

# Clinical And Laboratory Characteristics of Diphtheria Patients Treated at RSUP Haji Adam Malik in 2020 - 2023

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## Abstract

**Background:** In 2017, diphtheria outbreaks occurred in several provinces in Indonesia. In North Sumatra, data on diphtheria cases are rarely published. Therefore, information is needed to assess the clinical and laboratory characteristics that are associated with an increase in mortality of diphtheria. This study aims to determine the clinical dan laboratory profile of children with Diphtheria **Methods:** Retrospective cohort study to assess the association of clinical and laboratory characteristics with mortality. Research data was obtained from medical records of patients aged 1-18 years diagnosed with diphtheria clinically at H. Adam Malik Hospital Medan in the period January 2020 to December 2023. **Results:** The majority of children with diphtheria were male (56,8%) and the mean age of 8,14. Most patients did not receive any immunization for diphtheria (54,1%). During this period, the mortality rate was 16,2%. All participants experienced fever and sore throat. Pseudo-membrane was found in 36 cases (97.3%) followed by bullneck appearance (73%) and myocarditis (45,9%). Leukocytosis was found in 78,4% of cases while positive bacterial culture and thrombocytopenia were found in 59.5% and 51.4% of the cases **Conclusions:** The clinical profile of Diphtheria at Haji Adam Malik Hospital Medan showed that all cases with fever and sore throat, most of cases had pseudo-membrane, bullneck, and myocarditis. Leukocytosis, bacterial culture and thrombocytopenia showed over half of the cases.

**Keywords:** Diphtheria, pseudo membrane, *Corynebacterium diphtheriae*

Diphtheria is an acute infectious disease caused by Gram-positive anaerobic bacteria, *Corynebacterium diphtheriae*, which affects the upper respiratory tract in children aged one to ten years old.(1,2) Diphtheria potentially causes public health problems or even epidemics because it is easily transmitted from person to person through inhaled droplets and skin contact with diphtheria carriers.(3,4)

Diphtheria can be prevented by vaccination which has been routinely implemented around the world. Yet, the global occurrence of Corona Virus Disease 19 (COVID-19) pandemic causes alterations in health programs, immunization services, and surveillance of diseases that can be prevented by immunization.(5) The COVID-19 pandemic, followed by a regional quarantine period and travel restrictions interrupted routine vaccination programs in various countries. People refuse to visit the doctor for routine screening and vaccination due to fear of COVID-19 infection.(6,7)

In 2021, the WHO announced that diphtheria caused 8,368 cases worldwide.(8) In Indonesia, diphtheria infections were found in most regions. The total number of cases of diphtheria is 235 with 25 death cases and the Case Fatality Rate (CFR) of 11%. Despite a lower incidence rate compared to 2020 (259 cases), the mortality rate was increased compared to 2020 (13 cases) with CFR 5.02%.(3) This phenomenon is possibly explained by the lack of diphtheria immunization or incomplete immunization, which worsened the patient's condition.(3) In North Sumatra, the total of cases of diphtheria in 2019 was 17 cases (0 death cases) with the highest incidence in the district of Simalungun (5 cases) and Medan (3 cases).(2)

Diphtheria has a wide range of clinical symptoms, such as asymptomatic, swallowing difficulty, low-grade fever, sore throat, pseudo-membrane formation, and bullneck appearance. Early clinical examination and diagnosis are the cornerstone to avoid detrimental complications such as myocarditis, airway obstruction, and muscle paralysis.(1,9) Similarly, laboratory findings also vary in diphtheria infection. Thrombocytopenia is rarely found in diphtheria infections, except in severe conditions. Thrombocytopenia was also found in 31.3% of children with diphtheria treated in the intensive care room, and a thrombocyte count of less than  $150 \times 10^9$  cells/L was

associated with death. Leucocytosis may occur but without any pathognomonic patterns. Neutrophilia, higher levels of C-reactive protein (CRP), and leukocyte rates above  $25 \times 10^9$  cells/L are associated with mortality in myocarditis associated with diphtheria.(10)

## 2. Methods

### 2.1 Study Design

This study used a retrospective cohort design to analyze the association of clinical and laboratory findings with in-hospital mortality in children with diphtheria infections in Haji Adam Malik Medan General Hospital during 2020-2023. This study had been approved by the ethics committee (Approval no. 1152/KEPK/USU/2023).

