

STUDY OF CARDIAC INVOLVEMENT IN DIPHTHERIA

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ABSTRACT

BACKGROUND

Diphtheria still endemic in many developing countries and is responsible for high case fatality. Myocardial involvement is a serious complication of diphtheria and diphtheria myocarditis frequently complicated by arrhythmias causes sudden death if not managed properly. So, early and adequate administration of Anti-Diphtheritic Serum (ADS) and frequent monitoring particularly 24 hrs. ECG monitoring is helpful to detect any serious cardiac arrhythmias.

METHODS

A prospective study on patients who were culture positive diagnosed on the basis of WHO definition were treated and analysed in respect to homographic details, immunisation strategy, and clinical features with particular attention to myocarditis.

RESULTS

In the study, common age group affected by diphtheria was 5 to 10 years. Incidence of myocarditis more in same age group. Out of 64 patients with myocarditis, 23 patients died.

CONCLUSION

Incidence of diphtheria has increased in the recent years. Commonly effected age group is 5 to 10 years and most of them are presented with asymptomatic myocarditis. Symptomatic diphtheritic myocarditis has high mortality rate even with aggressive management. Patient who presented with either LBBB alone are with combination of other conduction of abnormalities has high mortality rate.

KEYWORDS

Diphtheria, Myocarditis.

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INTRODUCTION: Diphtheria is still endemic in many developing countries and is responsible for high case fatality.^[1] The incidence of diphtheria in the developed nations has steadily declined following effective immunisation programme since the 1920's. However, resurgence had been observed mainly due to waning immunity in adults and importation of new cases from the endemic regions.^{[1],[2]} In India, diphtheria still remains endemic with fulminant complications and mortality especially in children above 5 years.^[3] Several factors like inadequate vaccine coverage, poor socio-economic status, delayed reporting, and non-availability/delayed administration of diphtheria antitoxin further contribute to high mortality.^[4] The level of immunity declines in late childhood and adolescence due to lack of booster doses, waning immunity with age, and decreased reservoir of C. diphtheria in the community leading to gap in the immunity and outbreaks of diphtheria.

Myocardial involvement is a serious complication of diphtheria and occurs in up to half of cases.^[3] Diphtheria myocarditis is frequently complicated by arrhythmias that can cause sudden death if not managed properly. The patients with cardiac involvement maybe asymptomatic (ECG change and/or raised SGOT) or symptomatic (features of heart failure). The ECG changes of myocarditis maybe sickle-like sagging of the ST segment (specific for diphtheritic myocarditis), arrhythmias (supraventricular or ventricular), abnormal Q waves, repolarisation abnormalities, ST-segment elevation >1 mm in at least two chest leads or one limb lead, T-wave inversion (except in leads V1 and aVR), isoelectric T waves and QTc interval >0.39 s for men and >0.41 s for women, atrioventricular block, bundle-branch block, hemiblock, etc.^[5]

Patients who presents with extensive patch and bull neck usually have more incidence of cardiac involvement.^[6] So, early and adequate administration of ADS with frequent monitoring particularly 24h ECG monitoring is helpful to detect any serious cardiac arrhythmia. WHO recommends immediate administration of diphtheria antitoxin and antibiotics following clinical diagnosis pending the culture reports for confirmation.^[5] The diphtheria vaccine is one of the major approaches for the control and prevention of diphtheria (at least 90% coverage).^[7]

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METHODS AND STUDY:

AIMS AND OBJECTIVES:

- To study cardiac involvement in clinical cases of diphtheria confirmed by throat swab culture positivity for *Corynebacterium diphtheria*.
- To study the clinical presentation, ECG changes, 2D echo features of diphtheritic myocarditis.
- To study the prognosis and clinical outcome in patients with diphtheritic myocarditis.

Type of Study: Prospective.

Duration of Study: From 2014 June to August 2015.

Total Number of subjects included in the study will be approximately 100 cases.

100 culture positive diphtheria cases diagnosed on the basis of WHO definition from "Sir Ronald Ross Institute of Tropical and Communicable Diseases", Nallakunta, Hyderabad, India, and Osmania General Hospital, Hyderabad, India, from June 2014 to August 2015 were treated and analysed in respect to demographic details, immunisation status, and clinical features with particular attention to myocarditis.

Study Protocol: All patients were initially admitted in Diphtheria Ward in "Sir Ronald Ross Institute of Tropical and Communicable Diseases", and in ICU of Osmania General Hospital, Hyderabad. Written consent was obtained in all cases. Each patient was monitored closely for any development of shortness of breath, palpitation, chest discomfort, and hypotension. ECG was done in all at the time of admission and repeated as and when required. 2D ECHO was done in all at the time of admission in OGH and repeated as and when required. Temporary pacemaker insertion was done in all patients who developed complete heart block.

Inclusion Criteria: All cases of clinical diphtheria with nasal, oropharyngeal, faucial, laryngeal patch confirmed by throat swab culture positivity for Klebs-Loffler bacillus.

Exclusion Criteria:

- Documented evidence of previous ECG abnormalities.
- Documented evidence of previous cardiomyopathy.
- Previous 2D echo abnormalities.
- Presence of hypertension.
- Presence of coronary artery disease and any underlying heart disease.

RESULTS:

Age Group	No. of Patients
<5 Yrs.	2
5-10 Yrs.	39
11-15 Yrs.	34
16-20 Yrs.	13
>20 Yrs.	12

Table 1: Clinical Cases of Diphtheria in Relation to Age

In this study, the most common age group affected by diphtheria was 5-10 years (39 cases) followed by 11-15 years (34 cases), 16-20 years (13 cases), and >20 years (12 cases). Least common age group affected was <5 years (2 cases).

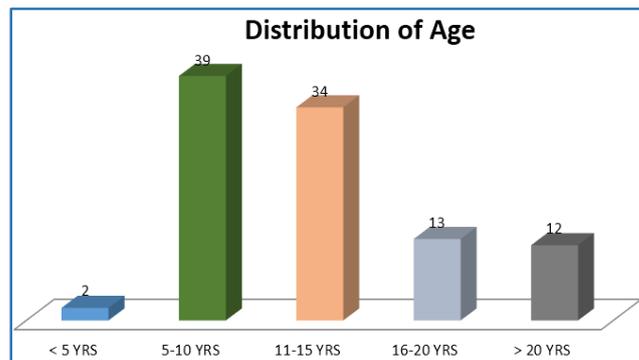


Fig. 1

Sex	No. of cases
Male	51
Female	49

Table 2: Clinical Cases of Diphtheria in Relation to Gender

Out of 100 patients, 51 were males, 49 were females. No significant sex difference noticed in prevalence of diphtheria.

