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Original Article

Clinical spectrum and outcomes of pediatric diphtheria

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Abstract

Background Although vaccination programs have succeeded in reducing the incidence of diphtheria, it remains a health problem in Asia, including Indonesia.

Objective To investigate the clinical spectrum and outcomes of pediatric diphtheria in Wahidin Sudirohusodo Hospital.

Methods This study was a retrospective review of childhood diphtheria medical records from January 2011 to December 2017 in Wahidin Sudirohusodo Hospital, Makassar, South Sulawesi. Recorded data consisted of age, gender, nutritional and immunization statuses, signs and symptoms, throat swab culture results, complications, and outcomes.

Results Of 28 subjects aged 9 months to 17.10 years, the majority were >5 years (57.1%) and male (60.7%). Subjects' mean age was 6.15 years and 82.1% of cases were well nourished. Overall, 85.7% had received complete immunizations, while 14.3% were not immunized, having received neither basic nor booster vaccines. The presenting manifestations were fever, pseudomembranes, and sore throat in all subjects, enlarged tonsils (78.57%), dysphagia (67.86%), cough (57.14%), headache (57.14%), hoarseness (67.86%), bull neck (25%), and myocarditis (14.3%). Most subjects had hospital stays of >10 days (67.9%). Mortality was 14.3%, usually in those admitted with a late, deteriorating condition and dying before getting optimal treatment. Poor outcome was significantly associated with the lack of basic or booster immunizations, poor nourishment, bull neck, myocarditis, and hospital stays < 5 days ($P<0.05$ for all).

Conclusion The clinical spectrum and outcomes of pediatric diphtheria in this study are relatively similar to reports from other hospitals. Mortality was mostly in patients who lack basic or booster immunizations, are poorly nourished, or have bull neck, myocarditis, or hospital stays < 5 days. **[Paediatr Indones. 2019;59:38-43; doi: http://dx.doi.org/10.14238/pi59.1.2019.38-43].**

Keywords: *clinical spectrum; outcome; diphtheria*

Diphtheria, taken from the Greek, "diphtera" which means leather hide, was first identified by Hippocrates.[1] It is an acute, fatal, bacterial toxin-induced disease caused by Corynebacterium diphtheria. The disease has been almost completely eradicated in developed countries, including many European nations. However, diphtheria remains an important cause of child mortality in developing countries and although the incidence has declined, still accounts for 80-90% of the global burden.[2] In 2015, India contributed 2,365 (52.21%) of the 4,530 diphtheria cases reported globally.[3] Although vaccination programs have succeeded in reducing the incidence of diphtheria worldwide, diphtheria remains a health problem, especially in Asia. The *World Health Organization* (WHO) reported that the number of diphtheria cases in 2013 was 4,680, which were widespread and mostly concentrated in the Asian continent, including India (3,313 cases), Indonesia (775 cases), Iran (190 cases),

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Pakistan (183 cases), and Nepal (103 cases). Indonesia had the second highest number of diphtheria cases.[4,5] This disease mostly occurs in children under 5 years of age, but may also occur in children over 5 years (5-19 years) and in adults.[6] Several studies have shown that low vaccination coverage, crowding, migration, or a combination of host, agent, and environmental factors, can influence the incidence of diphtheria,[7,8] in addition to nutritional status, parental behavior, and personal hygiene of children.[9]

Many outbreaks of diphtheria have been reported in various states of India in recent times.[10-14] A diphtheria outbreak of 593 cases in Indonesia was documented by several provincial health offices between 1 January and 1 November 2017, many occurring in East Kalimantan in children aged 1-10 years.[15]

Since there has been a lack of studies on childhood diphtheria in Wahidin Sudirohusodo Hospital, Makassar, we aimed to investigate the clinical spectrum and outcomes of childhood diphtheria in our facility.

Methods

This retrospective study included patients with diphtheria aged less than 18 years and hospitalized in the Pediatrics Ward of Wahidin Sudirohusodo Hospital, Makassar, South Sulawesi, from January 2013 to September 2018. Patients with incomplete medical records were excluded. All patients with suspected, probable, or confirmed cases of diphtheria based on the *WHO* definition guidelines were enrolled in the study.[16,17]

The DTP vaccination is recommended to be administered at age of 2, 3, and 4 months and booster at age of 7, 10, and 12 years, and repeated every 10 years. If a subject received basic and booster vaccination then her/his immunization status was categorized as complete. If a subject did not received either basic nor booster vaccination then her/his status was no immunization.[17]

Signs and symptoms of diphtheria included malaise, sore throat, low-grade fever, nasal discharge, bloody nasal discharge, hoarseness, cough, pain with swallowing, noisy breathing (inspiratory stridor), shortness of breath, chills, fatigue, cyanosis, headache, rapid breathing, lymphadenopathy, cardiac arrhythmia, and myocarditis.[18,19] Suggestive signs and symptoms of diphtheria, such as fever, cough, sore throat, dysphagia, difficulty swallowing and/or breathing, hoarseness, enlarged tonsils with evidence of pseudomembranes around the tonsils and surrounding areas, and bull neck were collected from subjects' medical records and further analyzed.

