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Viral Profile and Clinical Characteristic in Acute Asthma Exacerbation Patients

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Abstract

Background: Asthma is a heterogeneous disease characterized by chronic airway inflammation. The virus infection in respiratory tract will activate greater pro-inflammatory cytokines in asthma patients. The enhancement of pro-inflammatory cytokines induces various clinical symptoms. This study aims to investigate the respiratory virus and clinical characteristics among patients with acute asthma exacerbation.

Methods: In this study, subjects were divided into 3 groups based on acute asthma exacerbation triggers. The first group triggered by virus infection; the second group triggered by non-virus infection with ILI; and the third group without any infection. Nasopharynx or throat swabs were collected to detect any respiratory virus. Virus was detected by Multiplex PCR (xTAG Respiratory Viral Panel Fast V2/ LUMINEX)

Results: According to PCR examination, the prevalence of virus infection was 46.2%. Only two types of viruses identified, which were Influenza A virus and Rhinovirus. All patients in the second groups showed a symptom of cough with purulent sputum, while no patients from the other two groups showed similar symptoms**.** PEFR and % PEFR prediction of patients with Influenza A virus infection were higher than in Rhinovirus infected-patients (210 L/min and 48.6% vs 195 L/min and 45%).

Conclusion: Acute asthma exacerbation is one of the most reasons patients came to emergency ward. The majority of acute asthma exacerbation was caused by infection, and most of it was viral infection. Clinical sign differs according to the trigger, therefore the use of antibiotics should be avoided, unless there are signs and symptoms of bacterial infections.

Key Words: *Acute asthma exacerbations; Clinical Characteristics; Viral profile*

Introduction

Asthma is a heterogeneous disease characterized by chronic airway inflammation. The chronic inflammation in respiratory tract is marked by several respiratory symptoms such as hard to breath, chest tightness, and cough with various intensity from time to time.[1] The case of acute asthma exacerbation caused by virus infection occurs 80% in children and more than 50% in adults.[2] By recognizing the causes and mechanisms of asthma exacerbations and its clinical symptoms, it will improve the accuracy of diagnosis, prognosis, and further treatment.

Asthma is a disease which considered as the ten most frequent cause of death in Indonesia. Based on the data

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of Study of Family Health Survey in 1986, asthma was in the fifth rank of the 10 most frequent causes of illness in Indonesia. Another previous study in 1992 reported that asthma was in the fourth rank (5.6%) of the 10 most frequent causes of death in Indonesia. Indonesian pneumobile project and respiratory questioner of Institute of Respiratory Medicine New South Wales in 37 public health centers in East Java, Indonesia, reported asthma prevalence in the group of age 13–70 years old was 7.7%.[3] In 2001, the data of Asthma Centre in Jakarta reported 2,210 asthmatics visited Emergency Unit. According to data from Dr. Soetomo General Hospital, the number of patients with acute asthma exacerbations steadily decreased in 1986, 1990, and 1994 (12.7%, 9.3%, and 8.8%, respectively).[3]

The virus infection in respiratory tract will activate greater production of pro-inflammatory cytokines in asthma patients compared to patients without asthma history. High production of pro-inflammatory cytokines leads to various clinical symptoms in asthma patients.[2] The clinical symptoms that occur consist of respiratory tract obstruction caused by inflammation and Influenza Like Illness (ILI); and virus infection (Rhinovirus, Coronavirus, Influenza virus).[4]

The administration of antibiotics to asthma exacerbation patients due to viral infection is actually unnecessary, however some clinicians still confer this therapy to patients. The absence of epidemiology data about the cause of airway infection in asthma exacerbation patients in Indonesia can be attributed to this. The knowledge of viral profile and clinical characteristics in acute asthma exacerbation patients who visit the emergency ward is very essential for clinicians, ultimately who work in the emergency room. Therefore, this study aimed to investigate the viral profile and clinical characteristics in acute asthma exacerbation patients.