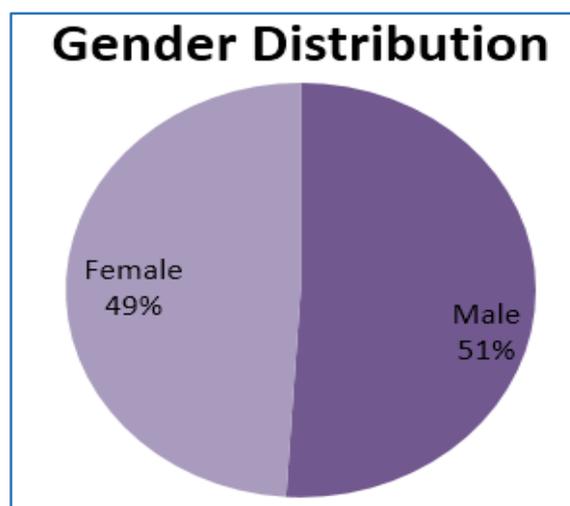


Fig. 2

Culture Positive and KLB Positive	Culture Positive and KLB Negative
40	60

Table 3: Correlation of Culture Positivity and Smear for KLB Positivity

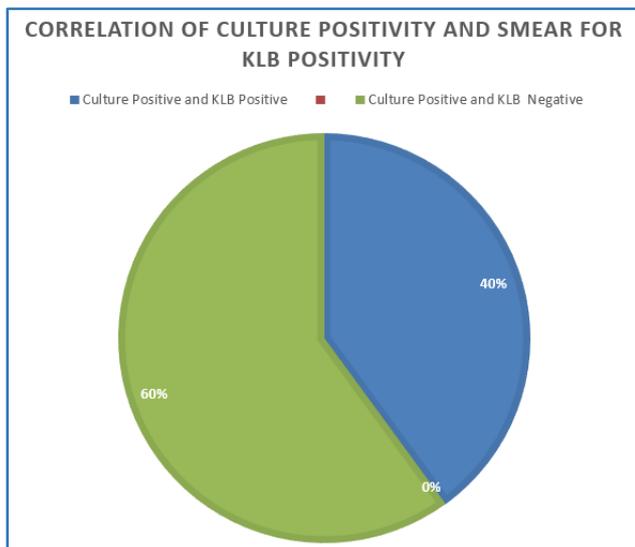


Fig. 3

Common clinical features were fever seen in 82, throat pain in 83, difficulty in swallowing in 58, shortness of breath in 26, bull neck in 16 [Figure 1], renal failure in 11, hoarseness in 8, but less common features were nasal regurgitation in 2 cases, stridor in 1, and limb weakness in one case each.

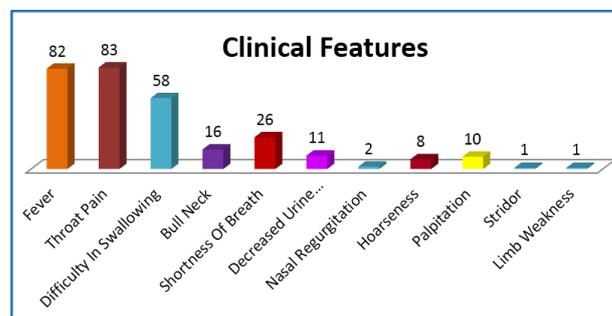


Fig. 4

Clinical Features	No. of Cases
Fever	82
Throat Pain	83
Difficulty in Swallowing	58
Bull Neck	16
Shortness of Breath	26
Decreased Urine Output	11
Nasal Regurgitation	2
Hoarseness	8
Palpitation	10
Stridor	1
Limb Weakness	1

Table 4: Clinical Features

Age Group	No. of Cases	Immunised	Unimmunised
<5 Yrs.	2	0	2
5-10 Yrs.	39	1	38
11-15 Yrs.	34	5	12
16-20 Yrs.	13	0	3
>20 Yrs.	12	2	4

Table 5: Distribution of Cases According to Vaccination Status

In this study, eight (8) patients were adequately immunised (Received three or more doses of diphtheria toxoid-containing vaccine by age 2), 92 patients were unimmunised. Patients above 10 years of age didn't receive booster dose (Adult diphtheria-tetanus vaccine) for statistical purposes. Patients partially immunised and unknown immunisation status are taken as unimmunised.