Pseudomembranes were defined as typical tough, gray-white membranes overlying the inflamed, edematous mucosa of the tonsils, pharynx, larynx, or trachea, strongly adherent to the underlying tissue, with attempts to dislodge it usually resulting in bleeding. Bull neck was defined as an obviously swollen neck due to swollen cervical lymph nodes, soft tissue edema and mucosal edema. Myocarditis was defined as signs and symptoms of cardiac involvement such as weak and irregular pulse, tachypnea, tachycardia, cyanosis, dyspnea, weakness, diminished heart sounds, cardiac dilation, gallop rhythm, or changes to the electrocardiograph (ECG) pattern, particularly ST-T wave changes and heart block after 1 to 2 weeks of illness.[18,20,21]

Nutritional status was based on the Waterlow (body weight/body height percentile) and *WHO* (body weight/body height SD) criteria and categorized as well-nourished [>90 / (+2 SD) - (-2 SD)], undernourished [70-90/ (< - 2 SD) - (- 3 SD)], poorly nourished [< 70/ (- 3 SD)], overweight [>110/ (>(+ 2 SD) – (+ 3 SD)], and obese [>120 / (+ 3SD)].[22,23]

Other data obtained from subjects' medical records were age, gender, nutritional status, immunization status, throat swab culture results, complications, medical interventions, and patient outcomes (survived or died). All patients were treated with appropriate antibiotics and anti-diphtheria serum (ADS) in the pediatrics ward and those with complications were treated with appropriate management in the pediatric intensive care unit based on *WHO* guidelines.[18] Data were analyzed using the *Statistical Package for the Social Sciences (Windows Version 21.0*; SPSS Inc., Chicago, IL, USA). Clinical spectrum of the childhood diphtheria patients was analyzed by means of descriptive statistics and shown as ranges, means, and percentages, whereas outcomes were analyzed using Chi-square test. Results were considered significant for P values <0.05. This study

was approved by the Ethics Committee of Wahidin Sudirohusodo Hospital, Makassar.

Results

There were 28 pediatric diphtheria patients with complete medical records during the study period, ranging in age from 9 months to 17.10 years, with the mean age of 6.15 years. The majority of patients (16/28) were above 5 years. Subjects' male: female ratio was 1.54:1, with 17/28 boys. Most patients had well-nourished nutritional status (23/28). Three patients were hospitalized in 2013, three in 2014, two in 2015, six in 2016, eight in 2017, and six in 2018.

Of 28 subjects, 24 had received complete immunizations and 4 had not been immunized. All patients presented with fever, pseudomembranes, and sore throat (28/28), followed by enlarged tonsils (22/28), dysphagia (19/28), cough (16/28), headache (16/28), hoarseness (19/28), and bull neck (7/28). Myocarditis was seen in 4/24 patients and was the only complication observed in our study. Length of hospital stay was mostly ≥ 10 days (19/28) and varied from 3 to 23 days, with a mean of 12.43 days. Mortality was 4/28 and usually in those entering the hospital with a late, deteriorating condition and dying before getting optimal treatment (**Table 1**). Poor outcome was significantly associated with a lack of basic or booster immunizations (P=0.000), poor nourishment (P=0.000), bull neck (P=0.000), myocarditis (P=0.000), and length of hospital stay < 5 days (P=0.001) (**Table 2**).

Table 1. Clinical spectrum of patients with diphtheria

Characteristics	(N=28)
Age, years	
Mean age (SD)	6.15 (3.8)
Median (range)	12 (0.9 -17.1)
Age group, n	
<5 years	12
5-10 years	13
>10 years	3
Sex, n	
Boys	17
Girls	11
Nutritional status, n	
Well-nourished	23
Undernourished	2
Poorly nourished	3
Length of hospital stay, n	
< 5 days	2
5-10 days	7
≥10 days	19
Signs and symptoms, n	
Fever	28
Sore throat	28
Dysphagia	19
Hoarseness	19
Cough	16
Headache	16
Enlarged tonsils	22
Pseudomembranes	28
Bull neck, n	
Yes	7
No	21
Myocarditis, n	
Yes	4
No	24
Vaccination, n	
Yes	24
No	4
Outcomes, n	
Survived	24
Died	4

Discussion

During the 6-year study period, 28 patients with diphtheria were admitted to Wahidin Sudirohusodo Hospital, Makassar, with an age range of 9 months to 17.10 years and mean age of 6.15 years. The majority of patients were above 5 years of age (16/28), similar to that reported by Meshram *et al.* (55.32%; mean age of 6.46 (SD 3.08) years),[24] Kole *et al.* (64.28%),[25] Basavaraja *et al.* (74.1%),[26] and Bandichhode *et al.* (66.66%).[27] Another study documented that their youngest patient was also 9 months of age and the others mostly between 5 to 10 years of age.[28]

