

Fetal asthma

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- A 20-year-old woman with asthma was taken to the emergency room because of cardiorespiratory arrest. The patient had had severe asthma since childhood.

- She was born after a normal pregnancy.
her mother smoked three packs of cigarettes per day during pregnancy and during the patient's childhood.

- Asthma developed at the age of 4 years, and exacerbations occurred frequently thereafter, triggered by cold air, hot humid air, physical activity,
- respiratory infections, anxiety, and exposures to paint and to cats and birds that were kept in her home or the homes of relatives.

- Attacks often occurred at night or in the early morning.

- She was **incosistentent in her use of inhalers** and oral medications; she used inhaled bronchodilators up to 10 time per day when she had symptoms.
- At the age of 15 years, she told hospital staff that she rarely took her medications regularly.

- Oxygen desaturation occurred during some asthma episodes, including an episode of status asthmaticus at the age of 8 years, with an oxygen saturation of 80% while the patient was breathing ambient air and had a respiratory rate of more than 50 breaths per minute.

comorbidities

- The patient had a history of obesity, gastroesophageal reflux for which she took esomeprazole, depression, wrist fractures, chickenpox, and pinworms.

Social and drug history

- She had no allergies to medications. She had missed many months of school because of asthma and had left school at the age of 15 years.. She told some caregivers that she **smoked cigarettes** but also told many others that she did not smoke

- ▶ In the early hours of the morning of admission, the patient's mother noted that the patient was awake and using a nebulizer, as she did frequently.

When her mother next saw her, approximately 2 hours later, the patient was lying on the floor, unresponsive, without spontaneous respirations or pulse. The patient's mother called emergency medical services (EMS).

- ▶ On examination by EMS providers, the patient was cold, cyanotic, and in asystole. The trachea was intubated, and cardiopulmonary resuscitation was initiated. Epinephrine (1 mg) and atropine (1 mg) were administered intravenously; this was repeated twice without response. . She remained in asystolic cardiac arrest, despite aggressive resuscitation attempts. The body was transferred to hospital, and an autopsy was performed.

- ▶ This case highlights the problem of asthma-associated mortality, with more than 4000 deaths from asthma occurring annually in the United States.¹

- ▶ There are many possible causes of death in a patient with asthma in whom respiratory failure develops. Patients with corticosteroid-induced chronic immunosuppression are predisposed to life-threatening infections, anaphylaxis, and acute hypersensitivity reactions; however, this patient did not have a history or laboratory evidence to suggest any of these diagnoses, nor did she have any underlying cardiac disease.

- ▶ Why did this patient die from asthma? The answer may lie with the treatment plan, the compliance of the patient with the plan, and the inherent severity of her disease (so severe that no measure taken could have saved her).

- ▶ Asthma mortality varies among and within countries .
Based on World Health Organization (WHO) data, age standardized death rates per 100,000 range from 40.79 in Kiribati, 11.35 in India, 1.72 in China, 1.06 in Russia, 1.06 in the United Kingdom, 0.96 in France, 0.95 in the United States, 0.39 in the Netherlands, and 0.34 in Italy

- ▶ Patients who have frequent and severe asthma symptoms and evidence of airflow limitation are at greatest risk; however, cluster analysis has identified significant patient heterogeneity. Fatal and near-fatal asthma exacerbations can occur sporadically and inexplicably in a minority of asthmatics whether the baseline level of disease activity is mild, moderate, or severe. Therefore, any acute exacerbation of asthma may be a potentially fatal attack.

- ▶ Mild asthma is currently defined as asthma that is well controlled on low dose ICS or as-needed-only ICS-formoterol
- ▶ The utility and relevance of this definition is much less clear
- ▶ The term ‘mild asthma’ is often interpreted very differently
- ▶ Patients and clinicians often assume that ‘mild asthma’ means no risk and no need for controller treatment
- ▶ BUT: up to 30% asthma deaths are in patients with infrequent symptoms (Dusser, Allergy 2007; Bergstrom, Respir Med 2008)

epidemiology

- ▶ In the United States, fatalities from asthma most commonly occur in lower income urban populations .
Disparities in income, education, and access to health care are widely recognized as important contributors to differences in mortality rates among different sociodemographic groups.
In this regard, an analysis showed that the higher risk of death in African American patients compared with White patients is not explained by race differences in deaths occurring in hospital and are therefore likely due to differences that precede hospitalization, such as differences in management at home or during transportation to the emergency department

Are mortality preventable

- ▶ Even in the modern treatment era with an emphasis on inhaled glucocorticoids, mortality among asthmatic patients is mainly due to asthma.