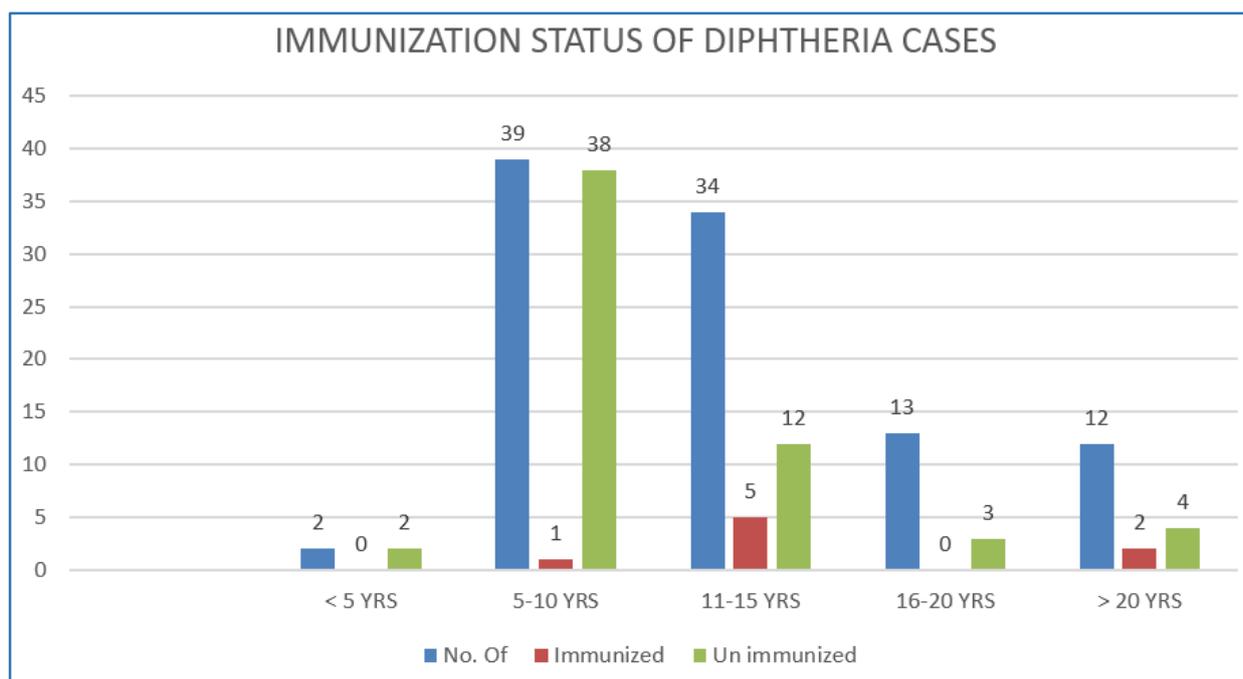


Fig. 5

Age	Symptomatic Myocarditis	Asymptomatic Myocarditis
<5 Yrs.	0	2
5-10 Yrs.	15	19
11-15 Yrs.	7	10
16-20 Yrs.	4	3
>20 Yrs.	1	3

Table 6: Distribution of Myocarditis in Relation to Age

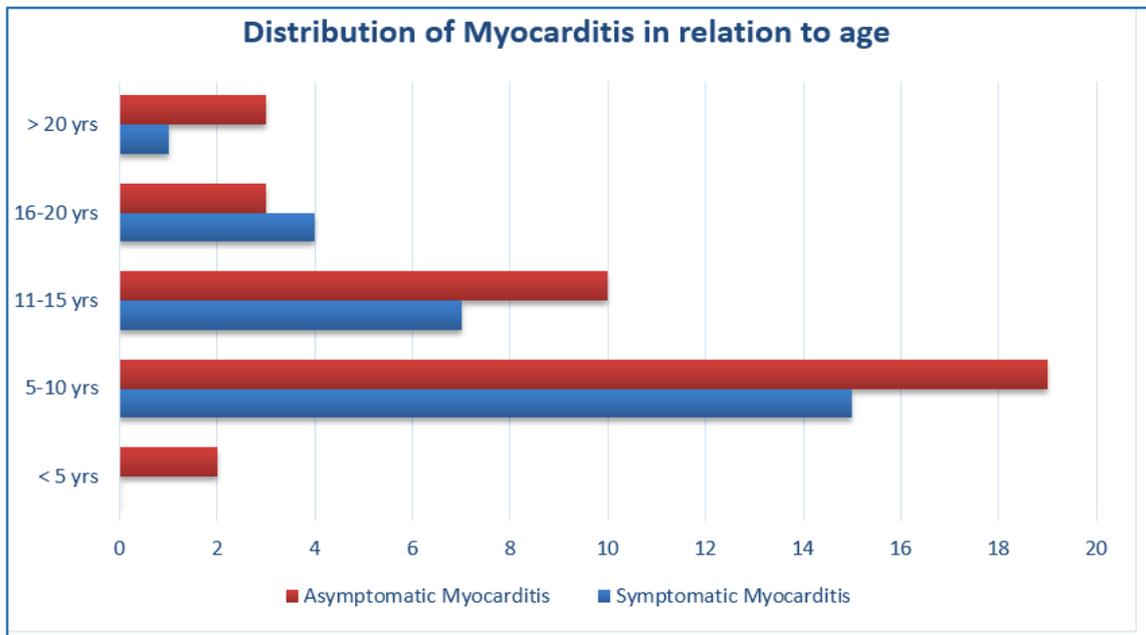


Fig. 6

Sex	Symptomatic Myocarditis	Asymptomatic Myocarditis
Male	12	22
Female	15	15

Table 7: Distribution of Myocarditis in Relation to Gender

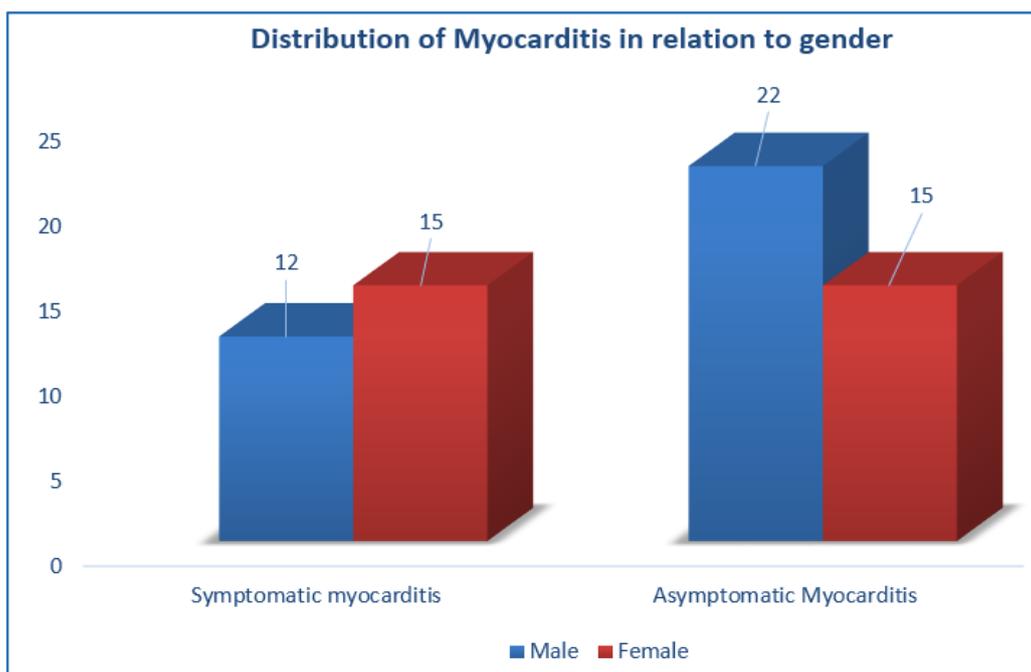


Fig. 7

Age	Culture Positive Cases (n=100)	Asymptomatic Myocarditis (n=37)	Symptomatic Myocarditis (n=27)
<5 Yrs.	2	2(100%)	0
5-10 Yrs.	39	19(48.71%)	15(38.46%)
11-15 Yrs.	34	10(29.41%)	7(20.58%)
16-20 Yrs.	13	3(23%)	4(30%)
>20 Yrs.	12	3(25%)	1(8.3%)

Table 8: Distribution of Myocarditis in Relation to Culture Positivity for C. Diphtheria

Out of the 2 cases in the age group of 0-5 years, 2 cases have asymptomatic myocarditis 5-10 years 19 cases, 11-15 years 10 cases, 16-20 years 3 cases, >20 years 3 cases. No case of symptomatic myocarditis is seen in the age group of <5 yrs. 15 cases are seen in 5-10 years age group, 7 cases in 11-15 years age group, 4 cases in 16-20 years age group, and 1 case in >20 years age group. The incidence of myocarditis is more common in the 5-10 years age group.

