Asthma death

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Abstract

English:

The prevalence of asthma is still high in many countries. However, the asthma mortality rate has been significantly decreased after the epidemic of asthma death in the 1970s. The epidemic was occurred in New Zealand and was associated with the use of high-dose inhaled fenoterol at that time. The increased use of inhaled corticosteroids (ICS) in asthma management is proposed as the key factor in the declining trend of asthma mortality rate. The risk factors of asthma-related deaths included history of near-fatal asthma requiring intubation and mechanical ventilation, hospitalisation or emergency care visit for asthma in the past year, currently using or having recently stopped using oral corticosteroids, not currently using ICS, overuse of short-acting β_2 -agonists, history of psychiatric disease or psychosocial problems, poor adherence with asthma medications and/or poor adherence with (or lack of) a written asthma action plan, food allergy in a patient with asthma, and air pollution.

Keywords

asthma death • asthma mortality • epidemic of asthma death • risk factor of asthma-related death

Decesele datorate astmului

Rezumat

Romanian:

Prevalenta astmului este inca mare in multe tari. Totusi, rata mortalitatii prin astm a scazut semnificativ dupa epidemia de decese din anii 1970. Epidemia a survenit in Noua Zeelanda si a fost asociata cu utilizarea inhalatorie de doze inalte de fenoterol de la acea vreme. Cresterea utilizarii corticosteroizilor inhalatori in managementul astmului este considerata factor-cheie al trendului descendent al ratei mortalitatii in astm. Factorii de risc ai mortalitatii legate de astm include istoric de astm aproape fatal necesitand intubatie si ventilatie mecanica, spitalizari sau vizite in urgenta pentru astm in anul anterior, utilizarea curenta sau oprirea recenta a utilizarii de corticosteroizi orali, lipsa utilizarii corticosteroizilor inhalatori in tratamentul curent, suprautilizarea β_2 -agonistilor cu durata scurta de actiune, istoricul de afectiune psihiatrica sau probleme psihosociale, aderenta slaba la recomandarile terapeutice sau/si aderenta slaba la (sau lipsa de) plan de actiune scris pentru managementul astmului, alergii alimentare la un pacient cu astm, poluarea atmosferica.

Cuvinte-cheie

decese datorate astmului • mortalitate in astm • epidemia deceselor prin astm • factori de risc de mortalitate in astm

Introduction

Asthma is still a health problem globally with an increasing prevalence in some countries (1). In Indonesia, the prevalence of asthma was 2.4% with the recurrence proportion of 57.5% in 2018 (2). After the epidemic of asthma in the late 1970s, the mortality rate of asthma drastically

decreased in the last few decades (3). The use of inhaled steroid was suggested as the key factor of this phenomenon (4,5). However, even when the effective drugs were widely available and affordable, the level of asthma control was still low in many countries (6–8). The National Review of Asthma

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Deaths (NRAD) in the United Kingdom (UK) released a report in 2014 stating that the risk factor in two-thirds of asthma death cases was preventable (6).

This literature review discusses the epidemic of asthma death, the trend of asthma mortality after the epidemic and the risk factors of asthma-related deaths.

Epidemic of asthma death

In the 1960s, the first epidemic of asthma death was reported in England and Wales. The epidemic coincided with the increase in sales rate of pressurised β_2 -agonist aerosols containing isoprenaline (isoproterenol) (9). A study done in England and Wales at that time suggested that the epidemic of asthma death was indeed caused by pressurised β_2 -agonist aerosols. However, because no epidemic occurred in other countries where the pressurised β_2 -agonist aerosol was available, a hypothesis arose suggesting that epidemic in England and Wales was caused by the high-dose formulation of isoprenaline, called isoprenaline forte. This formulation dose contained 400 mg isoprenaline per inhalation, which was five times higher than the standard formulation of isoprenaline (10). This hypothesis was strengthened with the data that showed that the epidemic of asthma death occurred only in countries where isoprenaline forte sales rate was high and did not occur in those with the low sales rate of isoprenaline forte. The mortality of asthma decreased after the warning issued, and the sales rate of isoprenaline forte dropped (11).

