks gestation.

The mortality rate was 72.2% (57 cases) in ARF compared to 26.3% (45 cases) in sepsis without ARF.

Table (3): Effect of compounding factors among both studied groups.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Group (I) n (%)</th>
<th>Group (II) n (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EOS (&lt;72 HRS)</td>
<td>43 (54.5%)</td>
<td>67 (39.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>LOS (&gt;72 HRS)</td>
<td>36 (45.5%)</td>
<td>104 (60.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Nephrotoxic drugs</td>
<td>38 (48.1%)</td>
<td>89 (52%)</td>
<td>NS</td>
</tr>
<tr>
<td>Perinatal asphyxia</td>
<td>26 (33%)</td>
<td>59 (34.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>DIC n (%)</td>
<td>51 (64.6%)</td>
<td>50 (29.2%)</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Shock n (%)</td>
<td>57 (72.1%)</td>
<td>48 (28%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>MV n (%)</td>
<td>35 (44.3%)</td>
<td>54 (31.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Maternal drug intake n (%)</td>
<td>41 (51.8%)</td>
<td>62 (36.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality n (%)</td>
<td>57 (72.2%)</td>
<td>45 (26.3%)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>
Fourty three cases (54.5%) of ARF had EOS, and 45.5% of cases had LOS, compared to 39.2% & 60.8% of cases respectively in non renal failure cases. Table (3).

Dessimated Intravascular Coagulation (DIC) occurred in a significantly higher frequency in cases with ARF (64.6% Vs 29.2%, \( p < 0.05 \)). Similarly, shock complicating sepsis – ARF was significantly higher than in non ARF sepsis cases (72.1% versus 28%, \( p < 0.001 \)). On the other hand, nephrotoxic drugs, as a compounding factor, had no statistically significant effect upon the occurrence of ARF among the two groups, and accounted for 48.1% in ARF group versus 52% in sepsis without ARF, while perinatal asphyxia was present in 33% & 34.5% of cases of sepsis with and without ARF respectively. More cases with ARF were mechanically ventilated (44.3% Vs 31.6%) although the difference was not statistically significant among both groups. The maternal drug intake in the peripartum period had no significant effect on the occurrence of ARF (51.8% Vs 36.2%). Most neonates had more than one predisposing factor. Among admitted neonates with ARF, mortality rate was significantly higher than among cases without ARF (72.2% & 26.3% respectively, \( p < 0.001 \)) Fig. (2).

![Fig. (2): Comparison of coexisting risk factors in both groups.](image)

**Discussion**

Acute renal failure (ARF) is a common complication of neonatal sepsis and carries an ominous prognosis. Prevalence of ARF with neonatal sepsis in our study accounted for 31.6% of studied cases. Although ARF in neonates has been reported to be predominantly oliguric, it was observed that ARF secondary to neonatal sepsis was predominantly non oliguric. Fortunately the prognosis for non-oliguric ARF is excellent unless multiorgan failure result. In our study, ARF was predominantly non-oliguric, while oliguric ARF accounted for 16.5% of cases with neonatal sepsis. Predisposing factors such as perinatal asphyxia, DIC and shock compromises the renal blood flow and hence the reduction in glomerular filtration rate (GFR) with resulting oliguria. Anticipation of such conditions and appropriate corrective measures should be implemented to improve renal perfusion and GFR.

Very low birth weight infants are at high risk for the development ARF. Prematurity and low birth weight infants constituted a large population of our study cases (75.6% & 72.4% respectively), which might explain the high incidence of ARF in our cases. In our study group, ARF occurred in 29.9% & 44.4% of cases between 32-36 weeks gestation an < 31 weeks gestation respectively. Only 15.2% of term cases suffered ARF-neonatal sepsis. Eighty-seven percent (87.4%) of low-birth weight babies (<2500 grams) & 30.3% of ELBW (<1000 grams) had ARF.

The prevalence of ARF in boys is more than girls (male to female ratio 1.54:1), which is in agreement with reports from other studies [7,11,12]. Airede and colleagues reported a male-female ratio of 3.3:1 in neonates with ARF [11]. The high frequency of ARF in boys is assumed to be the result of the increased susceptibility of boys to several predisposing factors such as sepsis and respiratory distress syndrome.