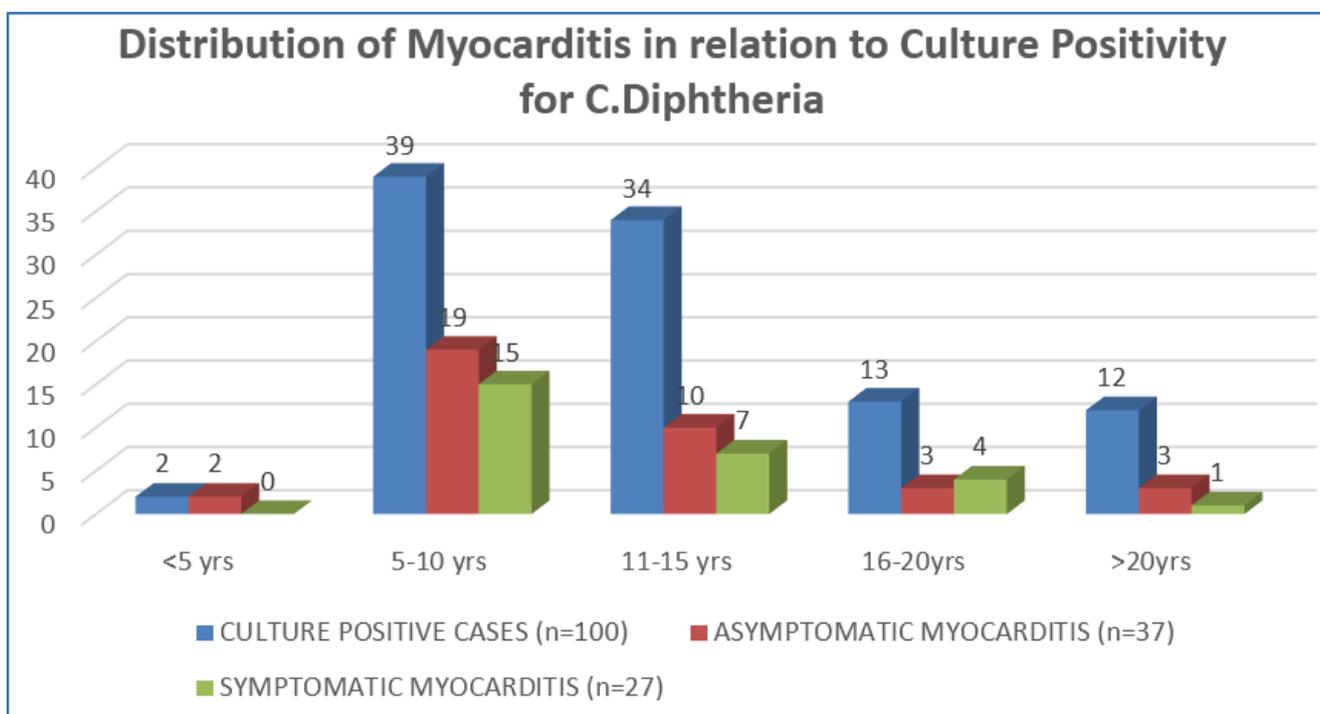


Fig. 8

ECG Abnormalities	No. of Cases
Deep symmetrical T wave inversions in all leads except AVR and V1	23
CHB	10
LBBB	8
ST Depression	7
VT/VF	5
RBBB	4
ST Depression plus T inversion	4
VPCs	3
Sinus bradycardia	1

Table 9: ECG Abnormalities in Diphtheritic Myocarditis

The ECG changes of myocardial involvement were symmetrical T wave inversion in precordial leads in 23 patients, CHB in 10 patients, LBBB in 8 patients, ST depression in 7 patients, RBBB in 4 patients, ST depression with T wave inversion in 4 patients, VPCs in 3 patients, sinus bradycardia in 1 patient. The most common ECG abnormality in this study in cases of asymptomatic myocarditis was symmetrical. T-wave inversions in all precordial leads except in V1, AVR. The most common ECG abnormality in cases of symptomatic myocarditis is complete heart block and the least common is sinus bradycardia.