### 2.2 Study Participants

This study retrieved data from medical records of all patients aged below 18 years old with diphtheria infection based on clinical findings and bacteria culture during the study period. Cases with incomplete data on medical records were excluded

### 2.3 Data Extraction and Collection

All data were directly extracted from medical records. These data include clinical findings (presence of fever, sore throat, bullneck appearance, pseudo-membrane, myocarditis, neuritis, and airway obstruction) and laboratory findings (leukocytosis, thrombocytopenia, and bacterial culture). Other information such as diphtheria infection status (suspect, probable, and confirmed) and history of immunization were also extracted. The patient's outcome was in-hospital mortality. All data were collected in a dedicated spreadsheet.

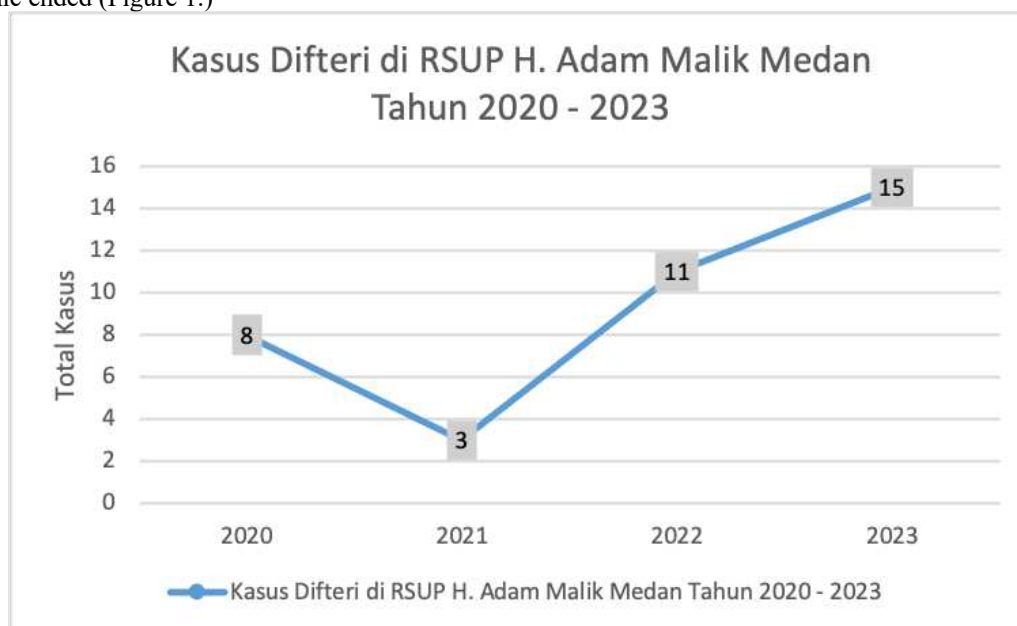
### 2.4 Statistical Analysis

Categorical data is presented in the form of frequency distributions and percentages. Numerical data is presented in percentages. The data collected was processed and analyzed using the help of the Statistical Package for Social Science (SPSS) computer software version 23.0

## 3. Result

### 3.1 Baseline Characteristics

A total of 37 children with diphtheria were included in this study. Based on year-on-year cases of diphtheria, the number of cases decreased during the COVID-19 pandemic and increased after the global pandemic ended (Figure 1.)



**Figure 1. Year-on-year cases of Diphtheria**

The majority of children with diphtheria were male (56,8%) and the mean age of 8,14. Most patients did not receive any immunization for diphtheria (54,1%). During this period, the mortality rate was 16,2% (Table 1.)

**Table 1. Baseline Characteristics**

Variables	n = 37
Sex, n (%)	
Male	21 (56,8)
Female	16 (43,2)
Age, years	
Mean (SD)	8,14 (4,15)

Median (Min-Max)	8 (1 – 18)
History of Immunization	
Complete	1 (2,7)
No Booster	4 (10,8)
Incomplete	12 (32,4)
Absence	20 (54,1)
Outcome, n (%)	
Recovered	31 (83,8)
Dead	6 (16,2)

### 3.2 Clinical and Laboratory Findings

All participants experienced fever and sore throat. Pseudo-membrane was found in 36 cases (97.3%) followed by bullneck appearance (73%) and myocarditis (45,9%). Leukocytosis was found in 78,4% of cases while positive bacterial culture and thrombocytopenia were found in 59.5% and 51.4% of the cases, accordingly (Table 2).

