

AIM OF THE WORK

The aim of the present work is to determine the occurrence , types and predisposing factors of acute renal failure (ARF) in septic neonates admitted to NICU at El- Shatby University Children Hospital.

PATIENTS AND METHODS

Study design:

Non interventional cross-sectional analytic study conducted to detect the occurrence, types of acute renal failure 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.

Study setting:

This study was conducted in the NICU at Alexandria University Maternity Hospital from September 2012 to April 2013.

Target population:

One hundred septic neonates among those admitted at the neonatal intensive care unit at Alexandria University Maternity Hospital.

Inclusion criteria:

Neonates suffering from sepsis

Exclusion criteria:

- Neonates with major congenital anomalies (renal or extrarenal).
- Conditions affecting the kidney not related to sepsis e.g:
 - Hypoxic ischemic encephalopathy
 - Heart failure

Patients were included in the study if they had two or more clinical signs and at least one laboratory findings suggestive of septicaemia such as:^(47,48,49)

1. Clinical signs like temperature instability, lethargy, irritability, change in tone, feeding problems, apnea, tachypnea, changes in skin colour (mottling, cyanosis and pallor), hepatomegaly, splenomegaly.
2. Laboratory findings of septicaemia including :
 - * Positive culture (blood /urine /CSF/ BAL)
 - * Leucocytosis
 - * Quantitative C-reactive protein (>10 mg/dl).
 - * Leucopenia
 - * Thrombocytopenia
 - * I/T ratio >0.2

- Diagnosis of meningitis were established if :
 - * High leucocyte count with predominance of neutrophils
 - * High protein concentration in cerebrospinal fluid * Hypoglycorrhachia
 - * Growth of bacteria in CSF culture^(47,48,49).

Patients were diagnosed with acute renal failure based upon:

Blood urea nitrogen >20mg/dl and /or serum creatinine >1.5mg/dl on 2 separate occasions at least 24 hours apart.

- * Oliguria was defined as urine output <1 ml/kg/hr⁽¹⁸⁾.
- * Metabolic acidosis was diagnosed if blood ph <7.20 and HCO₃ <12mmol/L.
- * Abdominal ultrasonography was only done when anomalies and obstructive uropathy was suspected.

Differentiating between prerenal and intrinsic renal disease

Has been done using fractional excretion of sodium (FENa) and renal failure index (RFI).

- * 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^(26,42).

	Prerenal	Intrinsic renal
Urine sodium (normal range =20-110mEq/L)(mmol/L)	<30	>60
Fraction excretion of Na (normal value at birth =0.2%)	< 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 renal failure are a RFI of over 8 or a FENa of > 6%⁽³²⁾.

Data collection:

The studied infants were subjected to:

1. Detailed history taking and clinical examination:

- a. History was obtained from hospital records and was recorded in a transform sheet to collect data with special stress on:
 - Relevant maternal prenatal and natal data.
 - Resuscitation data and APGAR score.
 - Gestational age.
 - Birth weight.
 - Baby's medical history as regard age of onset of sepsis, culture positivity, meningitis, potential risk factors for ARF (NEC, DIC, shock, oliguria and administration of nephrotoxic drugs).
 - Interventions as umbilical catherization and mechanical ventilation.
- b. Thorough clinical examination was done.
- c. Urine collection.

2. Laboratory studies

a. Bacteriological studies:

- | | |
|----------------------------|---|
| * Blood culture | * Urine culture |
| * CSF cytology and culture | * Broncho alveolar lavage when indicated. |

b. Blood studies:

- Complete blood count.
- CRP(quantitative).
- Blood chemistry (BUN, Creatinine (by modification of kinetic Jaffe reaction), Sodium, Potassium and Phosphorus).
- Arterial blood gases.

c. Urinary studies:

- Urinary sodium concentration (by integrated multisensor Technology).
- Urinary creatinine concentration.

d. Urinary indices:

- Renal failure index.
- Fraction excretion of sodium.

3. Abdominal ultrasonography:

Was only done when anomalies and obstructive uropathy are suspected.

Ultrasonography was done to exclude renal anomalies in 18 patients, and was found to be normal, except for 4 cases suffering from polycystic kidney and 2 cases with posterior urethral valve so therefore were not included in our 100 septic newborns. In the rest ultrasonography was not done as anomalies were not suspected.