In the mid 1970s, the epidemic of asthma death reoccurred. This time, it happened in New Zealand (12,13). Even though the data showed that asthma mortality also increased in other countries where fenoterol was available at that time, the increase in the mortality rate was the highest in New Zealand. In the late 1970s, the asthma mortality increased almost three times in New Zealand (13). The epidemic occurred in the same period of time with the introduction of new inhaled β_2 -agonist fenoterol. Fenoterol was marketed with the dose twice higher (200 mg) than salbutamol, the more widely used inhaled β_2 -agonist at that time (12,14). A case-control study published in 1989 showed that fenoterol was associated with the increased risk of asthma death in New Zealand (14). After it was published, New Zealand authorities revoked fenoterol from the list of drugs covered by the health insurance, which eventually eliminated fenoterol completely from the circulation. The release of New Zealand authorities' policy was associated with a significant decline in asthma mortality in New Zealand (11,13,15). Later in 1992, a study revealed that fenoterol was associated with near-fatal asthma (16). Moreover, Garrett et al. showed in 1995

that the increase in asthma mortality in New Zealand in the 1970s was concomitant with the launch of fenoterol in the market, and furthermore, the asthma mortality indeed decreased in 1989 after fenoterol was regulated by New Zealand authorities (17). Around the time when the epidemic happened, the hypothesis suggesting that the epidemic in New Zealand was correlated with the lack of use of inhaled corticosteroids (ICS) emerged. However, it was not supported by the trend of ICS sales rate data at the time of epidemic and asthma mortality rate after the epidemic (14). Moreover, New Zealand was one of the countries with the highest number of use of ICS at that time (15).

In 1997, a study was conducted to observe the trend in sales of inhaled fenoterol and inhaled β_2 -agonists and asthma mortality between 1970 and 1992 in nine countries where inhaled fenoterol was available, including New Zealand. The results showed that in New Zealand when the sales of fenoterol and inhaled β_2 -agonists increased twofold, asthma mortality decreased by 40%. This study concluded that the overall sales of inhaled β_2 -agonists, including fenoterol, are not associated with asthma mortality (13). This study supported the previous one that stated that inhaled β_2 -agonists, not specifically fenoterol, played a role in heightening the mortality of asthma (16). However, Beasley et al. showed that the substitution to use back to regular inhaled β_2 -agonists only happened in 1979 in New Zealand, while the epidemic subsided in 1976 (18). Furthermore, overall inhaled β_2 -agonists sales rate increased in 1989–1990, whereas the fenoterol sales and asthma mortality drastically declined in that period of time. All these evidences revealed that even though overall inhaled β_2 -agonists associated with asthma mortality, the epidemic of asthma death in New Zealand in the 1970s was indeed caused by the use of high-dose fenoterol.

Trend of asthma mortality after the epidemic of asthma death

The awareness of the potential risk of overuse of bronchodilators and the emerging evidence of effectiveness of ICS in decreasing morbidity and risk of asthma mortality caused a transformation in asthma management in the late 1980s. ICS are currently used in asthma treatment worldwide. The use of ICS in the asthma management proved to be associated with a progressive decline in asthma mortality globally. Asthma mortality had been reduced to 63% in 20 years between 1985 and 2005. A study conducted in 20 countries showed that asthma mortality in the population group of age 5–34 years decreased from 0.62 deaths per 100,000 people per year in 1985–1986 to 0.23 deaths per 100,000 people per year in 2004–2005 (3). The more recent study done in 46 countries also displayed a decline in asthma mortality from 0.44 to

0.19 deaths per 100,000 people per year in 1993 and 2006, respectively. The number plateaued until the end of the study in 2012 (19).

In 2014, NRAD in the UK reported that more than half of asthma death is caused by preventable risk factors (6). The characteristics of the asthma death were almost similar with those in 1970s and 1980s, including the lack of awareness in asthma severity, delay in seeking for medical supports, inadequate use of long-term ICS and oral corticosteroids (OCS) during exacerbation, overuse of β_2 -agonists, not doing the routine control, smoking and mental health problems.

In the United States (US), the incidence of asthma death significantly declined from 2.1 to 1.2 deaths per 100,000 people per year in 1999 and 2015, respectively. The number of asthma deaths decreased in all age groups; however, the steepest decrease was in the 65-year-old group (19). In Japan, more than 7,000 patients with asthma died per year in the 1970s (20). However, this number continuously reduced to 1,794 in 2017 (21). In Europe, the number of asthma-related deaths reduced to 80% between 1985 with 6,287 deaths and 2012 with 1,164 deaths (22).

