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Intravenous aminophylline treatment for severe asthma exacerbation in a toddler: an evidence-based case report



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ABSTRACT

Introduction: Asthma is the most prevalent chronic condition in childhood causing enormous morbidity and mortality worldwide. Acute severe exacerbations are potentially life-threatening and often need hospitalization. Incomplete or poor response to initial treatment requires additional interventions that commonly are intravenous second-line drugs, of which Aminophylline is one of them. Although Aminophylline is costly and effective, views are polarising that its use is unsafe. Herein we report a case of intravenous aminophylline use in severe asthma exacerbation in a toddler.

Case description: A 3-year-old boy previously diagnosed with asthma came to the emergency room due to severe shortness of breath. He had breathlessness which was more pronounced when he was lying down. He looked restless and irritable. Bilateral wheezing, tachypnea, tachycardia and chest withdrawal were noted. Because of poor response to standard initial treatment, intravenous Aminophylline was given and showed complete relief without the occurrence of the anticipated serious adverse event.

Conclusion: When first-line inhaled/nebulized medication fails to control a child's asthma exacerbation, Aminophylline may be utilized. It must be considered a cost-effective treatment for acute asthma exacerbations, especially for developing countries with limited health budgets, even though it is thought to have a narrow therapeutic range and a large inter-individual variance in clearance.

Keywords: Aminophylline, severe asthma attack, asthma exacerbation.

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INTRODUCTION

The most common chronic pediatric illness, asthma, has a significant global impact on morbidity and mortality. According to statistics from the International Study of Asthma and Allergies in Childhood (ISAAC), the incidence of asthma among children in Indonesia varies by province and ranges from 4-11% in children aged 6-7 to 6-13% in children aged 13-14. Children frequently suffer from acute asthma attacks, among the most frequent causes of ER visits and hospitalization.¹ Exacerbation could frequently occur depending on asthma severity level and symptom control. The degree of exacerbation ranges from very mild to life-threatening attacks. It makes asthma a national burden, especially in children who are unresponsive to standard treatment. The financial expenses of asthma are significant and comprise both direct non-medical costs and direct medical

costs, such as ER visits or hospitalizations for acute exacerbations. Globally, the economic costs of asthma outweigh those of HIV infection, TB, and tuberculosis combined. Asthma costs developed nations between 1 and 2 percent of their healthcare budgets.²

Acute severe exacerbations with incomplete or poor response to initial treatment require additional interventions. Intravenous administration of β_2 -agonists, in the form of terbutaline or salbutamol or Aminophylline, are commonly considered.³ Aminophylline has a narrow therapeutic range and small hepatic metabolism and clearance variations, increasing the risk of adverse drug reactions.⁴ Aminophylline is costly, especially for developing countries with limited health budgets. However, some views point out that Aminophylline is considered "it is dangerous and unsafe," "it is the devil's poison,"; and "should be removed from the shelves of the emergency

department."⁵ The Global Initiative for Asthma (GINA) guidelines strongly recommend against using Aminophylline for acute exacerbation.⁶ This report herein a case of intravenous aminophylline use in severe asthma exacerbation in a toddler.^{1,2}

CASE DESCRIPTION

A 3-year-old boy was referred from a private hospital due to shortness of breath. The patient had dyspnea a day before hospital admission. He had a mucus-producing cough two days before the admission and a runny nose and fever.

The referring hospital gave 4 nebulizations, each with an hour interval, of salbutamol-ipratropium bromide and budesonide and a 2.5 mg intravenous injection of dexamethasone. However, this did not improve the shortness of breath.

He was diagnosed with asthma last year but received no inhaled controller medication. His parents usually give him

a salbutamol inhalation when he gets shortness of breath at home. They said that the patient had three exacerbations in the last year. The last exacerbation occurred three months ago.

His perinatal history was uneventful. His elder brother had also been diagnosed with asthma. The patient got breastfed exclusively up to two years of age and had 3-4 times daily family meals. His development history was uneventful, and he already had complete basic immunization.