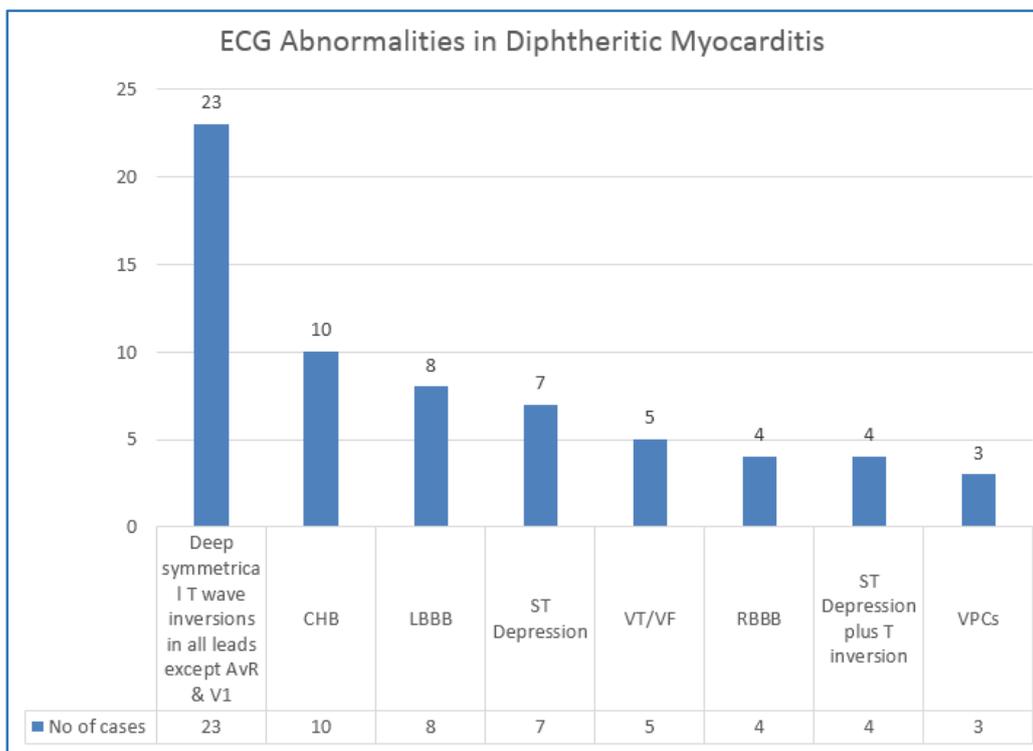


Fig. 9

ECG Abnormalities	No. of Cases	Deaths	Percent
LBBB	8	8	100
CHB	10	9	90
RBBB	4	3	75
VT/VF/VPC	8	3	37.5
T-Wave Inversion in Precordial Leads	23	0	0
ST Depression	7	0	0
ST Depression With T Inversion	4	0	0
Sinus Bradycardia	1	0	0

Table 10: Mortality in Diphtheritic Myocarditis in Relation to ECG Changes

100% mortality was observed in patients who presented with LBBB, 90% in CHB, 75% in RBBB, 37.5% VT/VF/VPC whereas no mortality was observed in patients who presented with T-wave inversions in precordial leads, ST depressions, ST depression with T-wave inversion, sinus bradycardia.

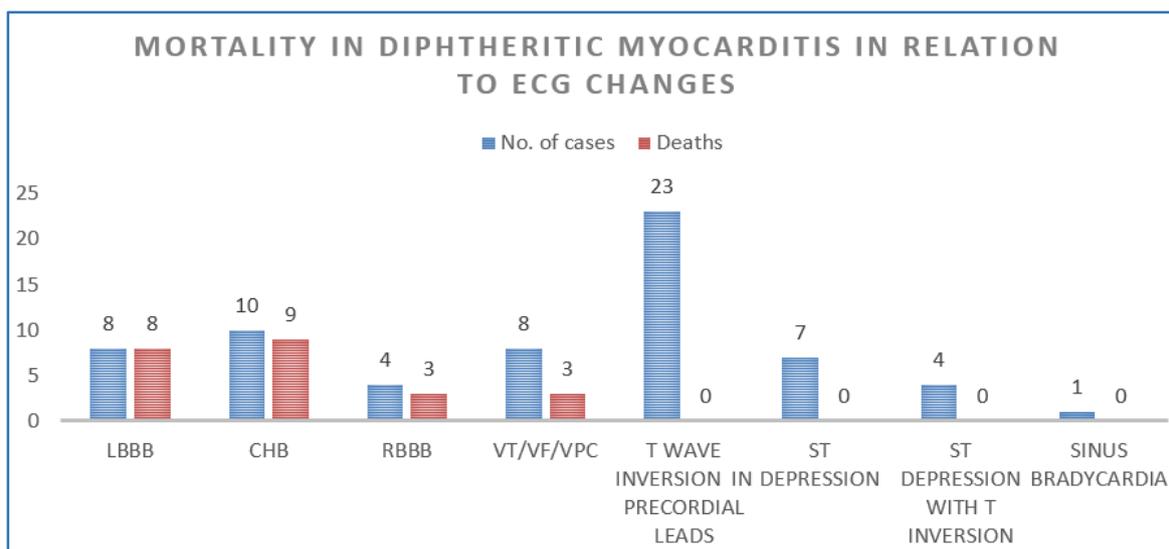


Fig. 10

Ejection Fraction	No. of Patients
<10%	1
10%-30%	8
31%-50%	3
>50%	15

Table 11: 2D-Echo Findings in Cases of Diphtheritic Myocarditis

- Global hypokinesia with chamber dilation is seen in four patients of symptomatic myocarditis.
- RA, RV dilation with RV dysfunction is seen in two patients.
- LA, LV dilation with LV dysfunction is seen in eleven patients.
- 2D ECHO is normal in all asymptomatic myocarditis patients (37).

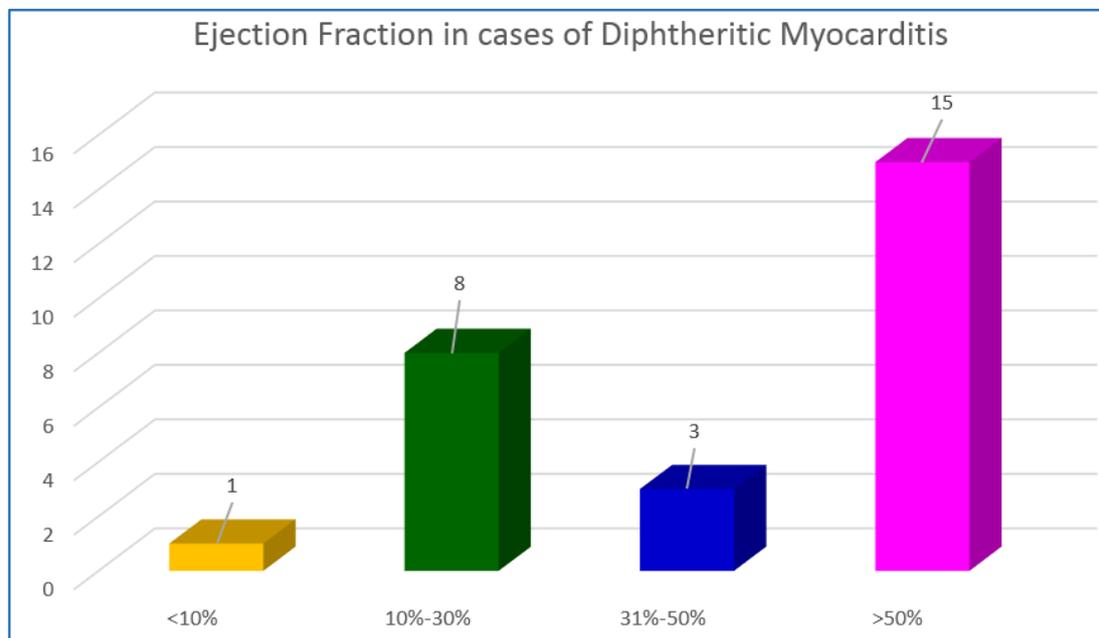


Fig. 11

Cases with Symptomatic Myocarditis	Cases with AKI	Need for RRT
27	11	6

Table 12: Acute Kidney Injury in Symptomatic Diphtheritic Myocarditis

In this study, acute kidney injury was seen in 11 patients with 27 symptomatic myocarditis and 6 patients needed renal replacement therapy.