**Table 2. Univariate Analysis of Clinical and Laboratory Findings to Mortality**

Variables	n (%)	Outcome	
		Dead	Recovered
<b>Clinical Findings</b>			
Fever	37 (100)		
Yes		6 (16,2)	31 (83,8)
No		0	0
Sore Throat	37 (100)		
Yes		6 (16,2)	31 (83,8)
No		0	0
Bullneck	27 (73)		
Yes		5 (18,5)	22 (81,5)
No		1 (10)	9 (90)
Pseudo-membrane	36 (97,3)		
Yes		6 (16,7)	30 (83,3)
No		0	1 (100)
Neuritis	1 (2,7)		
Yes		0	1 (100)
No		6 (16,2)	31 (83,8)
Airway obstruction	10 (27)		
Yes		5 (50)	5 (50)
No		1 (3,7)	26 (96,3)
Myocarditis	17 (45,9)		
Yes		6 (35,3)	11 (64,7)
No		0	20 (100)
<b>Laboratory Findings</b>			
Leukocytosis	29 (78,4)		
Yes		6 (20,7)	23 (79,3)
No		0	8 (100)
Thrombocytopenia	19 (51,4)		
Yes		6 (31,6)	13 (68,4)
No		0	18 (100)
Bacterial Culture	22 (59,5)		
Positive		6 (27,3)	16 (72,7)
Negative		0	15 (100)

## 4. Discussion

### 4.1 Clinical Findings in Diphtheria Infection

Based on this study, the most common symptoms of diphtheria are fever and sore throat (100%) and bullneck appearance (73%). A study in India showed a slightly different result. The most common clinical findings were enlarged tonsils (99.3%), followed by fever (98.7%), sore throat (88.7%), swallowing difficulties (88%), and bullneck appearance (14.7%).(11) While clinical study in India showed that all participants with diphtheria infections had fever and severe sore throat. While 93,7% had enlarged tonsils, 78,1% had bullneck appearance,

and 84,8% had respiratory difficulties upon hospital admission.(12) Some clinical findings associated with death were hoarseness, dyspnea, bull neck appearance, and stridor ( $p<0.001$ ). (13)

#### 4.2 Laboratory Findings in Diphtheria Infection

Leukocytosis (78.4%), was the most common laboratory finding in this study. Similarly, a study in Indonesia showed that leukocytosis occurs in 75.2% of cases. On the contrary, a study in India with 177 cases of diphtheria showed that leukocytosis only occurred in 8.3% of cases.(14)

Almost 60% of current cases were positive for bacterial culture. This finding is similar to a previous study in India which showed that positive culture was only found in 65.6% of cases.(15) Another evidence even reported a lower rate of positive culture in 16% of included cases.(10,16) Although positive bacterial culture is the gold standard for *Corynebacterium* spp. Identification, several factors such as previous antibiotics administration, inadequate sample, or transportation aspects might cause false negative results.

#### 4.3 Study Strengths and Limitations

To the best of our knowledge, this is the first study analyzing the association between clinical and laboratory findings to mortality in children with diphtheria infections in North Sumatra. Our study also evaluates the probability of death in diphtheria pediatric patients with airway obstructions which can be used by pediatricians as an initial guide in assessing the risk of mortality.

The limitation of this study includes a retrospective cohort design which is unable to provide detailed information regarding onset, contact risk, and history of traveling. Second. not all patients with myocarditis underwent cardiac marker analysis due to resource limitations, Finally, our sample was relatively small.

#### 5. Conclusion

The clinical profile of Diphtheria at Haji Adam Malik Hospital Medan showed that all cases with fever and sore throat, most of cases had pseudo-membrane, bullneck, and myocarditis. Leukocytosis, bacterial culture and thrombocytopenia showed over half of the cases.

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