INTRODUCTION

Among hundreds of infectious diseases known today, tetanus is a potentially fatal disease, which still remains an important public health problem in developing countries1, which requires continuous and strong efforts of both public and private sectors for the eradication. The current burden of tetanus in Pakistan is alarming like other vaccine preventable diseases although the exact figures...
are not available. Tetanus is caused by clostridium tetani, which produces a powerful neurotoxin, 
etanospasmin affecting the central nervous 
system.\textsuperscript{2} Patient develops frequent body spasms, 
locked jaw and dysphagia.\textsuperscript{3} Wide swings in blood 
pressure and heart rate are common secondary 
to autonomic instability due to disinhibited 
autonomic discharge.\textsuperscript{4-6} Neuronal binding of toxin 
is irreversible and clinical recovery follows the 
growth of new nerve terminals explaining the usual 
prolonged course of illness.\textsuperscript{7} Treatment is aimed 
at neutralizing the toxin, controlling the muscle 
spasms, stabilizing the autonomic instability, 
managing the wound and monitoring the vital 
organ’s functioning. Multiple drugs are given 
simultaneously to achieve these goals.

Various factors have been related to high mortality 
rates seen in tetanus like grade of severity of the 
disease itself and development of cardiovascular, 
pulmonary and renal complications.\textsuperscript{8}

Acute kidney injury (AKI) is a frequent and lethal 
complication of tetanus.\textsuperscript{9} A recent multivariate 
analysis of 236 ICU tetanus patients disclosed 
a direct association between AKI and tetanus 
mortality.\textsuperscript{10} This study was carried out to find the 
frequency of AKI in tetanus patients managed in 
a public hospital in Karachi, (to prevent AKI in 
future, in such cases).

**METHODS**

This was a retrospective study. Children aged 
one month to twelve years admitted in PICU with 
the clinical diagnosis of tetanus over past three 
and half years i.e. from July 2013 to December 2016 
were recruited for the study. Data were collected 
and reviewed form the file records for the course of 
illness, development of AKI, length of stay in PICU 
and the final outcome. As per PICU protocol, all 
the admitted tetanus patients were monitored for 
fluid volume and perfusion status, blood pressure 
centiles, input and output. Blood biochemistry, 
renal function tests and urine analysis was done in 
all patients.

**Inclusion Criteria:** Children aged one month to 
twelve years with clinical diagnosis of tetanus 
without pre-existing kidney disease.

**Exclusion Criteria:** Children with tetanus having 
preexisting kidney disease.

One case was excluded from the review on this 
basis with abnormal renal functions and ultrasound 
scan.

pRIFLE criteria was applied to all cases of tetanus 
to categorize them as having AKI or not, on the 
basis of Estimated Creatinine Clearance (ECCL). 
It was calculated on daily basis and the drug 
dosage adjustments were done accordingly. All the 
patients were also monitored for signs of autonomic 
instability, seen commonly in tetanus.

Data were analyzed using SPSS version 16. 
Descriptive statistics were applied to describe the 
results in terms of frequencies and percentages. 
Comparison was done between AKI and non-AKI 
cases, as well as between AKI survivors and AKI 
non-survivors. P values < 0.05 was considered as 
significant.

**RESULTS**

During the study period, 44 patients of tetanus 
were enrolled (see Table-I for descriptive

| Characteristic | No | % |
|---------------|----|---|
| 1. Sex:       |    |   |
| Male          | 24 | 54.54 |
| Female        | 20 | 45.45 |
| 2. Age groups:|    |   |
| < than 5 year | 22 | 50  |
| 6 – 9 year    | 14 | 31.81 |
| > 10 year     | 08 | 18.18 |
| 3. Grade of Severity: |    |   |
| Grade I       | 0  | 0   |
| Grade II      | 7  | 15.90 |
| Grade III     | 27 | 61.36 |
| Grade IV      | 10 | 22.72 |
| 4. Developed AKI: |    |   |
| Yes           | 14 | 31.81 |
| No            | 30 | 68.18 |
| 5. Final Outcome: |    |   |
| Discharge     | 29 | 65.90 |
| Expiry        | 15 | 34.09 |
| 6. Autonomic Instability |    |   |
| 37            | 84.09 |
| 7. Ventilator requirement |    |   |
| 32            | 72.72 |
| 8. CRP:       |    |   |
| < 50          | 20 | 45.45 |
| > 50          | 24 | 54.54 |
| 9. TLC:       |    |   |
| <5,000/mm\textsuperscript{3} | 5  | 11.36 |
| >20,000/mm\textsuperscript{3} | 39 | 88.63 |
| 10. Average length of stay (days): |    |   |
| 20 days       | 30 | 68.18 |
| 25 days       | 14 | 31.81 |