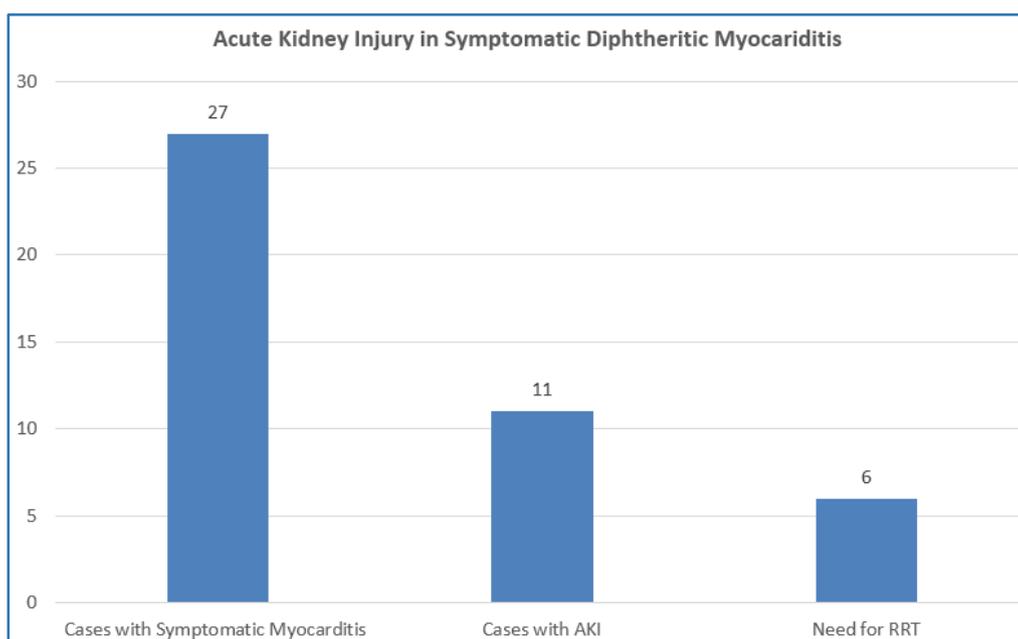


Fig. 12

	Asymptomatic Myocarditis	Symptomatic Myocarditis	Total
Died	0	23	23
Survived	37	4	41
Total	37	27	64

Table 13: Statistical Significance of Symptomatic Myocarditis with Mortality

Chi Square=49.2, Degree of freedom=1, P value <0.000001 (Highly Statistically Significant).

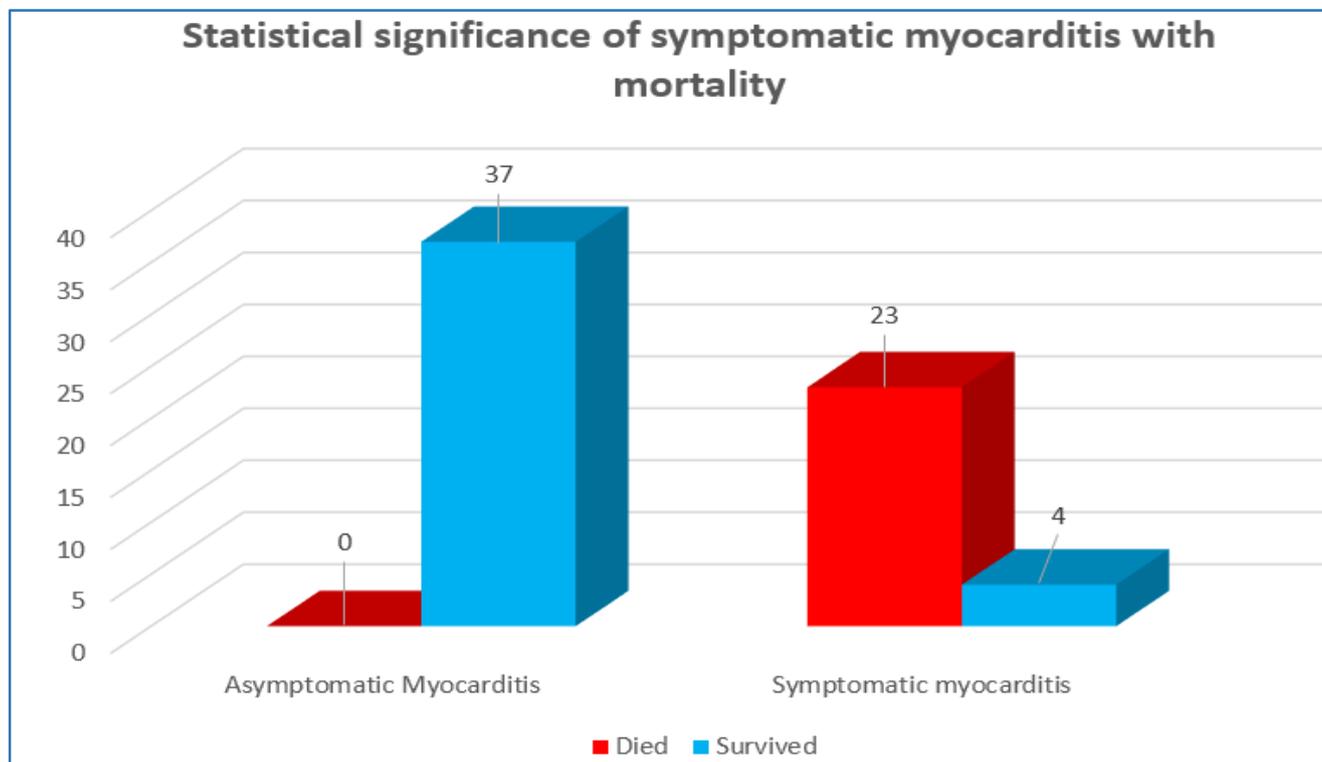


Fig. 13

Cause of The Death	No. of Patients
Malignant arrhythmias	17
Cardiogenic shock with acute kidney injury	6

Table 14: Cause of Death in Diphtheritic Myocarditis

Total 23 patients died of whom 17 patients died due to malignant arrhythmias, 6 patients died due to cardiogenic shock with acute kidney injury. Temporary pacemaker support was given for 5 patients of whom only one patient recovered with 80% mortality.