He suffered from severe respiratory distress upon his first presentation in the emergency room. Profound wheezing, along with rapid breathing and chest indrawing, was noted. He seems restless and breathless, which worsens when he lies down. There was tachycardia (150 bpm)

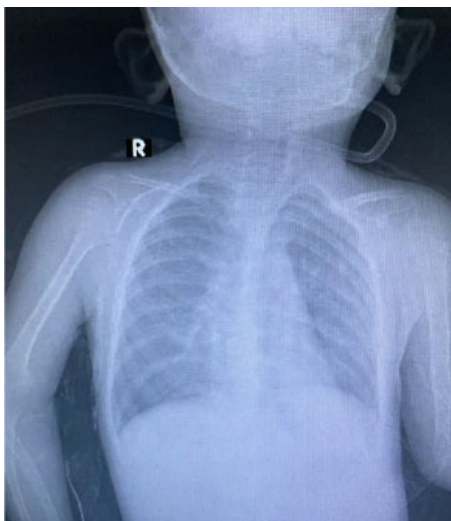


Figure 1. Chest x-ray showed hyperinflation and infiltrates of bronchopneumonia.

and tachypnea (50 tpm). His temperature was 38.3°C. Using an 8-10 lpm non-rebreathing oxygen mask, peripheral oxygen saturation was 98%. Crackles and wheezing were noted on chest examination. Other physical examination findings were within normal limits.

The nutritional status was normal. He weighed 13 kgs (-2SD to mean) and heightened 97 cms (-1SD to mean). The head circumference was 49.5 cm (-1SD to mean), the arm circumference was 15.5 cm (-1SD to mean), and the weight-to-height ratio was in -2 to -1 SD Z-score.

Laboratory examination showed leukocytosis and neutrophilia. Chest x-ray showed hyperinflation and infiltrates of bronchopneumonia (Figure 1).

We started loading a dose of 80 mg and continued by 0.5 mg/kg/hour of Aminophylline and 9 mg 3 times daily of methylprednisolone intravenously. We also gave nebulization of salbutamol-ipratropium bromide combination every 2 hours and budesonide. Intravenous ceftriaxone was given for pneumonia. He got a hypoallergenic diet and soya milk.

DISCUSSION

Asthma is a diverse illness that is typically distinguished by chronic airway inflammation. The history of respiratory symptoms such as wheezing, shortness of breath, chest tightness, and cough, which fluctuate in intensity over time, as well as variable expiratory airflow limitation, describe it.⁷ Three primary mechanisms are involved in the pathophysiology of an acute asthma exacerbation: bronchospasm,

inflammation and edema of the bronchial mucosa, and increased mucus production (Figure 2).

Infectious, noxious, and environmental insults can harm the airway epithelium by bringing in proinflammatory cells and cytokines. The pathophysiology of asthma is influenced by proinflammatory cytokines, chemokines, Th-2 lymphocytes, eosinophils, and mast cells, among other factors. Asthma is also characterized by structural remodeling of the airway epithelium, which includes angiogenesis, mucous gland hyperplasia, thickening of the basement membrane, sub-basement membrane fibrosis, and thickening of the epithelial basement membrane.^{8,9}

Based on frequent asthma symptoms and the degree of asthma, we can classify asthma into intermittent, mild persistent, moderate persistent, and severe persistent (Table 1). This classification is useful for determining medication management in patients.¹⁰ The patient had been diagnosed with asthma since 2 years old and had asthma attacks 3 times last year. The last relapse was 3 months ago. According to this, the patients can be classified as having intermittent asthma. The patient did not receive medication every day, only treated with salbutamol nebulization at home whenever he got shortness of breath.

The term “acute asthma exacerbations” (AAE) or “flare-ups” refers to acute or subacute episodes of progressively worsening asthma symptoms linked to airflow obstruction.⁸ Lower respiratory tract infections and severe asthma are strongly correlated. The frequency of exacerbations correlates with the severity of asthma, and they frequently occur when pathogenic bacteria and viruses are found in the airways.¹¹ A change in innate immunity may be related to the history of pneumonia. It is still unknown whether asthma, particularly severe asthma, predisposes to or follows the development of pneumonia. Given the high morbidity and mortality linked to these illnesses, bacterial and viral respiratory infections have grown in importance in AAE in children. During severe acute exacerbations, infectious agents must be treated quickly and empirically, but the initial treatment regimens can vary widely and include bacterial, atypical and viral,