The neonates were categorized into two groups:

Group (1): Septic neonates with AKI.

Group (2): Septic neonates without AKI.

Statistical analysis of the data ^(51,52)

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. Qualitative data were described using number and percent. Quantitative data were described using Range (minimum and maximum), mean, standard deviation and median. Comparison between different groups regarding categorical variables was tested using Chi-square test. When more than 20% of the cells have expected count less than 5, correction for chi-square was conducted using Fisher's Exact test or Monte Carlo correction. The distributions of quantitative variables were tested for normality using Kolmogorov-Smirnov test, Shapiro-Wilk test and D'Agostino test, also Histogram and QQ plot were used for vision test. If it reveals normal data distribution, parametric tests was applied. If the data were abnormally distributed, non-parametric tests were used. For normally distributed data, comparison between two independent population were done using independent t-test, also paired t-test is used to analyse two paired data. For abnormally distributed data, comparison between two independent population were done using Mann Whitney test Wilcoxon signed ranks test is used to analyse two paired. Significance test results are quoted as two-tailed probabilities. Multivariate logistic regression was assessed to find the most predictive factor affection ARF. Significance of the obtained results was judged at the 5% level.

Ethical consideration:

Approval for the study was obtained from the department and Faculty Ethical Review Committee. Moreover, an informed consent was obtained from all parents.

RESULTS

A total of 100 septic newborn infants admitted to the NICU at the AUCH were enrolled in this study. Prevalence of cases with acute renal failure was 20%. The acute renal failure patients 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) (fig 4 and 5). Nonoliguric renal failure was more common constituting 75% of cases, with oliguria being only 25% of the cases (fig.6).

Ultrasonography was done to exclude renal anomalies in 18 patients which were suspected by clinical examination, and was found to be normal, except for 4 cases suffering from polycystic kidney and 2 cases with posterior urethral valve so therefore were not included in our study.

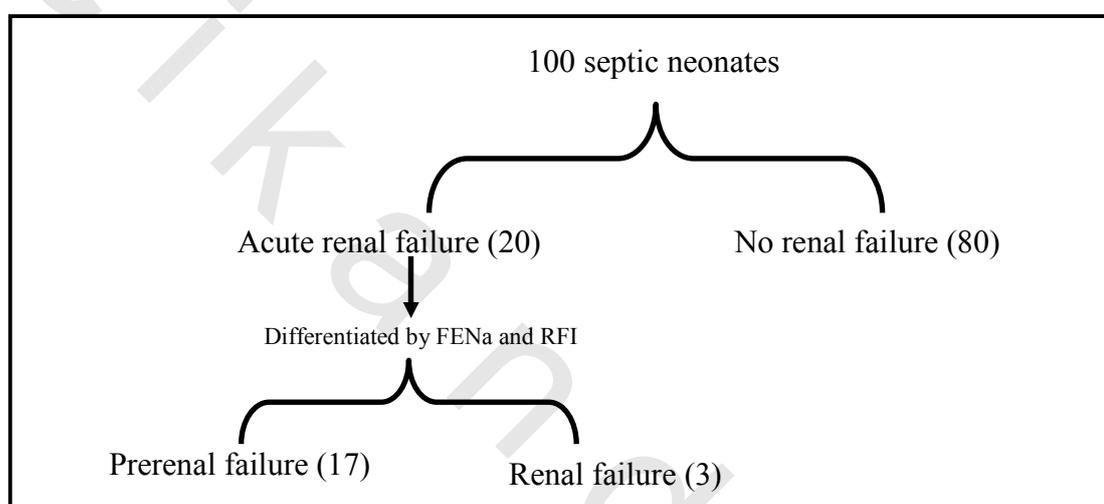


Figure (4): Acute renal failure among the studied septic neonates.

