Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.64, No.1(2024). p.36-43 ; DOI: https://doi.org/10.14238/pi64.1.2024.36-43

Original Article

Clinical spectrum and outcomes of the 2019-2020 pediatric diphtheria outbreak in Yemen

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Abstract

Background Diphtheria is an acute bacterial infectious disease characterized by serious morbidity and mortality. Outbreaks continue to occur in developing countries despite national vaccination programs. Vaccination, early recognition the disease, and adequate intervention are needed to avoid devastating outcomes.

Objective To describe the clinical spectrum of childhood diphtheria and its association to outcomes during the 2019-2020 diphtheria outberak in Yemen.

Methods This was a retrospective study to assess the demographic, clinical features, and outcomes of paediatric respiratory diphtheria in patients with diphtheria during the outbreak from September 2019 until May 2020 admitted at Mukalla Maternity and Children Hospital. We used *SPSS 22* version for data analysis.

Results There were 34 culture-confirmed diphtheria cases included in this study, their age ranged from 13 months to 15 years old. Most of the cases (76.5%) happened to children at more than 5 years old. There was no gender difference. Of these 34-positive diphtheria, 79.4% from Hadramout and 17.6% from Shabwa governorate. Most of the cases (35.3%) were admitted in December. More than half of the patients (52.9%) were unimmunized. Fever, sore throat, and enlarged tonsils were presented in all patients, dysphagia (82.4 %), pseudomembrane (91.7%), bull neck (52.9%), and stridor (8.8%) were also found in some patients. Complications included acute renal failure (20.6%), disseminated intravascular coagulation (DIC), shock (17.6%), and myocarditis (8.8%). Significant poor outcome ($P < 0.05$) was associated with bull neck, myocarditis, acute renal failure, DIC, and shock. The case fatality rate (CFR) was 20.6%.

Conclusion Fever, sore throat, tonsillitis, pseudomembrane, and bull neck are high index suspicion of diphtheria and anticipation of ominous outcome. The shifting of occurrence of diphtheria to older age group indicates the need for booster(s) diphtheria toxoid vaccine in addition to improving and strengthening the current immunization program. **[Paediatr Indones. 2024;64:36-43; DOI: 10.14238/pi64.1.2024.36-43].**

Keywords: *poor birth outcome; malaria infection; remote area*

Diphtheria is an acute bacterial infectious disease in children. It produces a leather-like adherent pseudomembrane, a characteristic from which its name is derived; diphtheria is Greek for leather. It is a fatal disease and may cause serious complications if not diagnosed early and treated properly.[1]

The toxigenic strains of the Corynebacterium diphtheriae bacteria are responsible for the serious complications of the disease.[1,2] In developing countries, diphtheria is still endemic and remains a major threat to children. Cases from developing countries account for 80-90% of the diphtheria global burden of disease.[3,4]

Although national vaccination programs have succeeded in reducing the incidence of diphtheria worldwide, it remains a major health problem, especially in Asia.[5] Recently, several outbreaks have been reported in developing countries, such as India, Indonesia, Nigeria, and Vietnam.[6-8] From

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Submitted June 29, 2022. Accepted February 22, 2024.

2016 to 2019, diphtheria outbreaks were reported in multiple countries, including Bangladesh, Venezuela, and Yemen.[7] The burden of the disease is especially high in countries experiencing conflict or social disruption, such as Bangladesh and Yemen.[9] Yemen has experienced several outbreaks of diphtheria: in 1981-1982,[10] 2017-2018,[11] and 2019 -2020.