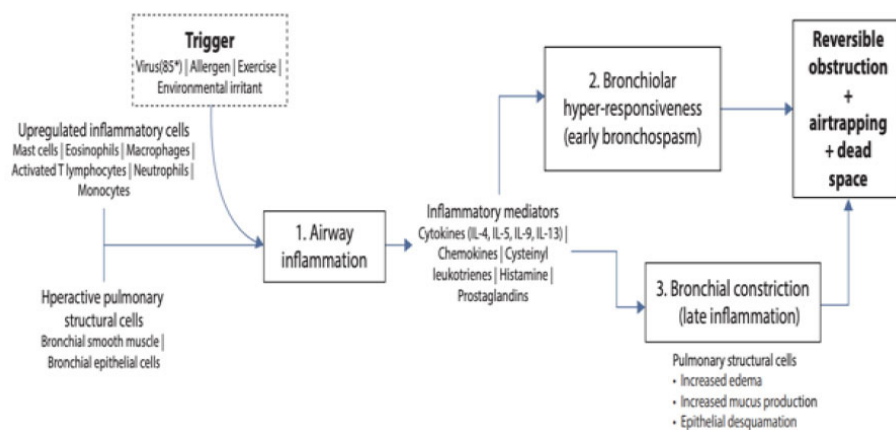


Figure 2. Pathophysiology of an acute asthma exacerbation.⁸

	Mild	Moderate	Severe	Critical
Symptoms				
Breathlessness/speech	Whilst walking	At rest	At rest (sits upright)	
Talks in	Sentences	Phrases	Words	
Mental status	Normal	May be agitated	Usually agitated	Drowsy or confused
Signs				
Work of breathing	Minimal intercostal retraction	Intercostal and substernal retraction	Significant distress; all accessory muscles involved; possible nasal flaring, paradoxical breathing	Marked respiratory distress OR exhaustion/ decreasing effort
Wheeze	Moderate wheeze	Loud expiratory and inspiratory wheeze	Audible wheezing	Silent chest
Oxygen saturations	>94%	91-94%	<90%	<90%
Peak expiratory flow versus personal best	>80%	60-80%	Best <60%	Unable to perform

Figure 3. Pathophysiology of an acute asthma exacerbation.⁸

depending on regional epidemiology.¹² Compared with healthy individuals, the risk of hospitalization by pneumonia is two to four times higher in asthmatics.¹¹ From medical history, this patient had complained of fever and cough one day before the hospital admission, and from physical examination, we found tachypnea and crackles in lung auscultation. Bronchopneumonia was noted from chest x-ray and laboratory examination; we could find leukocytosis with neutrophilia, which has a high tendency to bacterial pneumonia. So, he was treated with antibiotics empirically. Because early empiric therapy in infected pneumonia has been shown to reduce mortality, especially when initiated within the first 12 hours.¹²

AAEs are categorized by clinicians as mild, moderate, severe, or critical based on clinical assessment (also referred to as near-fatal or life-threatening AAE in some guidelines) (Figure 3).

Even though most kids have mild-to-moderate asthma, they still risk having a severe acute exacerbation that can require PICU care. The terms “fatal asthma,” “near-fatal asthma,” and “catastrophic asthma” refer to conditions when there is hypercapnia, hypoxemia, and an imminent risk of respiratory arrest, death, or sequelae from asthma-related hypoxia.⁹ This patient got short of breath and was not relieved after salbutamol with ipratropium bromide, budesonide nebulization, and intravenous dexamethasone. From his

previous history, the patient could be classified with severe acute exacerbation because he complained of restlessness (altered mental status), was unable to talk because of his shortness of breath, wheezing sound and a history of oxygen desaturation.