Table-I: Descriptive characteristics of tetanus patients (Total No. = 44).
characteristics). Fourteen (31.81%) tetanus patients developed acute renal dysfunction according to pRIFLE criteria. There were overall 15 (34.09%) expiries among tetanus patients out of which 9 (60%) had AKI. (Table-II)

Among the AKI cases, none belonged to grade I or II tetanus severity i.e. all were severe and very severe cases according to ‘Ablett classification’ of tetanus severity. Oliguria was observed in five (35.71%) cases. Urine analysis was insignificant in most cases; mild proteinuria was observed in four cases. Urine was not checked for myoglobinuria.

AKI developed towards the end of first week in three cases, mid of second week in four cases and third week in seven cases. Since the AKI was categorized according to pRIFLE criteria, four patients had estimated creatinine clearance between 75 to 50% and 10 patients had ‘ECCL’ below 50% (Table-II). All the AKI non-survivors had ECCL below 50% (Table-III).

All those who developed AKI had autonomic instability with episodes of tachycardia, bradycardia, hypertension, hypotension and all of them required inotropes to sustain their heart rate and blood pressure norms. Ventilator requirement was seen in 12 out of 14 AKI victims (85.71%), whereas 20 out of 30 (66.66%) non-AKI tetanus cases were on ventilator (Table-II).

All tetanus patients received sedatives and muscle relaxants as per PICU protocol. However subsequent renal adjustments were done in the doses in AKI developers. Maximum diazepam requirement was 20 mg/kg/day in one AKI victim who was subsequently discharged. Similarly, maximum magnesium sulphate dose was 100 mg/kg/day q six hourly required by three patients, out of them two were discharged. Phenobarbital was given 5-8 mg/kg/day q 12 hourly and chlorpromazine given 0.5-1mg/kg/day in all the tetanus patients.

Regarding renal replacement therapy (RRT), peritoneal dialysis (PD) was done in four patients with AKI but it did not effect the outcome. Average length of stay was 25 days in AKI cases and 20 days in non AKI cases. (Table-II)

**DISCUSSION**

Tetanus is a disease of high mortality ranging 20% to over 50%. Patients usually require prolonged treatment with multiple drugs to control spasm.

### Table-II: Characteristics of tetanus patients with AKI (AKI +VE) Vs without AKI (AKI -VE) (Total No. = 44).

| Characteristic | AKI +ve (14) | AKI -ve (30) | P- Value |
|---------------|-------------|-------------|----------|
|               | No | %    | No | %    |         |
| Expiries      | 9  | 64.28| 6  | 20   | 0.004   |
| Blood Culture Positivity | 6  | 66.66| 9  | 30   | 0.001   |
| TLC >20,000/mm³ | 11 | 78.57| 6  | 20   | 0.001   |
| CRP >50       | 10 | 71.42| 14 | 46.66| 0.56    |
| Ventilator requirement | 12 | 85.71| 20 | 66.66| 0.188   |
| Severity of tetanus: |       |       |     |       |         |
| Grade III     | 10 | 71.42| 17 | 56.66| 0.52    |
| Grade IV      | 4  | 28.57| 6  | 20.0 |         |
| Average length of stay (days) | 25 | -    | 20 | -    |         |