Several factors influence the incidence of diphtheria, including low vaccination coverage, crowding, migration, and environmental factors. Moreover, delayed reporting of suspected cases to the hospital or healthcare also poses a problem.[1,12,13] Diphtheria mostly occurs in young children; however, since the introduction of toxoid immunization early in life, the disease has shifted to older age groups.[1,3,4,14] In order to prevent this, the *World Health Organization* (WHO) has recommended giving booster doses of diphtheria toxoid vaccine, one of the safest vaccines available, to school-aged children.[15]

The clinical manifestations of fever, sore throat, dysphagia, pseudomembranous tonsillitis, and bull neck should raise suspicion toward diphtheria. Patients exhibiting these symptoms should receive urgent necessary measures for confirmation, management, and prophylaxis.[1]

The disease is associated with certain complications, such as myocarditis, acute renal failure, and polyneuropathy. The risk for complications is correlated directly to the extent and severity of exudative local oropharyngeal disease, as well as delay in administration of antitoxin.[1,16]

In this study, we aim to investigate the clinical spectrum of childhood diphtheria in Yemen and its association with outcomes.

Methods

This retrospective study used data from medical records of suspected diphtheria patients aged less than 15 years admitted to the pediatric infectious ward of Mukalla Maternity and Children's Hospital, Hadramout, Yemen from September 2019 to May 2020. The hospital is a tertiary health facility for the Hadramout governorate and also serves the nearby governorates of Shabwa and Mahra. We included all children who were admitted for suspected diphtheria that was confirmed by a positive culture.

During the outbreak, the attending pediatrician admitted suspected diphtheria patients based on clinical features of fever, sore throat, difficulty or pain in swallowing, and inflamed tonsils with or without bull neck. Treatment was started as soon as possible and throat swabs were collected for culture. Other baseline examinations were also done, including electrocardiography (ECG). Necessary measures for patient isolation and protection of both medical and nursing staff, to whom toxoid vaccine was administered, were taken. The patients were isolated in eight single bedrooms.

The Yemeni diphtheria, tetanus, and pertussis (DTP) vaccine consists of three primary doses administered at 1.5, 2.5, and 3.5 months of life; no booster doses are given. The paediatrician ascertained immunization status from history taken from parents. The information available was whether vaccination status was complete (received three primary doses), incomplete (missed one or two doses), or unvaccinated (had not received any dose). The number of vaccination doses was not mentioned in the case sheets.

We recorded the patient's age, the presence of clinical manifestations (fever, sore throat, stridor, cough, difficulty in swallowing, bull neck, inflamed tonsils, and pseudomembrane), and complications (myocarditis, acute renal failure, and neuropathy). Pseudomembrane was defined as an adherent, gray-white membrane overlying the inflamed edematous mucosa of the tonsils and surrounding areas.[1] Bull neck was an obvious swelling of the neck due to enlarged cervical lymph nodes, soft tissue edema, and mucosal edema.[1] Myocarditis was defined as the presence of signs and symptoms of cardiac involvement, such as a weak and irregular pulse, diminished heart sounds, cardiac dilation, gallop rhythm, or ECG changes, particularly ST-T wave changes and heart block.[17,18] Outcomes were classified into survival or death.

Data were analyzed using *SPSS version 22* (*IBM*, Armonk, New York). The associations between clinical features and outcomes were analyzed using the chi-square test. Results were considered significant if the P value was <0.05. The study was approved by the Ethics Committee of the Mukalla Maternity and Children Hospital.

Results

There were 62 admitted cases of suspected diphtheria during the study period, ranging in age from 13 months to 15 years. Of these, 34 (54%) were culture-confirmed and included in the study. These consisted of 27 cases from Hadramout governorate, six cases from Shabwa governorate, and one case from Abyan governorate. Only five cases came from from Mukalla, the capital city of Hadramout governorate, while the remaining 22 came from nearby districts of Hadramout governorate. Epidemiological characteristics of the cases are described in **Table 1**.

Of the 34 subjects, 13 had received complete DPT vaccination (primary three doses in early infancy), 3 had incomplete vaccination, and 18 had not been vaccinated. Most cases occurred during winter months of December (12 cases), January (6 cases), and February (5 cases) (**Figure 1**). In this outbreak, there was an equal number of male and female cases. There was no significant difference in deaths between age groups (P=0.898). Length of hospital stay ranged from one to 13 days with a mean of 6.62, and there was no significant association between length of hospital stay and deaths (P=0.108).