Acute exacerbations require immediate emergency management, which includes determining the severity, treating hypoxemia, relieving breathing problems by using treatments to reduce bronchospasms and airway inflammation, monitoring responses, and escalating therapy if the patient is still not responding. Oxygen, short-acting β_2 -agonists for inhalation, ipratropium, and oral or parenteral corticosteroids are all included in the initial course of treatment.¹³ Additional interventions are frequently thought about by second-line pharmacological intravenous injection in severe acute exacerbations demonstrating incomplete or poor response to first treatment.¹⁴ In a study on how acute attacks were treated in the UK and the Republic of Ireland, salbutamol was administered in 55.5% of cases, magnesium sulfate in 60.9%, and Aminophylline in 47.3% of cases.^{15,16} The British Thoracic Society (BTS) suggests giving an infusion after a loading dose of 5 mg/kg of Aminophylline. A previous Australian study found that Aminophylline, with a loading dose of 10 mg/kg, significantly improved physiological recovery and decreased intubation rates despite the

drug’s unpleasant side effects like nausea and vomiting.^{17,18} In some children’s hospitals in Australia and New Zealand, Aminophylline is advised at a loading dose of 10 mg/kg.¹⁷ In the Global Initiative for Asthma (GINA) for children under 5 years, acute severe asthma exacerbation with poor response to initial short-acting b_2 agonists (SABA), the administration of ipratropium bromide or magnesium sulfate can be considered.

Aminophylline has been removed from GINA as a drug of choice for severe asthma therapy. In 2016, The National Guidelines for asthma in children (*Pedoman Nasional Asma Anak*, PNAA), severe acute exacerbation that shows an incomplete or poor response to initial treatment, additional interventions that are commonly considered intravenous administration were Aminophylline (Figure 4).^{1,3}

Aminophylline is a methylxanthine bronchodilator composed of theophylline, and ethylenediamine.⁵ Methylxanthines have been used to cure asthma for more than 50 years.^{19,20} Aminophylline has been hailed by UK pediatricians as the first line of the respiratory tract.²⁰ It is the more common form of methylxanthine used for intravenous administration and is available in generic form, which is certainly affordable. However, its efficacy, especially in children, and the effective doses are a matter of dispute.²¹

By inhibiting specific phosphodiesterase (PDE) enzymes, Aminophylline may have effects on cyclic adenosine monophosphate (c-AMP) that result in bronchodilation (Figure 5).²²⁻²⁴ The phosphodiester bond in the second messenger molecule cAMP and cyclic guanosine monophosphate is broken down by phosphodiesterase enzymes (cGMP).^{24,25} Inhibition of PDE results in increased cAMP and cGMP levels in smooth muscle cells, which lowers calcium levels in the cells and activates protein kinase A. Myosin light chain kinase activity rises as a result, while myosin light chain phosphatase activity falls. Airway blockage is reversed by bronchial smooth muscle relaxation, increased myosin light chain kinase activity, and decreased intracellular calcium concentration.²⁵ Its. Also relaxes the smooth muscle of the bronchial airways and pulmonary blood