Several clinical conditions contribute significantly to the development of acute renal failure and increase risk of death. We reported a neonatal mortality rate (NMR) of 72.2% in ARF associated sepsis cases, which was significantly higher than in sepsis without ARF (26.3%). Recovery occurred in 54.4% of ARF cases and the recovery rate was higher in the more advanced gestational age groups. Cases with more than one risk factor had a higher mortality. Several compounding factors, other than sepsis, contribute individually or in different combinations to the occurrence of ARF. Perinatal asphyxia, hypotension and shock, mechanical ventilation, DIC, nephrotoxic medications received by the neonate, and maternal medications are among several factors that influence the frequency of ARF in septic neonates [13].

The most common significant predisposing factors for ARF in our study were DIC and shock. Cases who suffered DIC and shock were associated with significantly increased mortality (\( p < 0.05 \)).
Perinatal asphyxia, mechanical ventilation, nephrotoxic medications, maternal medications did not alter the frequency of ARF in septic neonates.

The preterm neonate, were more vulnerable to develop any or several of these clinical conditions, exposing them to a lower GFR, oliguria, diminished creatinine clearance and increased Pcr. Maternal medication was the most common condition that contributed to ARF although the difference was not significant.

Nephrotoxic drugs induced ARF, displayed by Aminoglycoside nephrotoxicity typically presents with nonoliguric ARF, with urinalysis showing minimal urinary abnormalities. The incidence of aminoglycoside antibiotic nephrotoxicity is related to the dose and duration of the antibiotic therapy as well as the level of renal function prior to the initiation of aminoglycoside therapy. The etiology is thought to be related to the lysosomal dysfunction of proximal tubules and is reversible once the aminoglycoside antibiotics have been discontinued. However, after discontinuation of aminoglycoside, the serum creatinine may continue to increase for several days due to ongoing tubular injury from continued high parenchymal levels of the aminoglycoside [10]. Mothers of infants with acute renal failure received more drugs during pregnancy and delivery (mainly antihypertensives and NSAIDs). NSAIDs interference with endogenous renal prostaglandin production will increase angiotensin II-dependent vasoconstriction, leading to reduced GFR and renal insufficiency. It is therefore important to monitor closely renal function in pre-term infants receiving indomethacin. ACE inhibitors taken by pregnant mothers cause profound hypotension, anuria, and may even precipitate ARF in neonates.

In some studies, the mortality rate in oliguric ARF due to acquired conditions such as asphyxia and sepsis was 60%. [2,9] in our study the mortality was higher (72.2%) which might be due to the higher rate of prematurity in our study group.

In a study by Mathur and coworkers in India, 26% of septic neonates developed ARF [8] Mortality of ARF among septic neonates is high, 70.2% Vs 25% in septic neonates without renal failure. Similarly, like other studies, mortality of ARF in septic neonates was significantly higher than nonseptic patients in our study. Agras et al. [12] found a 25% hospital mortality rate in neonates with ARF. Premature infants constituted 31 % of their cases, and many (47%) of their patients had non-oliguric renal failure. Mathur et al. [8] prospectively studied mostly term neonates with sepsis and found a 26% incidence rate of ARF. The mortality rate was significantly higher in those with ARF than in those with no ARF (70.2% Vs 25%, p<0.001). Delayed presentation and recognition of neonatal sepsis is associated with rapid development of multiorgan dysfunction and increased risk of mortality. The mortality being several times higher in neonates with ARF demands a greater awareness of this entity among practitioners and better management of this condition.

The commonest significant predisposing factors for ARF in our patients with sepsis were shock and DIC. Perinatal asphyxia, mechanical ventilation and nephrotoxic drugs played important roles but did not significantly affect the occurrence of ARF. Acute renal failure associated with asphyxia was reported in several other studies to be predominantly nonoliguric [13,15]. Accordingly, Pcr should be monitored regularly in high-risk cases as not to overlook ARF and initiate early intervention. Acute renal failure occurred more frequently in low birth weight neonates with sepsis although the difference was not significant.

Conclusion:

Acute renal failure complicating neonatal sepsis carries a high mortality. It is predominantly nonoliguric. Supportive therapy is effective in most cases of neonatal ARF. Early recognition of predisposing risk factors for ARF and rapid effective correction of contributing conditions such as improper oxygenation, adequate ventilation and cardiac output, blood pressure abnormalities, and early treatment of sepsis is needed for prevention and effective management of ARF. The early detection of oliguria and monitoring of renal functions are imperative to reduce mortality and morbidity in neonatal ARF.

References