Methods

This study was a descriptive study conducted in the Emergency Unit of Dr. Soetomo General Hospital, Surabaya, Indonesia. All patients with acute asthma exacerbations, and aged 14 – 40 years old were included in the study. Subjects were divided into 3 groups based on acute asthma exacerbation triggers. The first group was patients with acute asthma exacerbations triggered by virus infection; the second group was patients with acute asthma exacerbations triggered by non-virus infection with ILI; and the third group was patients with acute asthma exacerbations without any infection. Throat or nasopharynx swabs were collected and sent to Institute of Tropical Disease, Airlangga University, Surabaya. The virus was detected by Multiplex PCR (xTAG Respiratory Viral Panel Fast V2/ LUMINEX which can detect RSV, InfV, HPIV, HBoV, CoV, HMpV, AdV, and HRV-EnV viruses).

This study followed the principles of the Declaration of Helsinki. This study also has received ethical clearance from Dr. Soetomo General Hospital before the study begins (Ethical Clearance Number 199/panke. KKE/III/2015).

Results

Characteristics of Subjects

Subjects included in this study were 26 patients, with 19 patients were female, and 7 patients were male. The mean of age of the subjects was 30 years old. Subjects mostly worked as private employees (38.3%). Furthermore, the subjects mostly senior high school graduates (69.2%). Based on Body Mass Index (BMI), 42.3% patients had normal BMI and 7.7% of them were obese. The mean period of asthma history was 16.4 years (Table 1).

Table 1. The Characteristics of Study Subjects

Characteristics of subjects	n (%)
Gender Male Female The average age (year)	 7 (26.9) 19 (73.1) 30.12
Job Unemployed Private Employee Entrepreneur Students	 8 (30.8) 10 (38.5) 3 (11.5) 5 (19.2)
Education Background Elementary School Junior High School Senior High School Undergraduate	 3 (11.5) 2 (7.7) 18 (69.2) 3 (11.5)
Income each month Less than IDR 1 million IDR 1-3 millions More than IDR 3 million	 9 (34.6) 16 (61.5) 1 (3.8)
BMI BMI < 18,5 18.5 ≤ BMI < 23 23 ≤ BMI < 25 25 ≤ BMI < 30 BMI ≥ 30 Average BMI	 2 (7.7) 11 (42.3) 4 (15.4) 7 (26.9) 2 (7.7) 23.37
The average of history period of asthma (year)	16.4

Characteristic of Asthma Exacerbation's Trigger

According to the PCR examination of throat or nasopharynx swab, the prevalence of virus infection was 46.2% (Figure 1). Only two types of viruses identified: Influenza A virus and Rhinovirus (Figure 2).

Figure 1. The causes of acute asthma exacerbations.