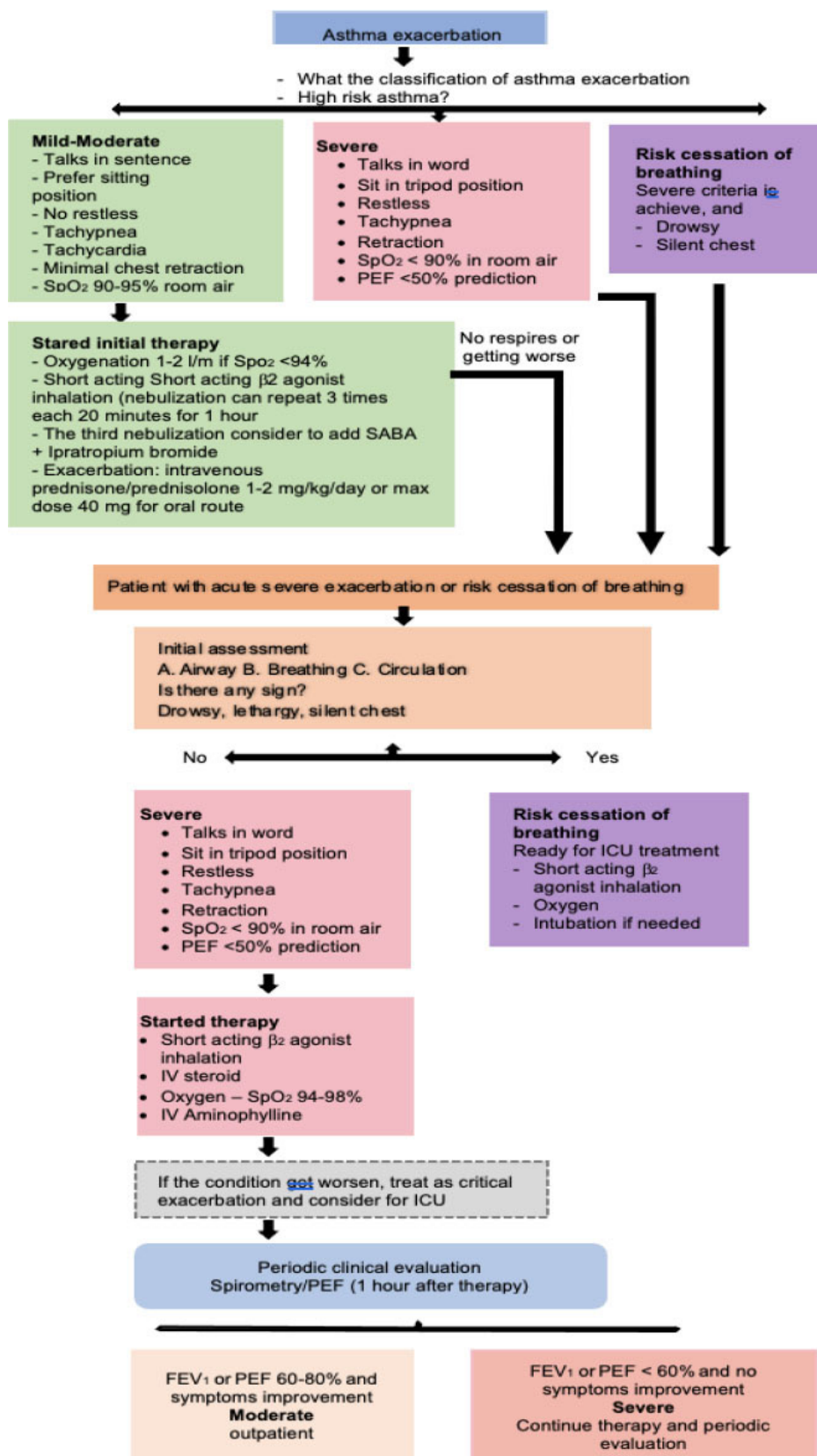


Figure 4. The flow chart of emergency management in hospital of asthma attacks in children.¹⁰

vessels and reduces airway responsiveness to histamine, methacholine, adenosine, and allergen.²⁶

Adenosine can elicit bronchoconstriction when administered orally to asthmatic patients while not affecting human airway muscle in vitro. Adenosine receptor blockage and catecholamine release with subsequent adrenergic activation are two other theories for how Aminophylline exerts its bronchodilator actions.^{22,24} Immunomodulation and anti-inflammatory effects may potentially be helpful in asthma exacerbations.^{22,23} Mast cells, basophils, neutrophils, macrophages, and platelets are among the inflammatory cells demonstrated in in vitro studies to be stabilized or inactive by theophylline. Another way that Aminophylline may lessen inflammation is through its effects on neutrophil apoptosis or histones required for the activation of inflammatory gene transcription. Low or subtherapeutic plasma theophylline concentrations may bring on these symptoms.²³

In National Guidelines asthma in children (PNAA), Aminophylline is administered intravenously in severe acute asthma at the following doses:¹⁰

- If the patient has not previously received Aminophylline, the initial (initial) dose of Aminophylline is 6-8 mg/kgs, dissolved in 20 ml of dextrose or normal saline, and administered for 30 minutes by infusion pump or micro burette.
- If the response is not optimal, it is continued with the administration aminophylline maintenance dose of 0,5-1 mg/kg/hour.
- If the patient has received Aminophylline (less than 8 hours), the dose is given in half, either the initial dose (3-4 mg/kgs) or maintenance (0.25-0.5 mg/kgs/hour).
- Whenever possible, aminophylline levels should be measured and maintained at 10-20 mcg/ml.
- Monitor for symptoms of Aminophylline's adverse drug reaction, the most common side effects are nausea, vomiting, tachycardia and agitation. Severe toxicity may cause arrhythmias, hypotension and convulsions.