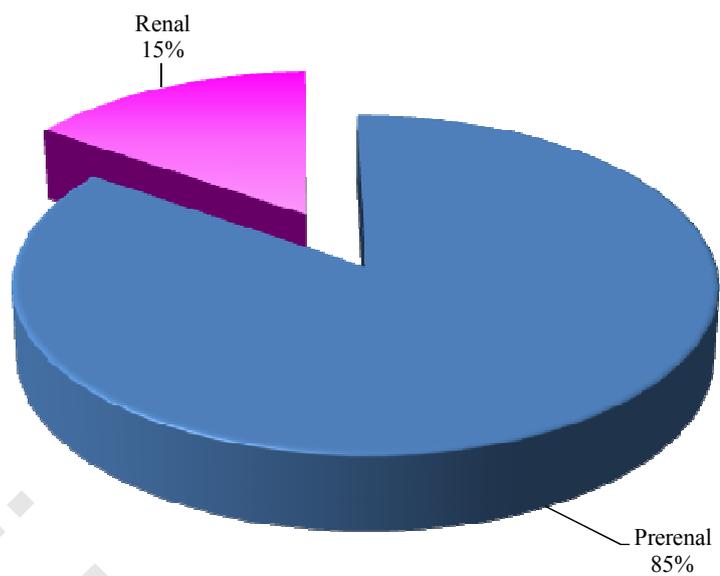


Figure (5): Acute renal failure among the studied septic neonates (n=20).

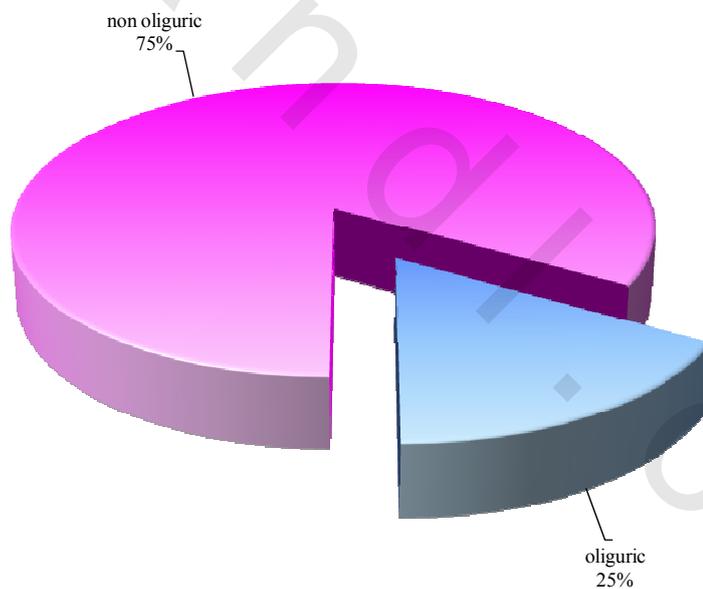


Figure (6): Acute renal failure among the studied septic neonates in relation to urine output (n=20).

Results

Table (3) The mean gestational age of the study population was 34 weeks; seventy percent were preterms. Males are more than females. Mean birth weight was 1932.6 grams. Most of the cases had early onset sepsis.

Table (3): Characteristics of studied neonates (n=100)

	No.	%
Sex		
Male	57	57.0
Female	43	43.0
Gestational age (weeks)		
<35 (preterm)	43	43.0
35 – <37 (late preterm)	27	27.0
≥37 (full-term)	30	30.0
Range	27.0 – 41.0	
Mean ± SD	34.03 ± 3.19	
Mode of delivery		
CS	79	79.0
NVD	21	21.0
Birth weight (grams)		
≥2500	25	25.0
1500 – <2500	32	32.0
<1500	43	43.0
Range	897.0 - 3800.0	
Mean ± SD	1932.63 ± 766.94	
Apgar score	1 min	5 min
Range	5.0-8.0	6.0-9.0
Mean ±SD	6.69±1.02	8.13±0.80
Age at onset of sepsis		
Early onset	66	66.0
Late onset	34	34.0

Results

Table (4) Displays the maternal data studied neonates. It is noted that 41 mothers had premature rupture of membrane. The percentage of antenatal administration of steroids and antibiotics were 31% and 22% respectively.

Table (4): Maternal data studied neonates (n=100)

	No.	%
Age of mother (years)		
<25	37	37.0
25-35	41	41.0
>35	22	22.0
Multiple pregnancy	21	21.0
Fever	11	11.0
Chorioamionitis	5	5.0
PROM	41	41.0
Preeclampsia	28	28.0
Maternal drug intake		
Antenatal steroids	31	31.0
Antibiotics	22	22.0

Table (5) Represents the bacteriological criteria of the studied neonates. Blood culture was positive in 19% of cases. Bronchoalveolar lavage and urine culture was positive in 17% and 2% respectively. None of cases had positive CSF culture.