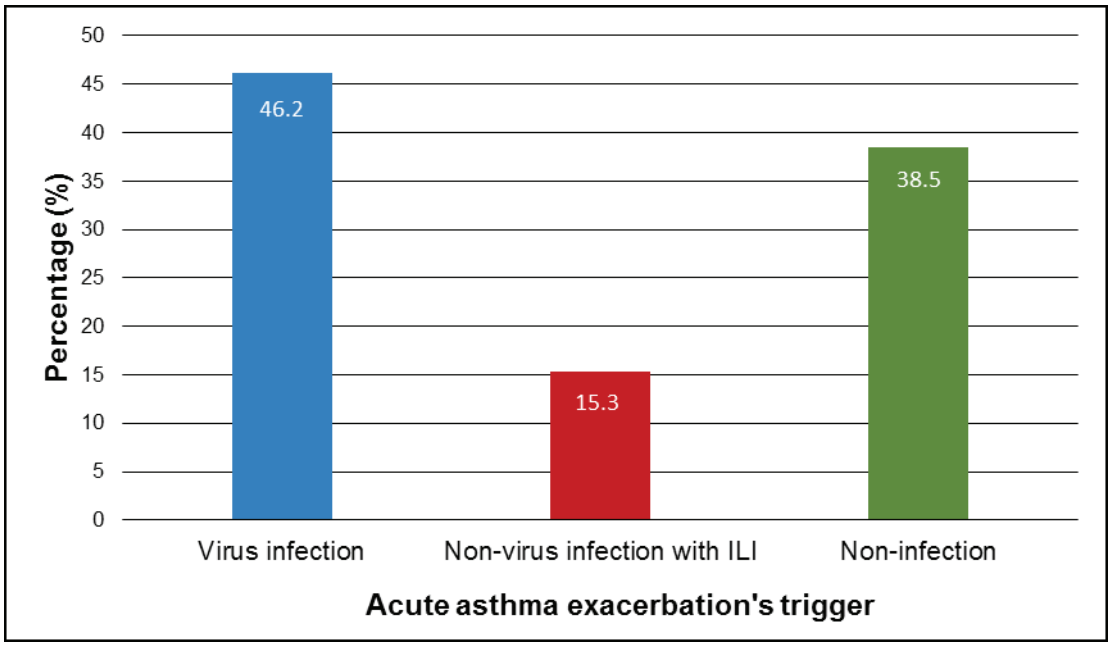
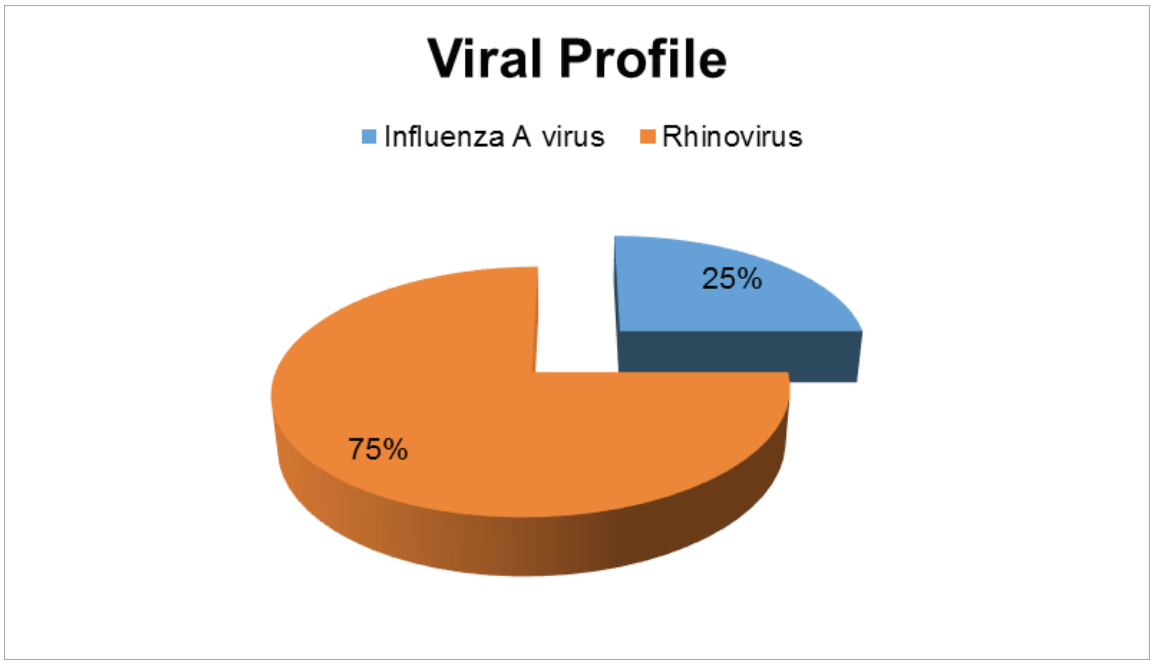


Figure 2. Viral profile of the causes of acute asthma exacerbations.



Clinical Sign and Symptoms

According to body temperature, the virus infection group showed the highest mean of body temperature (38.7ºC). In addition, Influenza A virus infection was found to promote higher body temperature than Rhinovirus infection (39.5ºC vs 38.5ºC). Moreover, the mean of peak expiratory flow rate (PEFR) and %PEFR prediction of patients with Influenza A virus infection was higher than in Rhinovirus-infected patients (210 L/min and 48.6% vs 19 5L/min and 45%).

Among all the three groups, group with virus infection showed the highest body temperature and %PEFR prediction. All patients in non-virus infection with ILI group showed a symptom of cough with purulent sputum, while other patients from the other two groups did not show similar symptoms (Table 2).