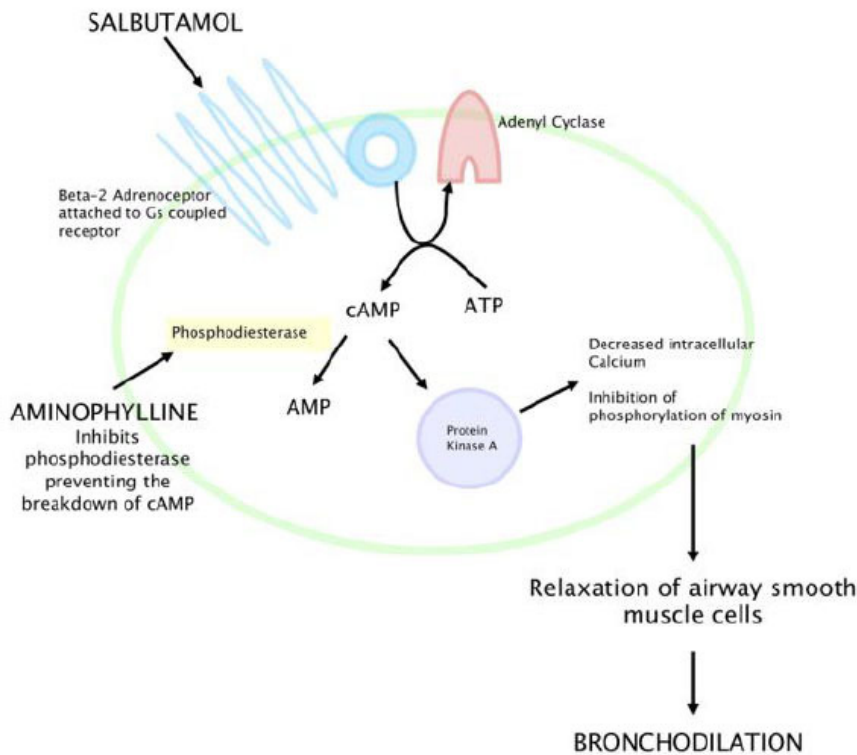


Figure 5. Illustration of the mechanisms by which salbutamol and Aminophylline may cause bronchodilation through increasing intracellular cyclic AMP levels.²²

Table 1. The degree of frequent asthma symptoms.¹⁰

Asthma Severity	Symptoms Frequency
Intermittent	Episodes of asthma symptoms less than 6 times a year or the distance between symptoms are more than 6 weeks
Mild Persistent	Asthma symptom episodes more than once per month, less than once per week
Moderate Persistent	Episodes of asthma symptoms more than once per week, but not every day
Severe Persistent	Episodes of asthma symptoms occur almost every day

- When clinical improvement has occurred, nebulization is continued every 6 hours until it reaches 24 hours, and steroids should be replaced by oral administration, and if necessary, Aminophylline is replaced by oral theophylline.
- If within 24 hours the patient remains stable, the patient can be discharged with a 2 agonist drug (inhaled or oral) every 4-6 hours for 3-5 days, used as needed until there are no symptoms. In addition, oral steroids were continued until the control patient was admitted to the outpatient clinic within 3-5 days for re-evaluation of management.

Aminophylline has a widely accepted therapeutic range of 10-20 mg/l, which

drives dosing decisions in children.^{17,24-27} The recommended dose is an initial slow bolus dose of 6-8 mg/kgs given over 20 minutes, followed by a maintenance drip of 1 mg/kgs/hour used to achieve levels within this range.^{10,17} Loading 1 mg/kg will increase serum aminophylline levels by 2 mg/ml. Aminophylline is believed to have a narrow therapeutic range and high inter-individual variation in clearance.²⁴⁻²⁶ Differences in theophylline plasma levels due to interindividual variability in aminophylline distribution and elimination kinetics will have unpredictable clinical effects.²⁴ The GINA report's recommendations for treating asthma in western nations do not include Aminophylline due to its limited

therapeutic range.