All our cases presented with fever, sore throat, and inflamed tonsils. In 24 cases, the onset of symptoms was three days or more prior to hospital admission. Pseudomembranes were found in all cases but one, while bull neck was seen in 18 cases (**Table 2**). Regarding complications, three patients had myocarditis, seven had renal failure, six had DIC and shock, and seven developed multiorgan failure. ECG was not done for all cases, but bull neck was significantly associated with ECG changes (P=0.020). None of our patients had neuropathy or laryngeal obstruction needing tracheostomy.

Table 3 showed the associations between various clinical characteristics with outcome. The clinical variables significantly associated with mortality were bull neck (P=0.005), myocarditis (P<0.001), and renal failure (P<0.001). The case fatality rate during this outbreak was 7/34, and most deaths occurred in children 5 years and older.

Discussion

There were 27 culture-confirmed diphtheria cases from Hadramout governorate, and 22 of them residing outside Mukalla, the governorate's capital city. This may be due to the lower vaccination rate in those areas as a consequence of the current crisis in Yemen. However, Mukalla itself experienced a surge of cases in the presently reported outbreak. There had been no diphtheria report in Mukalla city for a long time, even during the 2017-2018 diphtheria outbreak.[12] The re-emergence of diphtheria cases in Mukalla was most

Table1. Epidemiological characteristics of diphtheria outbreak 2019 – 2020 in Hadramout/ Yemen (N=34)

Characteristics	No. of cases	No. of deaths	CFR %
Age, n			
<5 years	8	2	5.9
5-10 years	14	3	8.8
>10 years	12	2	5.9
Sex, n			
Male	17	3	8.8
Female	17	4	11.8
Residence (governorate)*, n			
Hadramout	27	5	14.7
Shabwa	6	1	2.9
Other (Abyan)	1	1	2.9
Vaccination status, n			
Complete	13	3	8.8
Incomplete	3	0	0
Unvaccinated	18	4	11.8
Total	34	7	20.6

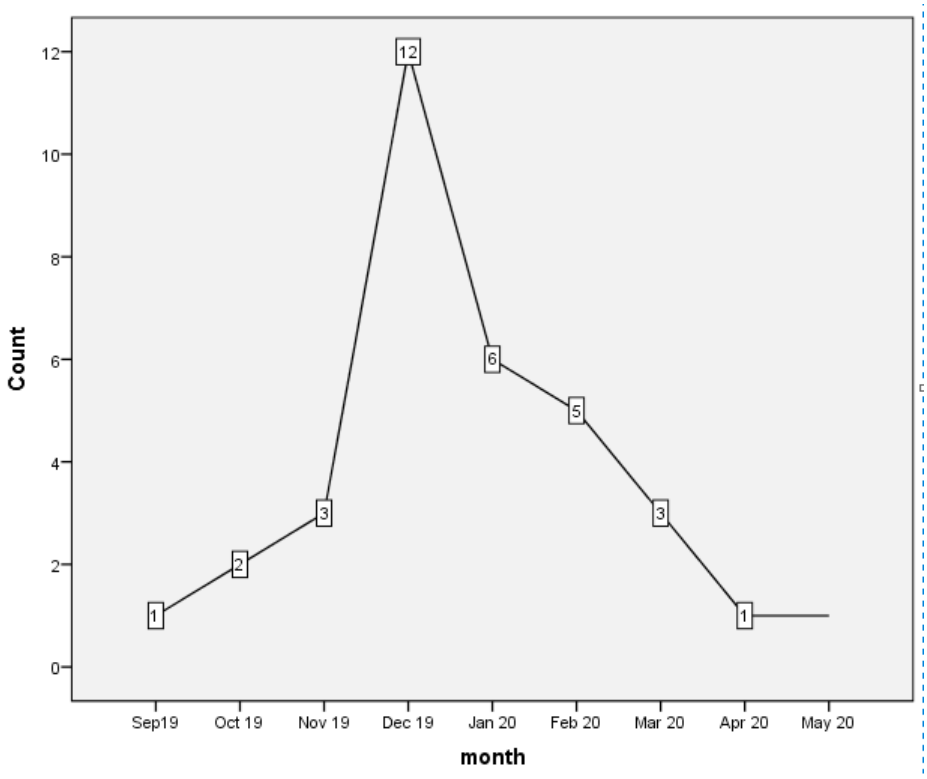

Figure 1. Monthly distribution of diphteria cases

Table 2. Clinical spectrum of patients with diphtheria (N=34)