Data from Persahabatan Hospital in Indonesia showed that the asthma mortality in inpatient ward in 1998–2001 were 2.23% (1/43), 2.17% (3/138), 1.7% (1/60) and 2.9% (3/104), respectively (23). The number was relatively stable and tended to decrease compared with the data from 2016 to 2018, which were 2.4% (1/41) in 2016, 2.2% (2/92) in 2017 and 0% (0/48) in 2018. In the emergency department, the number of asthma deaths was 0.06% (1/1,653), 0.07% (1/1,537), 0.05% (1/2,210) and 0.05% (1/2,210) from 1998 to 2001, respectively (23). The number of patients with asthma exacerbation in the emergency department in Persahabatan Hospital was 451 patients in 2016, 446 patients in 2017 and 524 patients in 2018. No asthma deaths were reported among these numbers in 2016–2018. Overall, the trend of asthma mortality rate has decreased and the rate is low in many countries including Indonesia.

The thunderstorm has been associated with asthma epidemic, especially in spring season when the atmosphere consists of an abundant amount of pollen. Thunderstorm-related asthma epidemic was previously reported in four-season countries, such as Australia, England and Italia. In 2016, a total of nine deaths and more than 8,500 emergency department visits due to asthma were reported after a thunderstorm in Melbourne, Australia (24). Interestingly, fatal asthma due to thunderstorm was also reported in the desert country Kuwait in 2016 (25). The high concentration of allergen carried by thunderstorm was the cause of this phenomenon. Besides pollen, the spore of outdoor moulds such as *Alternaria* and *Cladosporium* species may trigger asthma exacerbation during thunderstorm (6,24).

Risk factors of asthma-related deaths

Risk factors of asthma-related deaths are listed in Table 1 (26). Recently, air pollution has been revealed as a risk factor that increased asthma mortality in asthma patients (27).

A history of near-fatal asthma requiring intubation and mechanical ventilation

Near-fatal asthma is an acute asthma associated with a respiratory arrest or arterial carbon dioxide pressure >50 mmHg, with or without altered consciousness requiring mechanical ventilation (28). Near-fatal asthma can lead to fatal asthma due to arrhythmia and asphyxia followed by mechanical ventilation-associated complications such as barotrauma and ventilator-associated pneumonia. In a group of patients with a history of near-fatal asthma, deaths occurred within 3 months in nearly one-third of deaths and within a year in two-thirds of deaths (29). Patients with mild symptoms still had the risk of severe asthma exacerbation and fatal asthma attack (6,26).

Hospitalisation or emergency visits for asthma in the past year

History of hospitalisation or emergency visits for asthma in the past year represented uncontrolled asthma and exacerbations that could not subside with regular reliever drugs. The risk of near-fatal and fatal asthma was almost three times higher in asthma patients with a history of hospitalisation in the past year (30). Data from NRAD mentioned that 90 of 190 asthma patients (47%) who died previously had been hospitalised due to asthma, among them 15% in intensive care unit and 34% had a history of emergency department visits in the past year. Ten percent of asthma-related deaths happened within 28 days after hospitalisation (6).

Table 1. Risk factors of asthma-related deaths.

1.	A history of near-fatal asthma requiring intubation and mechanical ventilation
2.	Hospitalisation or emergency visits for asthma in the past year
3.	Currently using or having recently stopped using oral corticosteroids
4.	Overuse of SABAs (>1 canister of salbutamol or equivalent monthly)
5.	A history of psychiatric disease or psychosocial problems
6.	Not currently using inhaled corticosteroids
7.	A history of psychiatric disease or psychosocial problems
8.	Poor adherence with asthma medications and/or poor adherence with (or lack of) a written asthma action plan
9.	Food allergy in a patient with asthma
10.	Air pollution

SABAs, short-acting β_2 -agonists.

Currently using or having recently stopped using OCS

OCS are the initial therapy for patients with severe uncontrolled asthma or asthma exacerbation. Uncontrolled asthma is defined as asthma with at least one of the following characteristics (26):

1. poor symptom control (frequent symptoms or use of reliever drugs, limited activity due to asthma, night waking due to asthma) and
2. frequent exacerbations (≥ 2 times/year) requiring OCS or serious exacerbations (≥ 1 time/year) requiring hospitalisation.