The common side effects are nausea, vomiting, tachycardia and agitation, as demonstrated in several trials and a Cochrane review.^{17,22} According to one piece of research, high-loading doses of Aminophylline (7-10 mg/kg over 20 minutes) can cause vomiting or nausea and can be treated with antiemetics. However, more research should be done on combining Aminophylline with antiemetics. Negative side effects are not linked to lower loading doses (4-6 mg/kg load over 30 min). 5 Convulsions, hypotension, and arrhythmias may result in severe poisoning. Serum ammonium levels that are high are typically linked to death. Therefore, administering intravenous Aminophylline should be very careful and monitored closely.¹⁰ This is a significant justification for restricting its usage to pediatric patients, as there is inadequate proof that dosage modifications depending on a patient's age, weight, or past serum theophylline levels can improve the course of their asthma. However, in Indonesia, Aminophylline is still used to treat asthma exacerbations despite being abandoned in other countries due to problems with adverse medication reactions. Aminophylline is one of the asthma medications that is frequently used in Indonesian hospitals to treat asthma exacerbations. Even in 2019, the DOEN (Daftar Obat Essential Nasional) list includes Aminophylline.⁴

There are pros and cons administration of intravenous Aminophylline from some literature. Patients who are about to experience respiratory failure and those who have previously responded well to Aminophylline may want to consider using it in addition to standard medical treatment.¹ Child with severe acute exacerbations who have not reacted to the maximum amount of inhaled bronchodilators and systemic steroids may benefit from using Aminophylline.^{3,15,28} The addition of Aminophylline improved lung function (FEV1) within six hours of treatment, with an improvement in symptoms up to eight hours after therapy, and the positive effect persisted for 24 hours in children with sub-optimal response to one hour of treatment with maximized beta-agonist systemic

glucocorticoids, with or without inhaled anticholinergics.^{3,22,28} Aminophylline has been linked to improvements in pulmonary function, a considerable reduction in the length of hospital stays, and a decreased need for ventilation in serious instances.^{15,29} According to certain investigations, intravenous Aminophylline and β_2 agonist, were equally effective at restoring CAS scores and oxygen saturation.^{3,22} Other studies found that treating their patients with methylxanthine was as effective as terbutaline, and the total treatment costs were less than a tenth of those with methylxanthine. Given the very low cost and similar safety profile of theophylline, it must surely be considered a cost-effective treatment for acute asthma. Cochrane reviews of intravenous Aminophylline in adults and children fail to demonstrate any clinical benefit over intravenous β_2 agonists.^{1,15,21} The rationale for omitting Aminophylline is that a Cochrane review found it has limited efficacy and severe, potentially fatal, adverse effects. Tachycardia is a commonly reported side effect.^{24,26} Vomiting is also a common adverse effect that can occur at all concentrations but more so at levels of 20 mg/l. Seizures have been reported in children, but the mechanism and frequency are unknown.¹⁶ The systematic review also failed to show differences in the frequency of adverse effects in children within the therapeutic range compared.²⁶

This patient had been administered intravenous Aminophylline after poor response to SABA with ipratropium bromide, budesonide inhalation and intravenous steroid. The patient showed symptoms of improvement after intravenous Aminophylline. Aminophylline loading dose started from 6-8 mg/kg/day, followed by continuous infusion of Aminophylline with a dose of 0,5 mg/kg/hour. After clinical improvement, the aminophylline administration was stopped on the second-day treatment. While the therapy, there was no adverse drug reaction like nausea, vomiting, or tachycardia in the patient's monitoring. The patient was clinically monitored by vital signs and patient or parent's complaints. Aminophylline blood level was not monitored because of our laboratory hospital's limited facilities. For

outcomes, the patient was discharged in healthy condition 8 days after hospital treatment.

CONCLUSION

When first-line inhaled/nebulized medication fails to control a child's asthma exacerbation, Aminophylline may be utilized. It must be considered a cost-effective treatment for acute asthma exacerbations, especially for developing countries with limited health budgets, even though it is thought to have a narrow therapeutic range and a large inter-individual variance in clearance.

PATIENT'S INFORMED CONSENT

Written informed consent was obtained from the patient's parents.

CONFLICT OF INTERESTS

The author declares no conflict of interest regarding this study.

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AUTHOR CONTRIBUTIONS

All authors contributed equally to the manuscript's preparation and approved the final version for publication.

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