Characteristics	No of cases
Fever	34
Sore throat	34
Pseudomembranes (tonsillar)	33
Difficulty in swallowing (dysphagia)	28
Bull neck	18
Cough	4
Stridor	3
Duration of illness before hospitalization	
1 day	6
2 days	3
3 days or more	24
Length of hospital stay	
<5 days	3
5-10 days	28
>10 days	3
Outcomes	
Survived	27
Died	7

likely due to the internal movement of persons within the Hadramout governorate during the recent war, particularly from Ibb and Al Hodeida, where most of the cases of the 2017-2018 diphtheria outbreak were reported.[12]

Diphtheria is a disease that predominantly occurs when the temperature decreases.[19] However, in some developing countries it is reported throughout the year, particularly during the rainy season, as is the case in India.[3] Most of our cases occurred during the winter months.

No gender predominance was observed in our study, similar to findings in the 2017-2018 outbreak.[12] The same finding was reported by Basavaraja et al. in India.3 In contrast, Khan et al. reported more cases in boys than in girls (69.64% *vs.* 30.36%, respectively),[20] as did Nawing *et al.*[21] in Indonesia (17/28 *vs.* 11/28, respectively).

Our observation confirmed that the age distribution of diphtheria has shifted to the older age group, with 75.5% of cases occurring in school-aged children over 5-year-old, in contrast to the 1918-1982 outbreak, in which 67% of cases were under 5

Table 3. Outcome of diphtheria cases (N=34) during 2019 – 2020 outbreak in Hadramout/Yemen

Variables	Outcomes			P value
	Survived (n= 27)	Died (n=7)	Total (N=34)	
Age, n				0.898
<5 years	6	2	8	
5-10 years	11	3	14	
>10 years	10	2	12	
Sex, n				0.500
Male	14	3	17	
Female	13	4	17	
Duration of symptoms before admission, n				0.362
1 day	6	0	6	
2 days	2	1	3	
>3 days	19	6	25	
Bull neck, n				0.005
Yes	11	7	18	
No	16	0	16	
Vaccination, n				0.652
Complete	10	3	13	
Incomplete	3	0	3	
Not vaccinated	14	4	18	
Myocarditis, n				0.000
Yes	0	3	3	
No	27	4	31	
Acute renal failure, n				
Yes	0	7	7	0.000
No	27	0	27	
DIC and shock, n				0.000
Yes	0	6	6	
No	27	1	28	

years old.[11] A similar shift to the older age group was reported by Galazka *et al*.,[4] Basavaraja *et al*.,[3] and Gundam *et al*.[22] A worldwide analysis showed that 82% of diphtheria cases were aged 5 years and older.[23] This may be due to several factors, such as waning immunity with age and lack of booster vaccination doses.[24] For this reason, the WHO has recommended booster doses for diphtheria.[25] Such approach of administering booster doses of diphtheria toxoid has been documented in preventing diphtheria among school-aged children by the Russian Federation.[26]

There was a high percentage of unvaccinated patients in our study (52.9%) compared to reports from other developing countries. Studies in India and Indonesia have reported the proportion of unvaccinated cases to be 48% and 14%, respectively.3,22 In 2006, the estimated vaccination coverage in the Mukalla districts (including Mukalla city) was 82% fully vaccinated, 12% partially vaccinated, and 5% unvaccinated.[27] The drop in vaccination coverage to 52.9% reflects the current instability in Yemen.