Table (5) : Diagnostic bacteriologic profile of studied septic neonates (n= 100)

	No.	%
Positive Blood culture	19	19.0
Positive BAL	17	17.0
Positive Urine culture	2	2.0
Blood culture negative sepsis	81	81.0

Results

Table (6) Displays the laboratory parameters of negative blood culture in septic neonates. All cases had high CRP. Anemia was found in 74% of cases and polycythemia was present in 2.45%. As regard platelet count thrombocytopenia was in 71% of cases, leucocytic count was low in 50% and high in 25.9%. I/T ratio was > 0.2 in 17.2% of cases. CSF was done to indicated cases and pleocytosis was present in 27%. Arterial blood gases were done to all cases and metabolic acidosis was present in 24.6%.

Table (6): Laboratory data suggestive of sepsis in blood culture negative neonates (n=81)

	No.	%
CRP > 10 mg/dl	81	100.00
Anemia	60	74.0
Polycythemia	2	2.46
Thrombocytopenia	58	71.60
Leucopenia	41	50.6
Leucocytosis	21	25.92
I/T ratio>0.2	14	17.28
CSF pleocytosis	22	27.16
Acidosis	20	24.69

Table (7) Represents the renal functions of the septic neonates as there were two samples 24 hours apart at least, the mean of BUN in 1ST and 2nd samples were 19.5 and 18.7 respectively. The mean creatinine in 1ST and 2nd samples were 0.79 and 0.84 respectively. The mean of serum electrolytes, sodium, potassium and phosphorus were 138.2, 4 and 4, 7 respectively.

Table (7): Biochemical findings of the studied cases (n=100)

	Range	Mean ± SD	Median
BUN 1st sample	7.0-110.0	19.50+16.43	13.0
BUN2nd sample	6.0-76.0	18.76+14.53	13.0
Creatinine 1st sample	0.10-2.20	0.79+0.51	0.80
Creatinine 2nd sample	0.10-2.50	0.84+0.55	0.80
Na	128.0 – 155.0	138.26 ± 5.51	138.0
K	2.50 – 6.90	4.07 ± 0.76	4.0
Phosphorus	3.0 – 10.0	4.73 ± 1.20	4.20

Results

Table (8) displays the laboratory findings of the ARF cases. 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. The mean of serum electrolytes, sodium, potassium and phosphorus were 142, 4.6 and 6 respectively.

Table (8): Biochemical finding of renal failure cases (n=20)

	Min. – Max.	Mean ± SD	Median
BUN 1st sample	22.0 – 74.0	40.30 ± 16.81	32.50
BUN 2nd sample	24.0 – 76.0	42.95 ± 15.95	41.50
Creatinine 1st sample	0.79 – 2.20	1.59 ± 0.36	1.65
Creatinine 2nd sample	0.70 – 2.50	1.73 ± 0.37	1.80
Na	133.0 – 155.0	142.40 ± 5.73	141.0
K	2.50 – 6.90	4.69 ± 1.06	5.0
Phosphorus	4.0 – 10.0	6.06 ± 1.56	6.0

Table (9): displays the renal failure indices of AKI cases. The mean urinary sodium and urinary creatinine were 48.75 and 55. The mean FENa and RFI were 1% and 1.67. According to FENa and RFI patients were differentiated into prerenal failure and renal failure with 85% and 15% respectively. No cases of postrenal causes were identified among the septic neonate. It is noted that mean age at presentation of acute renal failure was 4.25 ± 2.12 days (not shown in table).

Table (9): Renal failure indices of acute kidney injury studied cases (n=20)

	Range	Mean ± SD	Median
U Na conc.	18.0 – 120.0	48.75 ± 25.35	50.50
U Cr conc.	21.80 – 89.0	55.08 ± 21.31	57.0
FENa (%)	0.20 – 2.80	1.01 ± 0.64	0.90
RF index	0.40 – 4.80	1.67 ± 1.20	1.25

Results

Table (10) shows the demographic data of studied septic neonates in relation to presence of acute renal failure. Prematurity and low birth weight were significantly high in patients with AKI compared to patients without acute renal failure. Also there was significant difference as regard age at presentation of sepsis between the two groups. Early onset sepsis was significantly higher in patients with AKI. As regard maternal risk factors there was no significant difference between two groups.