There were more boys (17/28) than girls (11/28) in our study, with a boy to girl ratio of 1.54:1, which was slightly different from previous studies with nearly equal boy to girl ratio (0.95:1).[24,29] However, Khan *et al.* noted more boys (69.64%) than girls (30.36%), with a ratio of 2.29:1.[28]

In our study of 28 patients, 24/28 had received complete immunizations, while 4/28 had received neither basic and nor booster immunizations. Different findings were reported by Meshram *et al.* (4.25% fully immunized, 57.45% partially immunized, and

Table 2. Outcomes of patients with diphteria

Clinical variables	Outcomes			P value
	Survived (n=24)	Died (n=4)	Total (N=28)	
Age, n				0.156
<5 years	12	0	12	
5-10 years	10	3	13	
>10 years	2	1	3	
Sex, n				0.636
Male	15	2	17	
Female	9	2	11	
Nutritional status, n				0.000
Well-nourished	22	1	23	
Undernourished	2	0	2	
Poorly nourished	0	3	3	
Length of hospital stay, n				0.001
<5 days	0	2	2	
5-10 days	6	1	7	
≥10 days	18	1	19	
Bull neck, n				0.000
Yes	3	4	7	
No	21	0	21	
Myocarditis, n				0.000
Yes	0	4	4	
No	24	0	24	
Complete vaccination, n				0.000
Yes	24	0	24	
No	0	4	4	

38.30% unimmunized),[24] Basavaraja *et al.* (48.3% fully immunized and 48.3% unimmunized),[26] and Ratageri *et al.* (42% fully immunized, 16% partially immunized, and 42% unimmunized).[30] Four patients in this study were unimmunized maybe due to missing the immunization schedule in Makassar as well as some districts in South Sulawesi, possibly because of lack of awareness, avoiding immunizations, migration, decreased enthusiasm to receive periodic routine immunizations, lack of emphasis on booster vaccination at school entry, not opening a multi-dose vial if not enough children are present, or postponing vaccination in children with minor illnesses.[31,32]

All patients in our study presented with fever, pseudomembranes in the throat, and sore throat, followed by enlarged tonsils, dysphagia, cough, headache, hoarseness, and bull neck. Ratageri *et al.* reported that the most common clinical presentation in their patients were pseudomembranes (100%), fever (92.8%), cervical lymphadenopathy (92.8%), followed by sore throat (64.2%), neck swelling (42.8%), dysphagia (35.7%), bull neck (28.5%), and halitosis (21.4%),[30] whereas Meshram *et al.* reported throat pain (95.74%), enlarged/congested tonsils (80.85%), respiratory difficulty (68.08%), dysphagia (59.57%), bull neck (48.94%), and voice change (36.17%).[24]

In our study, myocarditis was found in 4/28 of patients, as the only complication observed, but Meshram *et al.* found myocarditis in 42.55% of patients[24] and various studies in India found incidences of diphtheria myocarditis from 16 to 66%.[33-35] Basavaraja *et al.* showed that out of 45.16% patients with bull neck, 71.4% died; and out of 41.9% patients with myocarditis, 76.9% died.[26] However, in our study out of 25% patients with bull neck, 57.1% died, whereas all patients with myocarditis died. Khan *et al.* reported that out of 16% of their patients with myocarditis, 8.92% died.[28] The mortality from a study in India was 5%.[25] Cardiac involvement in diphtheria is caused by exotoxins produced by *Corynebacterium diphtheria*.[36,37] Mortality in our study was higher than that reported by previous studies and may be due to our different sample size or that some of our patients entered the hospital in a late, deteriorating condition

and died before getting optimal treatment.

Poor outcome of the patients in our study was significantly associated with a lack of basic or booster immunizations (P=0.000), poor nourishment (P=0.000), bull neck (P=0.000), myocarditis (P=0.000), and length of hospital stays < 5 days (P=0.001). Children with poor nutritional status may have immune deficiencies resulting in reduced response to vaccines.[38,39] Therefore, the key to preventing mortality from diphtheria in children is simultaneous improvement in their nutritional status and getting complete immunizations.

In conclusion, the clinical spectrum and outcomes of pediatric diphtheria in Wahidin Sudirohusodo Hospital, Makassar are relatively different to those reported from other countries. The mortality rate of our patients is 14.3%, most of whom had not received basic or booster immunizations, were poorly nourished, and had bull neck, myocarditis, and length of hospital stays < 5 days. The relatively high mortality is due to myocarditis, which highlights the necessity of early diagnosis and prompt treatment with ADS to reduce mortality. In addition, immunizations (basic or booster) should be encouraged in Makassar and South Sulawesi. We recommend that vaccination schedules include boosters, based on accurate surveillance, to reach high vaccination coverage in order to prevent diphtheria outbreaks and control the disease.

Conflict of Interest

None declared.

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