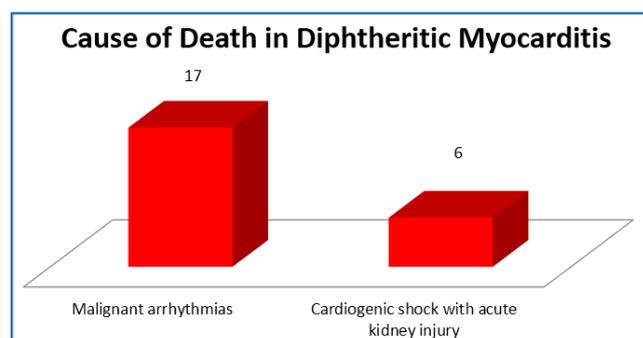


Fig. 14

DISCUSSION: In India, 3480 cases of diphtheria had been diagnosed and treated in 2009 with 113 deaths and a mortality rate of 3.5%, which is basically the tip of the iceberg. The endemicity of this disease in India even in the era of universal immunisation programme is possibly due to inadequate vaccination coverage (Only 66% children were vaccinated in 2008 in India), accommodation sharing, decreased incidence of skin infection by *C. diphtheriae* due to lifestyle changes (Conferring natural immunity), and ineffectiveness of the administered diphtheria vaccine. The studies in relation to diphtheritic myocarditis were done by I. Giegler, H. Feihring et al, study in Canadian Medical Association Journal; Rachel Kneen,^[8] Nguyen Minh Dung et al study in Vietnamese children; Celik T, Selimov N, Vekilova et al study from Department of Cardiology, Gulhane Military Medical Academy, Etlik, Ankara, Turkey; Anima h,^[9] Malay M, Santanu H, Rajashree R, Sita C, Baran SA. Department of Community Medicine, Burdwan Medical College. Havaladar, Parvat V, Sankpal, Mahadev N, Doddannavar, Ramesh P, Department of Paediatrics, District Hospital, Belgaum, India; AK Kole,^[10] R Roy, SS Kar, D Chanda. Cardiac involvement in diphtheria: Study from a tertiary referral infectious disease hospital. Ann Trop Med Public Health 2012; M. Jayashree,^[6]

N. Shruthi, and S. Singhi et al from the Department of Paediatrics, Advanced Paediatric Centre, Postgraduate Institute of Medical Education and Research, India; Stockins,^[11] B.A., Lanas, F.T., Saavedra, J.G. and Opazo, J.A. (1994), Prognosis in patients with diphtheric myocarditis and bradyarrhythmias: Assessment of results of ventricular pacing. *British Heart Journal*, 72, 190-191; M. Meera and M. Raja Rao (2014). Diphtheria in Andhra Pradesh - A Clinical-Epidemiological Study.

International Journal of Infectious Diseases, 19, 74-78.

In the present study, clustering of diphtheria cases was seen in the age group of 5-10 years (39 patients), in I. Giegler, H. Feihring et al study of the 82 Patients. The ages were between 4 and 24 years. The majority being 8-12 years old. In Rachel Kneen,^[8] Nguyen Minh Dung et al study, the median age was 5.5 years (Range, 0.75-14 years), in Anima H,^[9] Malay M, Santanu H, Rajashree R, Sita C, Baran SA. Department of Community Medicine, Burdwan Medical College.

The highest number of cases (31) were among the 6-10 year age group while the lowest was among the 16-20 year age group (12). Diphtheria in Andhra Pradesh, a clinical epidemiological study by Dr. Meera and Dr. Rajarao^[12] among the immunised, the most common age group affected was 5-20 years while among the non-immunised, it was 20-30 years. In the present study, there was no significant sexual difference in the occurrence of diphtheric myocarditis. In Rachel Kneen, 1, 3 Nguyen Minh Dung, 2 study 58% were males. In M. Jayashree,^[6] N. Shruthi, and S. Singhi study sex ratio was (boys:girls) 2.2:1

In present study, out of 100 cases of culture positive diphtheria only 8 patients were adequately immunised, 92 patients were unimmunised, and most of the unimmunised children fall in the age group of 5-10 years. In Kole AK,^[10] Roy R, Kar S. study of cardiac involvement in diphtheria: 40% patients were partially immunised whereas 60% patients were immunised. Diphtheria in Andhra Pradesh, A clinical epidemiological study by Dr. Meera and Dr. Rajarao,^[13] one thousand one hundred and ninety four (41%) patients gave a history of complete immunisation, non-immunised individuals - 1731 cases (59%). The most common clinical features in present study were fever (82 patients), throat pain (83 patients), difficulty in swallowing (58 patients), SOB (26 patients), bull neck (16 patients), decreased urine output (11 patients), palpitations (10 patients), hoarseness of voice (8 patients), stridor and limb weakness (Each one patient) where as in Kole AK,^[10] Roy R, Kar SS study, the most common clinical features are throat pain, palpitation, bull neck, shortness of breath, fever, nasal intonation/regurgitation, but less common features were difficulty in swallowing, stridor, bleeding from pseudomembrane, renal failure. In Dr. Meera and Dr. Rajarao^[12] study. All patients (n=2925) presented with fever, sore throat, and a pseudomembrane. Mild-to-moderate laryngitis was observed in 67%, rhinorrhoea in 63%, and lymphadenopathy and oedema in the neck region were seen in 33% of cases. Features of acute respiratory obstruction in the form of stridor were seen in 9% of cases

at the time of admission. Vomiting and abdominal pain were seen in 29% of patients.

Signs and symptoms suggestive of myocarditis developed in 16% of cases (vomiting and abdominal pain along with low blood pressure and tachycardia) 1-2 days after admission. In this present study, the ECG changes of myocardial involvement noticed in decreasing order of frequency were deep symmetrical T wave inversions in precordial leads except in AVR and V1 (23 patients), complete heart block (10 Patients), LBBB (8 Patients), ST segment depression (7 Patients), VT/VF/VPC (8 patients), RBBB (4 Patients), sinus bradycardia (1 patient).

