Predictors of Outcome in Patients with Diphtheria Receiving Intensive Care

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Forty eight patients with a clinical diagnosis of diphtheria, admitted to the Pediatric Intensive Care Unit (PICU) of a tertiary care teaching hospital, from December 1994 to 2002, were analyzed retrospectively with respect to demographic details, clinical features, immunization status, complications and mortality. Several variables were compared among the survivors and non-survivors to define the predictors of outcome More than half 27 (56.3%). of the patients were unimmunized. Complications seen were: airway compromise 34 (70.8%), myocarditis 32 (66.6%), renal failure 17 (35.4%) and thrombocytopenia 15 (31.3%). Out of the 48 patients, 21 survived and 27 died (56.3%). The immediate cause of death was myocarditis 23 (85%), airway compromise 3 (11.1%) and septic shock due to nosocomial sepsis(1). Inadequate immunization, hypotension at admission and presence of any complication like airway compromise, myocarditis and renal failure had a significant (P <0.05) adverse effect on outcome; multiple regression analysis ascertained that, development of myocarditis was the only independent predictor of death (Adjusted OR 0.061; 95% CI 0.009-0.397;P = 0.003).

Key words: *Diphtheria, Myocarditis, Predictors of outcome, Intensive care*

THE incidence of diphtheria in the developed nations has steadily declined following effective immunization programs since the 1920's(1). However, a resurgence of the disease has been observed in these countries, largely attributed to waning vaccine immunity in adults and importation of cases from the endemic developing world(2). The situation faced by us in the developing countries is different. Diphtheria still remains endemic with increase in the fulminant complications and mortality in the last two decades, especially in children above 5 years(3). Factors like inadequate vaccine coverage(4), poor socio-economic standards, overcrowding, delayed reporting to hospital, non-availability and delay in administration of antitoxin further contribute to the high mortality.

There have been descriptive studies from India on diphtheria(5,6) but none have focused on predictors of outcome and the impact of intensive care in these patients. The objective of this study was to examine the outcome and predictors of mortality of diphtheria in children receiving intensive care. This would help in early identification of the severity of illness and prioritization of intensive care especially in developing countries with limited resources.

Subjects and Methods

Forty eight consecutive patients with a clinical diagnosis of diphtheria(7), admitted to PICU of a tertiary care teaching hospital, between December 1994 to 2002 (9 years) were analyzed retrospectively with respect to demographic details, clinical features, immunization status, complications and

mortality. Several variables were compared among the survivors and non-survivors to define the predictors of outcome. Outcome was defined as either recovered or died.

Children were considered adequately immunized if they had received three or more doses of diphtheria toxoid containing vaccine by age 2 years (primary series)(8).

All children with a clinical suspicion of diphtheria were started on parenteral crystalline penicillin in the dose of 50,000 U-1,00,000 U in 4 divided doses. Antidiphtheritic serum (ADS) was given in a single dose as recommended(9) depending on the site and extent of disease. Throat swab for Albert's stain and culture were sent in all, at the time of admission. Patients with anticipated/ established features of any complications like airway obstruction, myocarditis, renal failure and thrombocytopenia were shifted to PICU for monitoring and management. After December 1997, all patients with diphtheria were started routinely on L-carnitine 50-100 mg/kg/day in 3 divided doses. Close contacts of the patient were administered erythromycin prophylaxis of 50 g/kg/day day in 4 divided doses for 7 days.

Data are presented as mean (SD) and median (range). Between groups comparison was done using Chi-square test for categorical data and Students' *t*-test and Mann Whitney U test for parametric and non-parametric data respectively. Survivors and non-survivors were compared using a univariate analysis to identify predictors having a significant association with mortality. Odd's ratio with 95% CI was computed for the significant variables. All variables found to be significant on univariate analysis ($P < 0.05$), were subjected to multiple logistic regression analysis, to determine the significant predictors of mortality.

Results

The age and sex distribution, clinical features, immunization status and complications of the study population are shown in *Table I*.