Table 2. The clinical characteristics of subjects (the average value)

Clinical symptoms	Temperature (°C)	PEFR (L/min)	% PEFR prediction	Purulent sputum (%)
Virus infection (mean)	38.7	195	45	0
Influenza A infection	39.5	210	48.6	0
Rhinovirus infection	38.5	190	44.1	0
Non-virus infection with ILI	38.6	180	35.2	100
Non infection	36.7	198	38	0

Subject Characteristics Based on Triggers of Asthma Exacerbation

The average age of patients with asthma exacerbations triggered by virus infection was 27.8 years old; by non-virus infection with ILI was 35.5 years old; and by non-infection was 30.7 years old. The average BMI in patients with asthma exacerbations triggered by virus infection was 22.6 (normal); by non-virus infection with ILI was 24.5 (obese grade I); and by non-infection was 23.8 (overweight). In addition, the average period of asthma history in acute asthma patients that triggered by virus infection was 14 years; by non-virus infection with ILI was 21.3 years; and by non-infection was 17.5 years (Table 3).

Table 3. The comparison of the average value in subject characteristics based on asthma exacerbation triggers

Clinical symptoms	Age (years)	BMI	The history period of asthma (year)
Virus infection	27.8	22.6 (normal)	14
Non-virus infection with ILI	35.5	24.5 (obese I)	21.3
Non-infection	30.7	23.8 (overweight)	17.5

Discussion

Acute asthma exacerbation is one of the most leading causes patients come to emergency room. Most of the exacerbation was triggered by infection, mainly virus infection. This study revealed that respiratory tract infections in patients with acute asthma exacerbations could be triggered by virus. The results showed that virus infection appeared in 46.2% patients; non-virus infection with ILI appeared in 15.3% patients (61.5% with ILI symptoms); and 38.5% patients were triggered non-infection. In line with the study by Nicholson et al.[5] that reported acute asthma caused by infection was 80%, and the 44% of them were caused by virus infection. Tan et al.[6] also obtained similar results, 47.8% of acute asthma exacerbations triggered by virus infection in respiratory tract.

Rhinovirus was considered as the most frequent causes of respiratory tract infection triggered by virus infection in the patients. Among 12 samples with positive results of virus detection, 75% of them were Rhinovirus and the other 25% were Influenza A virus. A study by Nicholson et al.[5] also suggested that 61.3%

of acute asthma attacks were triggered by Rhinovirus infection. In addition, Tan et al.[6] also stated that the most frequent trigger was Rhinovirus (47%). Rhinovirus infects respiratory tract by binding themselves to airway surface cell receptors, Intercellular Adhesion Molecule 1 (ICAM-1). In an in-vitro study,[7] Rhinovirus attached to ICAM-1 receptors in airway smooth muscle cells surface, stimulates contraction of airway smooth muscle cells to be enhanced. The improvement of airway smooth muscle cells contraction may occur, although the Cytopathic effect has not appeared. Rhinovirus also induces greater IL-8 and regulated on activation, normal T cell expressed and secreted (RANTES) release than other virus infection in asthma patients.[8] IL-8 is a chemokine that attracts neutrophils and promotes acute inflammation. IL-8 and neutrophils are considered to be difficult-to-treat asthma phenotypes. RANTES is a chemokine that has an important role in asthma exacerbation by inducing the recruitment of Th2-type T-cells and eosinophils.[8] Those study results may explain the reason Rhinovirus is mostly found as the cause in acute asthma exacerbation patients.

Over three decades ago, the knowledge of that upper respiratory tract infection related to acute asthma exacerbation has been developed. However, up until today, the exact mechanisms of how it happens is still be controverted. IL-6, sICAM-1 (soluble ICAM-1), ECP, histamine in serum, and leukotriene 4 in urine, are the factors that trigger respiratory tract inflammation and constriction, and this could lead to acute asthma exacerbation. In patients with upper respiratory tract infection, their level is significantly and statistically higher than in acute asthma exacerbation patients triggered by non-infection.[9]

Influenza Like Illness (ILI) symptoms can be found in patients with acute asthma exacerbations triggered by infections. In this study, in all acute asthma exacerbation patients triggered by infections had ILI symptoms such as fever with cough or sore throat. Previous study described that ILI symptoms have the possibility to enhance virus infection three times to 14 times higher.[10] Purulent sputum is a clinical symptom recognized in patients with acute asthma exacerbation triggered by non-virus infection. According to GINA report in 2015[1], one of the signs of bacterial infection occurrence in lungs which triggers acute asthma exacerbations is purulent sputum.