Difficult-to-treat asthma is asthma that is still uncontrolled despite Global Initiative for Asthma (GINA) step 4 or 5 treatment or that required such treatment to maintain good symptom control and reduce the risk of exacerbation. Severe asthma, a subdivision of difficult-to-treat asthma, is defined as asthma that is uncontrolled despite maximal therapy and treatment of contributory factors with good adherence or that worsens when high-dose treatment is decreased (26). Both difficult-to-treat asthma and severe asthma required OCS as its treatment; so in other words, currently using or have recently stopped using OCS represents the patient's asthma severity. This group of patients is at risk because of their poor asthma control.

Overuse of SABAs

Overuse of β_2 -agonists is one of the risk factors of asthma exacerbation and asthma-related deaths (26,31,32). This is the cause of the epidemic of asthma deaths in New Zealand as previously discussed. The NRAD in 2014 mentioned that there is a significant proportion of asthma patients who have been prescribed 12 inhaled SABAs and few controllers a year before they died (6). Furthermore, excessive prescribing of reliever and monotherapy long-acting β_2 -agonists (LABAs) are correlated with increased number mortality in asthma patients. Based on these findings, NRAD stated the use of more than one canister of reliever drug per month as the indication of poor control asthma and the need for further treatment evaluation (6). Overuse of β_2 -agonists, both SABAs and LABAs, induced downregulation of b-adrenergic receptors in the airway through pathways including uncoupling of b-adrenergic receptors with its intracellular receptor system, receptor internalisation and decrease in the pace and number of b-adrenergic receptors' synthesis in the airway (33). Patients with Arg16 genetic polymorphism are susceptible to have downregulation of b-adrenergic receptors following the excessive use of β_2 -agonists (34). Downregulation of b-adrenergic receptors can lead to bronchodilation desensitisation to β_2 -agonists therapy. Bronchodilator effect of salbutamol can reduce to only 50% even though it is given in a high dose up to 400 mg

following the overuse of salbutamol (35,36). The sensitivity to β_2 -agonists can rapidly recover after stopping the medication. For formoterol, the sensitivity regained after stopping for 3 days (35). Bronchodilator tolerance increases along with the severity of bronchoconstriction (37).

Gauvreau et al. compared two groups of mild, stable and allergic asthma patients. One group was given albuterol 800 mg/day for a week and the other was the placebo group. In the albuterol group, there was a significant increase in bronchus hyperreactivity and number of sputum eosinophil (38). Overuse of β_2 -agonists can cause tachyphylaxis; symptoms persist despite the use of β_2 -agonists. When this happens, patients tend to use the drug more frequently, which heightens the dose of SABAs. The adverse effect of high-dose use of SABAs includes metabolic effect such as hypokalaemia and cardiovascular effects such as ischaemia, heart failure, arrhythmia and cardiac arrest (39,40). Dispensing >1 canister salbutamol (200 dose) per month (≥ 12 canisters per year) or equivalent increases the risk of death. Risks are higher with nebulised SABA (26). GINA in 2019 no longer recommended SABAs only for the treatment of asthma in adults and adolescents.

Studies have been done to explain the mechanism of how epidemic asthma death happened in New Zealand. One of the studies mentioned that fenoterol was fully acting on β_2 -agonist receptors compared with other SABAs and this resulted in generating greater cardiac and metabolic effects (41). Moreover, the fact that fenoterol was available in higher dose formulation compared with other SABAs also contributed to the epidemic in New Zealand (42).

Not currently using ICS

ICS are the cornerstone of asthma management. Controlled asthma can be achieved by routinely using ICS. Nonetheless, there are still so many asthma patients who are not using ICS even though they were prescribed by the doctor. This can lead to poor outcomes such as frequent symptoms or exacerbation and death (6). Studies conducted to compare the ratio of asthma mortality with the use of ICS and SABAs showed that asthma mortality ratio was inversely proportional to the use of ICS; on the other hand, the asthma mortality rate was directly proportional to the use of SABAs (43,44).

In 2019, GINA released a recommendation to not treat asthma with an LABA without ICS (LABA monotherapy) (26). LABA should be given in combination with ICS. SABAs, as well as LABAs, have risks when given as monotherapy (16,26,45). GINA recommends giving rapid-acting LABA, formoterol, combined with ICS as asthma reliever therapy. This was done to prevent overuse of SABA. In 2006, randomised controlled trial Salmeterol Multi-Centre Asthma Research Trial was conducted involving 26,355 patients each of whom was given

either inhaled salmeterol or placebo in addition to their regular therapy. The serious adverse effect and asthma-related deaths were significantly found in inhaled the salmeterol group. The risk reduced if inhaled salmeterol was combined with ICS as the standard therapy (45,46).