### Table-III: AKI Survivors Vs AKI Non-Survivors (Total AKI victims = 14).

| Characteristics | Survivors | Non-Survivors | P. Value |
|----------------|-----------|---------------|----------|
| 1. Number      | 5         | 9             | 0.004    |
| 2. Grade of Severity: |       |               |         |
| Grade III      | 5         | 5             | 0.001    |
| Grade IV       | 0         | 4             |         |
| 3. Ventilator requirement | 3 | 9 | 0.135 |
| 4. TLC: >20,000/mm³ | 3 | 8 | 0.012 |
| 5. Blood Culture positively | 1 | 5 | 0.001 |
| 6. CRP > 100   | 1         | 6             | 0.098    |
| 7. Creatinine clearance b/w: |       |               |         |
| 75 – 50        | 4         | 0             | 0.206    |
| < 50           | 1         | 9             |         |
They are prone to develop various complications, which can alter the course and outcome of the illness.12-15

Altered renal physiology may be seen in tetanus. Studies have shown that up to 50% of patients with tetanus have a glomerular filtration rate (GFR) lower than 50ml/min in the first or second week of hospitalization.16 Acute kidney injury (AKI) is a known complication of tetanus. It has been reported with varied frequency ranging 14% to 39% from different areas. AKI was found to be 31.81% in our case series, reflecting a similar trend.

Studies published so far have used serum creatinine as a marker of AKI in tetanus and so did we. Although serum creatinine is no longer considered as an ideal marker as it does not increase until the GFR has moderately decreased i.e kidney function has already been lost by 25-50%.17,18 Serum creatinine values are also affected by muscle mass, hydration status, age, sex, gender and method of measurement.19 Trends are now toward search for early markers of AKI like serum cystatin C and NGAL (neutrophil gelatinase associated lipocalin.20,21 AKI was mostly non oliguric (64.29%) in our case series as reported in other previous studies. All the AKI cases belonged to severity grade III and IV of tetanus with the later having the worst outcome (Table-III). This was in contrast to few studies in which acute renal failure was not related to the severity of tetanus.16

Association of severity with the development of AKI seems logical because autonomic instability is more marked in severe cases. Renal dysfunction in tetanus is multifactorial and various pathophysiological mechanisms have been suggested.1,3,6 Autonomic instability has been proposed to be the most important factor for the development of AKI, both in adults as well as in paediatric patients.22 It was seen in all the AKI developers of our case series.

Uncontrolled muscle spasms causing rhabdomyolysis and ultimately myoglobinuria resulting in acute renal failure has always remained an important factor in adult tetanus patients.23 However it has not been emphasized in paediatric population especially in children younger than 10 years as a reason for AKI.24,25 This may be because children do not have muscle mass to such an extent to cause significant myolysis. In this retrospective review, none was investigated for its development.

Other contributing factors for AKI are the use of nephrotoxic drugs, mechanical ventilation and development of sepsis. Drug related nephrotoxicity was less likely in this series since the creatinine clearance was regularly checked and drugs adjusted accordingly.26 Ventilator dependency was seen in 12 (85.71%) AKI patients among whom nine patients (75%) expired, P value 0.04, thus making it a significant risk factor for poor outcome in AKI patients.

The lower the creatinine clearance, the worst was the outcome. Out of 14 AKI victims four had eccl between 75-50% and they were among AKI survivors. Whereas 10 had eccl below 50% i.e stage III according to ‘AKIN’28 and nine of them were non survivors, indicating that outcome of AKI is dependent upon its severity also, among other factors.29

Sepsis was an important contributor to AKI in this series with CRP being more than 100 in seven cases of AKI, six of them being non-survivors.30 Although the difference was large, but due to the small sample size, p value was insignificant (Table-III).

Raised TLC more than 20,000/mm³ as a marker of sepsis was seen in 39 (88.63%) cases. Eleven of them developed AKI among which eight expired (72.72%) P value 0.012. (Table-III) Blood Culture positivity was present in 15 cases of tetanus, six of them were AKI cases and five were AKI non-survivors P value-0.001, (Table-III). Only four AKI patients were subjected to RRT (peritoneal dialysis), which did not improve their outcome probably because of late institution.

CONCLUSION

Development of AKI in tetanus is multifactorial. Major contributors are severity of the tetanus itself, presence of autonomic instability, ventilator dependency, and sepsis. Presence of AKI worsens the outcome of tetanus in terms of survival, length of stay, hospital costs and ventilator days. Need for early rising biomarkers to intervene early is justifiable.

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