In a retrospective Australian study conducted from 2005 to 2009, 85 percent of 283 asthma-associated deaths were specifically due to asthma rather than to other comorbidities.

Notably, 70 percent of the deaths due to asthma had preventable or modifiable risk factors present.



▶ TEMPORAL PATTERNS OF FATAL ASTHMA

Slow onset asthma

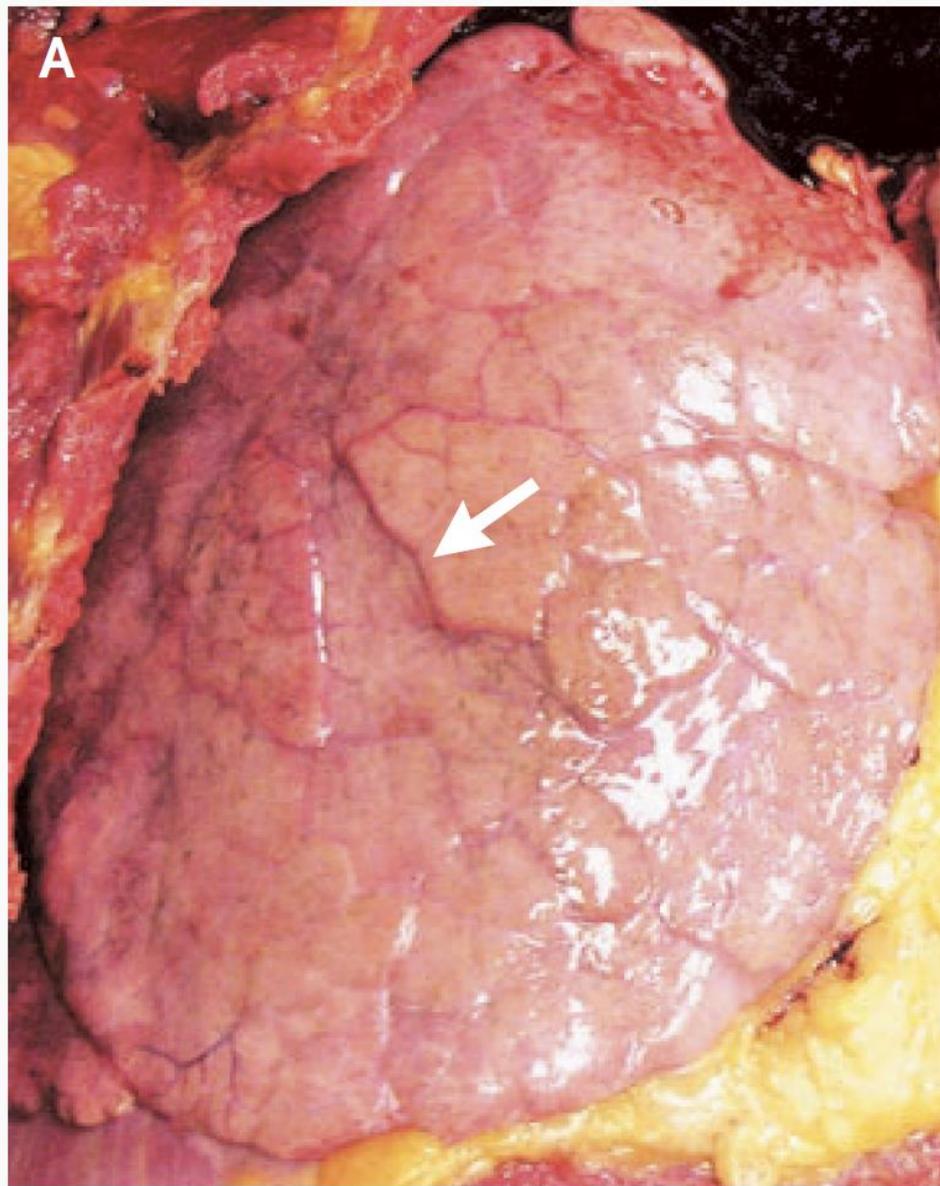
- ▶ Based on clinical and pathologic observations, it has been estimated that approximately **80 to 85 percent** of patients who die of asthma have a history of progressive symptoms for more than 12 hours and often for one to three weeks. At autopsy, the airways of patients who die of this "slow-onset" asthma typically feature an **eosinophilic inflammation** and obstruction of airway lumens by **tenacious mucus and desquamated epithelium** . These changes probably develop over days to weeks. This suggests that most of these patients would have had sufficient time to seek medical attention for worsening shortness of breath.