Of 34 patients with airway compromise, 24 (70.6%) had associated myocarditis and 10 (29.4%) had isolated airway problems. Tracheostomy was performed in all patients

TABLE I– *Clinical Characteristics of 48 Patients with Diphtheria.*

Age (yrs) mean ± SD (range)	5.15 ± 2.08 (1-9.5)
Sex ratio (boys : girls)	2.2 : 1
Site of involvment, n(%)	
Faucial	33 (68.8)
Pharyngolaryngeal	12 (25)
Laryngeal	1 (2.1)
Faucial + nasal	2 (4.2)
Immunisation status, n(%)	
Unimmunised	27 (56.3)
Partially immunised	11 (22.9)
Adequately immunised	4 (8.3)
Unknown	6 (12.5)
Albert stain positive, n(%)	17 (35.4)
Culture positive, n(%)	10 (20.8)
Clinical features, n(%)	
Fever	48 (100)
Bull Neck	32 (66.7)
Stridor	30 (62.5)
Hoarse voice	19 (39.5)
Difficulty in swallowing	16 (33)
Throat pain	11 (23)
Bleeding	4 (8.4)
Hypotension at admission	7 (14.6)
Complications, n (%)	
Airway compromise	34 (70.8%)
Myocarditis	32 (66.7%)
Renal failure	17 (35.4%)
Thrombocytopenia	15 (31.3%)

with airway compromise, without any procedural complication. Five patients were intubated for airway relief at the first instance; two of them died during intubation; one of whom had associated myocarditis. The other three needed tracheostomy later on.

Two deaths occurred among 10 patients with isolated airway obstruction one related to bleed in the airway and the other an intubation related complication.

The mean interval between onset of respiratory symptoms and myocarditis was 6.5 ± 2.4 days (range 1-11 days). Twenty (62.5%) of these children presented with conduction abnormalities and cardiogenic shock; other presentations included isolated cardiogenic shock (n = 6; 18.8%), arrhythmia (n = 5; 15.6%) and CCF (n = 1; 3.1%). Bundle branch block (BBB) was observed in 15 patients; 9 of them progressed to complete heart block. Ten patients had tachyarrhythmias (6 ventricular tachycardia, and 2 each of supraventricular and junctional tachycardia) Temporary pacing was done in 7 patients with complete heart block but none of them survived. Univariate analysis revealed that inadequate immunity, longer duration of bull neck and delayed administration of ADS were associated with development of myocarditis (*Table II*). However, on multiple logistic regression analysis, none of the variables were significant predictors of myocarditis.

Of the 32 patients with myocarditis 25(78.1%) died (Odd's ratio 25, 95% CI 3.4 - 210.3, P = 0.0001); eighteen due to conduction abnormality and cardiogenic shock, 3 secondary to isolated shock and 2 due to arrhythmia. Presence of cardiogenic shock was associated with the highest mortality (OR 33.3; 95% CI 5.0 - 287.6; P = 0.0001).

Of the 17 patients with renal failure; 3 patients were dialysed. Fifteen children with renal failure died; all of them had myocarditis and cardiogenic shock (OR 11.9, 95% CI 2-91.5, P = 0.0001).

Of the 15 children with thrombocytopenia

TABLE II–*Comparison of Myocarditis vs No Myocarditis.*

Variables	Myocarditis (n =32)	No myocarditis (n = 16)	'P' value
Age, years, mean±SD (range)	5.1 ± 2.2 (1-9.5)	5.20 ± 1.81 (2.5-9)	N.S.
Sex ratio (boys : girls)	2.5 :1	1.6 : 1	N.S.
Unimmunised, n(%)	22 (68.8)	11(68.7)	N.S.
Partially Immunised, n(%)	9	2	0.03 *
Adequately immunized, n(%)	1 (3.1)	3 (18.8)	0.03*
Bull neck, n(%)	25 (78.1)	7 (43.8)	0.017*
Duration of bull neck (mean±SD (range))	3.34±4.5 (1-25)	1.06±1.61 (1-5)	0.011**
Timing of ADS with respect to onset of disease mean±SD (range))	6.71 ± 4.81 (2-30)	4.62 ± 2.44 (1-11)	0.041**
Deaths, n(%)	25 (78.1)	2 (12.5)	0.0001*

* $p < 0.05$ by Chi square, ** $p < 0.05$ by Mann WhitneyU test.

(platelet count <150,000/cu mm), 9 manifested with skin and mucosal bleeds and 10 died (OR 1.9,95% CI 0.45 - 8.2, P = 0.32); all but one had associated myocarditis.