ICS are available as ICS-only and in combination with LABA. Combination of ICS-LABA increases and catalyses β_2 receptor gene transcription and therefore prevents the reduction in the number of β_2 receptors (downregulation) that can happen following long-term use of β_2 -agonists (47). Meanwhile, β_2 -agonists may enhance corticosteroid action by increasing glucocorticoid nuclear receptor localisation. Moreover, β_2 -agonists can also work in synergy with corticosteroid in suppressing inflammatory mediator release (47).

A history of psychiatric disease or psychosocial problems

Psychology and social factors play a key role in asthma death. Prevalence of anxiety, depression and panic attack are higher in asthma patients compared with control (6). Of 95 asthma deaths, 58% cases had psychosocial problems. Depression and denial of symptoms and the need for treatment are the most common problems (6,22). Furthermore, patients with depression and anxiety tend to have more frequent symptoms, which are often not a response to medical treatment in the emergency department, and have more frequent visits to the hospital due to the often appearance of symptoms (6).

Poor adherence with asthma medications and/or poor adherence with (or lack of) a written asthma action plan

A personal written asthma action plan (WAAP) has proven to be very effective. Forty-four (23%) of 195 patients who died due to asthma had a WAAP in primary and secondary care. On the other hand, 54 (65%) of 83 patients who died due to asthma and was currently supervised by specialists did not have an asthma review in the last 12 months (6). Guideline of asthma management GINA 2019 stated that all patients with asthma must have a guided self-management education (26). The guide should cover symptoms monitoring, WAAP, and/or lung function and it should be periodically reviewed by medical practitioners. A WAAP helped the patient to recognise and respond to worsening of asthma appropriately. The guide must specifically list instructions for the patients regarding modification of reliever and controller drugs, how to use OCS if needed, and when and how to access medical help. Moreover, the trigger of asthma can be identified and evaluated routinely with a WAAP. Education about a WAAP for the patient is important and beneficial to prevent self-modification therapy by the patient.

Food allergy

Food allergy as an asthma trigger is uncommon and rare (<2% cases). However, patient with asthma as comorbid is at a high risk for severe and fatal allergic reaction due to food allergy (anaphylaxis). This anaphylaxis reaction often resembles near-fatal asthma (48). Peanuts are the most common cause of anaphylaxis-related death in asthma patients in the US (49). Most of the cases with anaphylaxis-related deaths in the UK had a history of routine control in medical health care but still had uncontrolled asthma (50).

Air pollution

Air Quality Index (AQI) in Jakarta on August 2019 showed the high level of particulate matter ($PM_{2.5}$, 155 (51). High levels of AQI (>155) are categorised as unhealthy (52). Air pollution is associated with asthma exacerbation and the level of asthma control. A study in Hubei, China, in 2013–2018 showed that a high level of $PM_{2.5}$, NO_2 , and O_3 was significantly correlated to asthma death (27). These pollutants trigger airway inflammation and can act as oxidative stress. Sustained inflammation caused by inhaling polluted air may result in airway remodelling. Furthermore, ozone and nitrogen dioxide induce bronchial hyperreactivity (53). Sulphur dioxide (SO_2), carbon monoxide (CO) and PM_{10} are associated with asthma mortality. In the US, decrease in the level of SO_2 , CO and PM_{10} was correlated with the decline in the asthma mortality rate in 1993–2010 (54). These data emphasise the importance of controlling air pollution to prevent an increased risk of asthma death.

Conclusion

The endemic of asthma death, both in England and Wales in 1960s as well as in New Zealand in 1970s, was correlated with a high dose use of β_2 -agonists drugs. The trend of asthma mortality post epidemic is declining due to the use of ICS in asthma management. Risk factors of asthma-related deaths include a history of near-fatal asthma requiring intubation and mechanical ventilation; hospitalisation or emergency visits for asthma in the past year; currently using or having recently stopped using OCS; overuse of SABAs, especially use of more than one canister of salbutamol (or equivalent) monthly; not currently using ICS; a history of psychiatric disease or psychosocial problems; poor adherence with asthma medications and/or poor adherence with (or lack of) a WAAP; food allergy in a patient with asthma; and air pollution.

Conflicts of interest

None declared.

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