Table (10): Maternal and neonatal characteristics in relation to presence of acute kidney injury

	AKI Status				Test of Sig.	p
	Positive AKI (n=20)		Negative AKI (n=80)			
	No.	%	No.	%		
Sex						
Male	11	55.0	46	57.5	$\chi^2=0.041$	0.840
Female	9	45.0	34	42.5		
Gestational age						
<35 (preterm)	13	65.0	30	37.5	$\chi^2=4.937$	0.026*
35 – <37 (late preterm)	5	25.0	22	27.5	$\chi^2=0.051$	0.822
≥37 (full-term)	2	10.0	28	35.0	$\chi^2=4.762$	0.029*
Min. – Max.	28.0 – 39.0		27.0 – 41.0		t=1.332	0.192
Mean ± SD	33.40 ± 2.72		34.35 ± 3.33			
Median	34.0		35.0			
Mode of delivery						
CS	15	75.0	64	80.0	$\chi^2=0.241$	FE p=0.759
NVD	5	25.0	16	20.0		
Birth weight						
≥2500	3	15.0	25	31.3	$\chi^2=2.096$	0.148
1500 – <2500	11	55.0	21	26.3	$\chi^2=6.078^*$	0.014*
<1500	6	30.0	34	42.5	$\chi^2=1.042$	0.307
Min. – Max.	920.0 – 2880.0		897.0 – 3800.0		Z=0.418	0.676
Mean ± SD	1852.0 ± 607.11		1952.79 ± 803.99			
Median	2000.0		1931.50			
Age of presentation of sepsis						
Early onset	17	85.0	49	61.3	$\chi^2=4.022^*$	0.045*
Late onset	3	15.0	31	38.3		
Maternal Fever	3	15.0	8	10.0	$\chi^2=0.409$	FE p=0.689
Chorioamionitis	2	10.0	3	3.8	$\chi^2=1.316$	FE p=0.261
PROM	11	55.0	30	37.5	$\chi^2=2.026$	0.155
PET	7	35.0	21	26.3	$\chi^2=0.608$	0.436
Maternal drug intake						
Antenatal steroid	6	30.0	25	31.3	$\chi^2=0.012$	0.914
Antibiotic	6	30.0	16	20.0	$\chi^2=0.932$	FE p= 0.370

χ^2 : value of Chi square

FE: Fisher Exact test

t: Student t-test

Z: Z for Mann Whitney test

*: Statistically significant at $p \leq 0.05$

Results

Table (11) Demonstrates the potential risk factors for development of acute renal failure as shock, DIC, metabolic acidosis are significantly higher in patients with ARF in comparison to patients without ARF. PDA, NEC, meningitis, mechanical ventilation and umbilical catheterization were insignificant difference between both groups.

Table (11) : Potential risk factors for development of ARF (n=100)

	ARF				χ^2	p
	Positive ARF (n=20)		Negative ARF (n=80)			
	No.	%	No.	%		
Shock	9	45.0	16	20.0	5.333*	0.021*
DIC	4	40.0	13	16.3	5.440*	^{FE} p=0.030*
PDA	4	20.0	12	15.0	0.298	^{FE} p=0.733
NEC	4	20.0	7	8.8	2.068	^{FE} p=0.223
Meningitis	7	35.0	21	26.3	0.608	0.436
Nephrotoxic drugs						
Aminoglycosides	20	100.0	78	97.5	0.510	^{FE} p=1.000
Vancomycin	14	70.0	52	65.0	0.178	0.673
Indomethacin	1	5.0	3	3.8	0.065	^{FE} p=1.000
Mechanical ventilation	7	35.0	46	57.5	3.252	0.071
Acidosis	13	65.0	24	30.0	8.408*	0.004*
Arterial catheterization	3	15.0	17	21.3	$\chi^2=0.391$	^{FE} p=0.756
Venous catheterization	14	70.0	52	65.0	$\chi^2=0.178$	0.673

χ^2 : value of Chi square

FE: Fisher Exact test

*: Statistically significant at $p \leq 0.05$