Out of 48 patients, 21 survived and 27 died (56.3%). The immediate cause of death was myocarditis 23 (85%), airway compromise 3 (11.1%) and 1 septic shock due to nosocomial sepsis. The immunization status had a significant association with both clinical severity and outcome. One out of 4 with adequate immunization developed myocarditis as against 9 out of 11 with partial immunization (P = 0.039). There were no deaths in the immunized group in contrast to 7 and 15 deaths in the partially and completely unimmunised group respectively (P = 0.029).

On comparing survivors with non-survivors, we found that the latter were inadequately immunized, had presented more often with hypotension at admission itself and had increased incidence of complications like myocarditis, airway compromise and renal failure (*Table III*). On multiple regression analysis development of myocarditis was the only independent predictor of death. (Adjusted Odds' ratio 0.061, 95% CI 0.009 - 0.397; P = 0.003).

Discussion

Upper airway obstruction was the commonest complication seen in nearly three fourths of our patients, much higher than the 4-15% reported previously(10). Since only one fourth of our patients had laryngeal involvement, the other possible factors operating for airway obstruction could have been extensive pharyngotonsillar disease, florid soft tissue edema and necrosis or bleeding into the airways. This highlights the fact that signs of upper airway obstruction may occur in children with or without a laryngeal membrane and should be anticipated and aggressively treated.

Intubation in our experience was not a very successful airway relief procedure, as three of our intubated patients required subsequent tracheostomy and two others succumbed to procedure related problems. This was possibly related to the friable upper airways making the procedure difficult. Also it carries with it a high risk of dislodgement of the pseudomembrane. We found that tracheostomy was better,

TABLE III –*Comparison of Survivors vs Non-survivors (Complications).*

Complications	Non-survivors (n = 27)	Survivors (n = 21)	Odd's ratio	95% Confidence limit for OR	P value
Airway compromise	20	14	1.4	0.34-5.9	0.31
Isolated airway compromise	2	8	0.13	0.0- 0.82	0.009
Myocarditis	25	7	25	3.4- 210.3	0.0001
Cardiogenic shock	21	5	33.3	5.0- 287.6	0.0001
Arrhythmia	20	5	9.1	2.07- 43.9	0.0005
Renal failure*	15	2	11.9	2.00- 91.5	0.0001
Thrombocytopenia	10	5	1.9	0.45- 8.2	0.32

P < 0.05 by Chi square, * all had myocarditis as well.

Key Messages

- Respiratory diphtheria still remains a potentially fatal disease in our country primarily due to lack of adequate immunity.
- Myocarditis was the most important predictor of mortality
- Airway complications when treated early had a good prognosis: tracheostomy providing adequate airway relief.
- Improved vaccine coverage, early diagnosis, prompt administration of antitoxin are important in reducing the case fatality rate.

similar to previous observations(11). Perhaps it provided better conduit for tracheal toileting and was easier to maintain as compared to the endotracheal tube. Thus, prognosis with airway complications is good with timely interventions; with tracheostomy providing a safe and effective form of airway relief.

The incidence of myocarditis (66.6%) in our patients was also much higher than previously reported(6,12). Also, contrary to its typical description as end of second week complication, our patients had earlier onset time of less than a week from the onset of the upper respiratory disease(10,13).

We found conduction abnormalities leading to cardiogenic shock was the commonest manifestation, with bradyarrythmias in the form of BBB being more frequent than tachyarrhythmias. Both these findings were in concordance with previous studies(13,14).

Of the treatment options available, neither carnitine(15) nor pacing(14) has proven to be of any benefit.

The two factors studied to have some role in preventing myocarditis are adequate immunization and early administration of ADS (3,11,16). Case fatality rates in those who received antitoxin after a week were higher than in those who received ADS at the onset of respiratory illness(16). In our study too, myocarditis was more often seen in patients with inadequate immunization, and delayed treatment with ADS. These findings imply that myocarditis in unimmunised and partially immunized children with diphtheria can be fulminant. A high index of suspicion should be maintained in those with severe bull neck, and antitoxin given immediately, pending diagnostic confirmation. Availability of antitoxin must be ensured at all times.

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