Fever is a clinical symptom in patients with acute asthma exacerbations triggered by infection. This study presented the average body temperature in asthma patients triggered by infection was 38.7°C, while in non-infected patients was 36.7°C. Patients with acute asthma exacerbations triggered by infection both virus and non-virus had similar average body temperature. In other trial by Yang et al.[11] reported similar average body temperature in virus infection and non-virus infection (38.6°C). The average body temperature in asthma patients triggered by Influenza A infection was higher than in Rhinovirus-infected patients. The average body temperature in asthma patients triggered by Influenza A infection was 39.5°C, while in Rhinovirus-infected patients was 38.5°C. Study results by Al-Mahrezi et al.[12] supported this theory by reporting that the average body temperature in asthma patients triggered by Influenza A infection was 38.3°C, and 37.3°C in patients triggered by other virus infection. In patients with Influenza A infection, TNF-α, INF-α, IL-1, and IL-6 in blood was increased higher than other respiratory virus infection.[13,14] These cytokines were able to reach hypothalamus that induces prostaglandin release, particularly prostaglandin E2 (PGE2).[10,15]

The reduction of %PEFR prediction can be found in patients with acute asthma exacerbations. In this study, the %PEFR prediction in acute asthma patients triggered by virus infections was obtained to be 45%; by non-virus infection with ILI was 35.2%; and by non-infection was 38%. In the study by Yasuda et al.[9] suggested that %PEFR prediction was associated with IL-6 rate and sICAM-1 in blood of patients with acute asthma exacerbations. They found the rate of IL-6 and sICAM-1 in patients' blood with acute asthma exacerbations triggered by infection and non-infection was not significantly different (IL-6: 10.8±1.7 vs 8.9±3.1; sICAM-1: 398±22 vs 372±34). Thus, they concluded that %PEFR prediction was not associated with acute asthma exacerbation triggers (infection and non-infection). The average of %PEFR prediction in patients with asthma triggered by Rhinovirus infections was lower than asthma patients triggered by Influenza A virus. In this study, the average of %PEFR prediction in patients with acute asthma exacerbations triggered by Rhinovirus infection was 44.1%, while by Influenza A infection was 48.6%. The influenza infection airway obstruction was dominated by airway inflammation. On the other hand, in Rhinovirus

infection, airway obstruction was stimulated not only by inflammation but also by bronchial smooth muscle contraction.[7]

The age, history period, and BMI were factors that affected the reduction of %PEFR prediction. The mean of BMI patients in non-infection group was overweight, while in non-virus infection with ILI group was obese. This condition aggravated asthma exacerbations and led to the reduction of %PEFR. In obese patients, Leptin level was higher compared to non-obese patients. Leptin has a role in inflammatory response; when acute asthma exacerbation occurs, leptin level in blood will increase significantly, hence in obese patients with acute asthma exacerbation, severe deterioration of lung function will occur.[16]

Conclusion

This study revealed more information about viral profile and clinical characteristics of acute asthma exacerbation that mostly caused by virus infection, particularly Rhinovirus. There were distinct clinical characteristics: the average age, BMI, body temperature, and %PEFR prediction among patients with acute asthma exacerbation caused by non-infection, virus infection, and non-virus infection. This study results may be useful as data for clinician in emergency room to confer proper therapy according to the causes factor of asthma exacerbation.

Conflict of Interest : The authors confirm that this article content has no conflict of interest.

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Lampiran 4

Kelaikan Etik

KOMITE ETIK PENELITIAN KESEHATAN
RSUD Dr. SOETOMO SURABAYA

KETERANGAN KELAIKAN ETIK
(" ETHICAL CLEARANCE ")

199 / Panke.KKE / III/ 2015

KOMITE ETIK RSUD Dr. SOETOMO SURABAYA TELAH MEMPELAJARI SECARA SEKSAMA RANCANGAN PENELITIAN YANG DIUSULKAN, MAKA DENGAN INI MENYATAKAN BAHWA PENELITIAN DENGAN JUDUL :

"Profil Virus dan Karakteristik Klinis Pada Pasien dengan Serangan Asma Akut di Instalasi Rawat Darurat"

PENELITI UTAMA : Erwin Winaya, dr

PENELITI LAIN : Resti Yudhawati, dr., Sp.P

UNIT / LEMBAGA / TEMPAT PENELITIAN : RSUD Dr. Soetomo Surabaya

DINYATAKAN LAIK ETIK

SURABAYA, 19 MAR 2015

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