In Kole AK,^[10] Roy R, Kar SS study, the ECG changes of myocardial involvement were T-wave inversion and in precordial leads, inappropriate sinus tachycardia and ST segment depression in anterior precordial leads (Pseudo-infarct pattern), second-degree AV block, RBBB, multiple atrial ectopics, and sinus bradycardia. In a study conducted by Stockins,^[11] B.A., Lanas, F.T., Saavedra, J.G., and Opazo, J. A. (1994) prognosis in patients with diphtheric myocarditis and bradyarrhythmias: Assessment of Results of Ventricular Pacing, *British Heart Journal*; of the 167 patients with diphtheria, 46 developed diphtherial myocarditis (27%), twenty four of the patients with myocarditis developed bradyarrhythmias (52%), six patients developed sinus bradycardia, three atrioventricular dissociation (Atrioventricular junctional rhythm with a higher rate than the sinus node), one left anterior hemiblock, four right bundle-branch block, two left bundle-branch block, one bifascicular block (Left anterior hemiblock and right bundle-branch block), and seven third-degree atrioventricular block 45.

The 2D echo findings in present study were (a) Global hypokinesia with chamber dilatation is seen in four patients, (b) RA and RV dilation with dysfunction is seen in 2 patients, (c) LA and LV dilation with dysfunction is seen in 11 patients, (d) 2D echo was normal in all patients with asymptomatic myocarditis, (e) in present study, one patient showed EF of 10%-30% and three patients showed EF of 31%-50% and more than 15 patients showed EF of more than 50%. In present study, out of one hundred cases of diphtheria, myocarditis is seen in 64 patients (64%) and the myocarditis is symptomatic in 27 patients and it is more common in the age group 5-10 years and asymptomatic myocarditis is seen in 37 patients, which is also more common in 5-10 years age group. Out of 64 patients affected with myocarditis, there are 34 males and 30 Females. There is no significant sex difference in cardiac involvement of diphtheria.

In a study by M. Jayashree,^[6] N. Shruthi, and S. Singhi et al from the Department of Paediatrics, Advanced Paediatric Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India, forty eight consecutive patients with diagnosis of diphtheria, 32 developed myocarditis (66.6%). In present study, 100% mortality was observed in patients who presented with LBBB, 90% mortality was seen with CHB, and 75% mortality was seen in RBBB. Whereas, no mortality was observed in patients who presented with T-wave inversion in precordial

leads, ST depression, ST depression with T-wave inversion. In this study, out of 37 cases of asymptomatic myocarditis, there were no deaths and out of 27 symptomatic myocarditis cases, 23 patients died, which is highly statistically significant (p value < 0.000001). The causes of death in symptomatic myocarditis are malignant arrhythmias (17 deaths), cardiogenic shock with prerenal AKI (6 deaths). AKI was seen in 11 patients and out of them, 6 patients were treated with renal replacement therapy.

The mortality rate is very high even with pacemaker support and renal replacement therapy. Whereas in Kole AK,^[10] Roy R, Kar SS study, total five patients died of which two patients died due malignant arrhythmias (VT/VF) and other three patients died due to aspiration pneumonia-sepsis-ARDS secondary to neurological involvement. In a study by M. Jayashree,^[6] N. Shruthi, and S. Singhi et al from the Department of Paediatrics, Advanced Paediatric Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India, of the 32 patients with myocarditis 25(78.1%) died; eighteen due to conduction abnormality and cardiogenic shock, three died secondary to isolated shock and two due to arrhythmia. Presence of cardiogenic shock was associated with the highest mortality. 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. Havaladar et al. had carried out the study for the period of 10 years and found that myocarditis was becoming major cause of death (8 out of 16 deaths) in patients with diphtheria by gradually replacing major cause of death i.e. laryngeal obstruction or post-tracheostomy complications. In adults, diphtheria occurred possibly due to lack of booster doses and gradual waning of immunity with increasing age, unidentified and untreated diphtheria carriers, whereas patients below 5 years of age had diphtheria possibly due to modifying effect of passively acquired maternal antibodies in young infants, which could suppress the development of active immunity following early administration of DPT vaccine, diminished efficacy of administered vaccine, and improper vaccine preservation. In adults, diphtheria occurred possibly due to lack of booster doses and gradual waning of immunity with increasing age.^[13] Myocarditis was the most common complication observed in less than 10 years of age group whereas neurological complication was mainly seen in adults.

Majority of the patients with myocarditis were asymptomatic, had only ECG changes, SGOT elevation, and had a favourable outcomes. Another observation was that almost all patients developed cardiac involvement within first week of onset of respiratory symptoms and patients who had bull neck and extensive faucial patches had more incidence of cardiac involvement.^{[6],[14]} The patients who were adequately immunised and received ads earlier, improved with less complications in comparison to unimmunised/partially immunised patients who received ads late/inadequate doses.^[15] It had been observed that patients who had developed frank features of heart failure showed persistently elevated SGOT level, which was closely parallel

to the intensity of myocarditis and this may be used to monitor its course.^[16] The cause of renal failure was probably due to the effect of diphtheria toxin on renal tubular cells and cardiogenic shock with prerenal AKI. Though, the incidence of diphtheria has not much declined. The mortality was decreased gradually since the last 30 years mainly due to more vaccination coverage, early administration, and easy availability of ads, and improved healthcare.

It must be remembered that diphtheria is still with us and is still lethal; therefore, a high index of suspicion should be maintained in those with sore throat, bull neck, and faucial patch associated with unexplained tachycardia or neuropathy and in such cases antitoxin should be administered immediately pending diagnostic confirmation. Availability of antitoxin must be ensured at all times. Following public health measures are essential to reduce the incidence and epidemics of diphtheria: (a) 90% coverage with three doses of DPT vaccine in children below one year of age, (b) immunising adults with adult-type diphtheria-tetanus vaccine (Td-Vac) every 10 years, and (c) administration of Td vaccine instead of tetanus toxoid, etc., should be instituted to decrease the incidence of diphtheria.

CONCLUSIONS:

1. Incidence of diphtheria has increased in the recent years.
2. Most common age group affected is 5-10 years with no sex difference in occurrence.
3. Most of the patients are presented with asymptomatic myocarditis.
4. Symptomatic diphtheritic myocarditis has high mortality rate even with aggressive management including transvenous pacemaker insertion and renal replacement therapy.
5. Patients who presented with either LBBB alone or with combination of other conduction abnormalities has high mortality rate.
6. In patients with CHB even with temporary pacemaker support mortality is around 87%.
7. In the present study, urine for ketone bodies has good correlation with symptomatic myocarditis.

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