In our study, the most common clinical presentations were fever and sore throat, followed by pseudomembranes and difficulty swallowing. Similarly, Nawing et al. in Indonesia found that all patients came with fever, sore throat, and pseudomembranes, followed by 69% of patients with dysphagia.[22] A study in Jordan reported that 94.3% of patients had fever and sore throat, 91.4% of patients had dysphagia, and 80% had pseudomembranes.[28]

The clinical picture of bull neck varies among different reports and indicates a poor prognostic factor for morbidity and mortality of diphtheria. We found bull neck in 18 cases (52.9%), of whom 11/18 died. A previous study reported that 57.1% of their patients had bull neck, of whom 25% died.[22] Another study found that 45.16% of patients had bull neck, and 71.4% of those died.[3] Bull neck may herald cardiac involvement. In our study, although ECG was not done for every case, bull neck was significantly

associated with ECG changes (P=0.020). Similar findings were reported by a study which found that 84.2% of their patients with bull neck had abnormal ECG findings.[29] For this reason, ECG monitoring and cardiac assessment should be initiated in every case of diphtheria.

The most common complications in our study were acute renal failure (20.6%), DIC and shock (17.6%), and myocarditis (8.8%). A previous study reported myocarditis in 42.55%, acute renal failure in 4.25%, DIC and shock in 4.25%, and neuropathy in 8.52%.[30] None of our patients had neuropathy or laryngeal obstruction needing tracheostomy. Cardiomyopathy is reported as the most common and serious complication of diphtheria. It occurs in approximately 10% to 20% of patients and is responsible for 50% to 60% of deaths.[1] In our study, three patients (8.8%) had myocarditis and all of them died. In India, the incidence of diphtheric myocarditis varies from 16% to 66%.[23] Another study reported that 41.9% of patients had myocarditis, and 76.9% of them died.[3] A study in the Kyrgyz Republic reported that 52% of patients had diphtheritic carditis, and 7.3% of them died.[31] A clinical trial from Brazil found that the use of carnitine helped protect patients against diphtheric myocarditis.[32] None of our patients receive carnitine. In our study, not every case received detailed cardiac evaluation because of the high financial cost.

The essential mechanism of all complications is mediated by the toxin, which inhibits protein synthesis and directly attacks the chromosomal DNA, leading to cell death.[1,33] Hence, early detection of diphtheria and administration of anti-diphtheric toxin is important for the management of diphtheria and preventing complications.

In our study, myocarditis (P<0.001), acute renal failure (P<0.001), DIC and shock (P<0.001), and bull neck (P=0.005) were significantly associated with poor outcome. Nawing et al. reported that poor outcome of their patients was associated with a lack of basic or booster immunizations, poor nutrition, bull neck, myocarditis, and length of hospital stay of <5 days.[22] In our situation, more training and resources are needed for care in the pediatric intensive care unit and medical staff, as they play an important role in the management of diphtheria.

Our case fatality rate (CFR) was 20.6%, compared to 5.6% reported during the 2017-2018 diphtheria outbreak that covered all Yemen governorates.[12] The relatively small number of patients in the presently reported outbreak might explain the different results. Existing studies have also reported varying CFRs. In Indonesia it was reported as 14.6%,22 whereas in India, it ranged from 32% to 56.3%.[3] Many factors contribute to mortality in diphtheria, such as vaccination status, late anti-diphtheric toxin administration, and nutritional status.[22]

The fragile health system in Yemen, which has been devastated by the current war, and the internal movement of persons with low immunization coverage are potential risk factors associated with the resurgence and spread of diphtheria and other infectious diseases, such as cholera.[12]

Limitations of our study is the lack of detailed data on the number of DPT vaccine doses received by patients, as well as the lack of detailed cardiac evaluation in most cases.

We conclude that diphtheria continues to emerge in Yemen due to low vaccination coverage. The shift of diphtheria incidence to those over five years old necessitates the implementation of diphtheria booster vaccination strategies and improvement of vaccine coverage.

Conflict of interest

None declared.

Acknowledgements

The authors would like to express appreciation to the director of Mukalla Maternity and Children's Hospital for facilitating our work and providing easy access to medical records. The authors thank workers in the statistics department of the hospital for their cooperation and patience.

Funding acknowledgment

The authors received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

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