- ▶ In a minority of patients with fatal or near-fatal exacerbations of asthma, possibly **up to 20 percent** (8 to 14 percent of asthma exacerbations in general), death occurs less than 2 to 6 hours after symptom onset

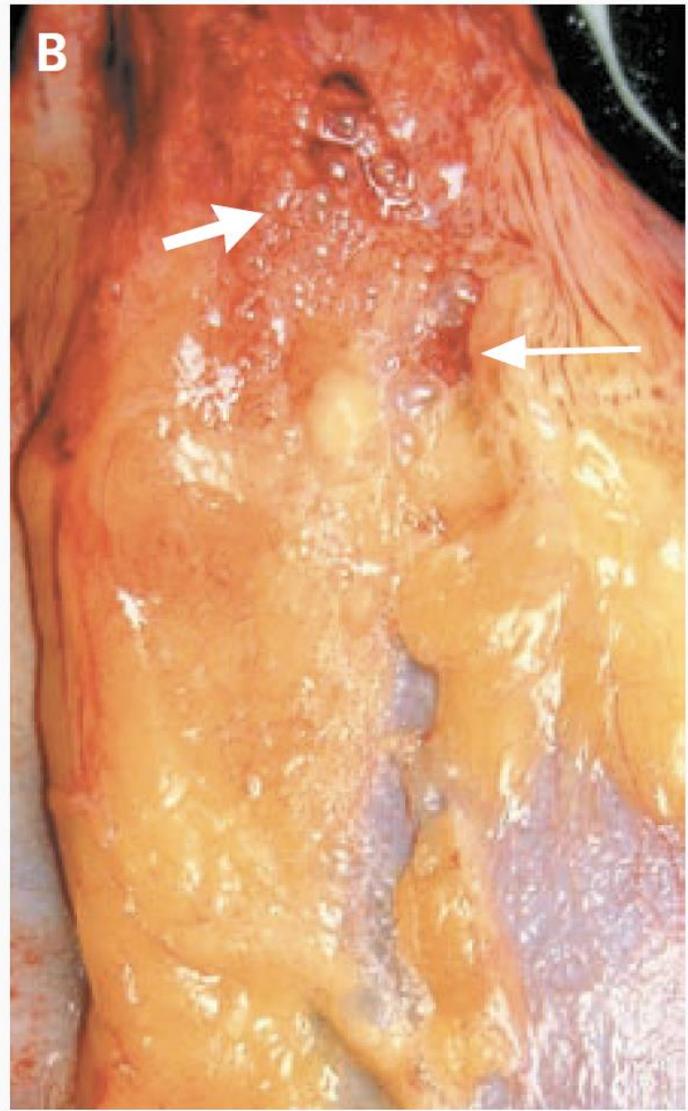
- ▶ The airways of these patients with "rapid-onset" fatal asthma do not have eosinophil-predominant inflammation or widespread mucus plugging typical of status asthmaticus. Instead, severe airway obstruction appears to be mainly due to smooth muscle bronchospasm and neutrophils are the predominant inflammatory cell in the airway mucosa.

- Unfortunately, specific characteristics that would help the clinician predict which patients are predisposed to rapid-onset asthma attacks have not been identified. Neither the severity of baseline asthma symptoms, years of asthma, smoking habits, asthma medication use, nor history of hospitalization for asthma help in identifying these patients.

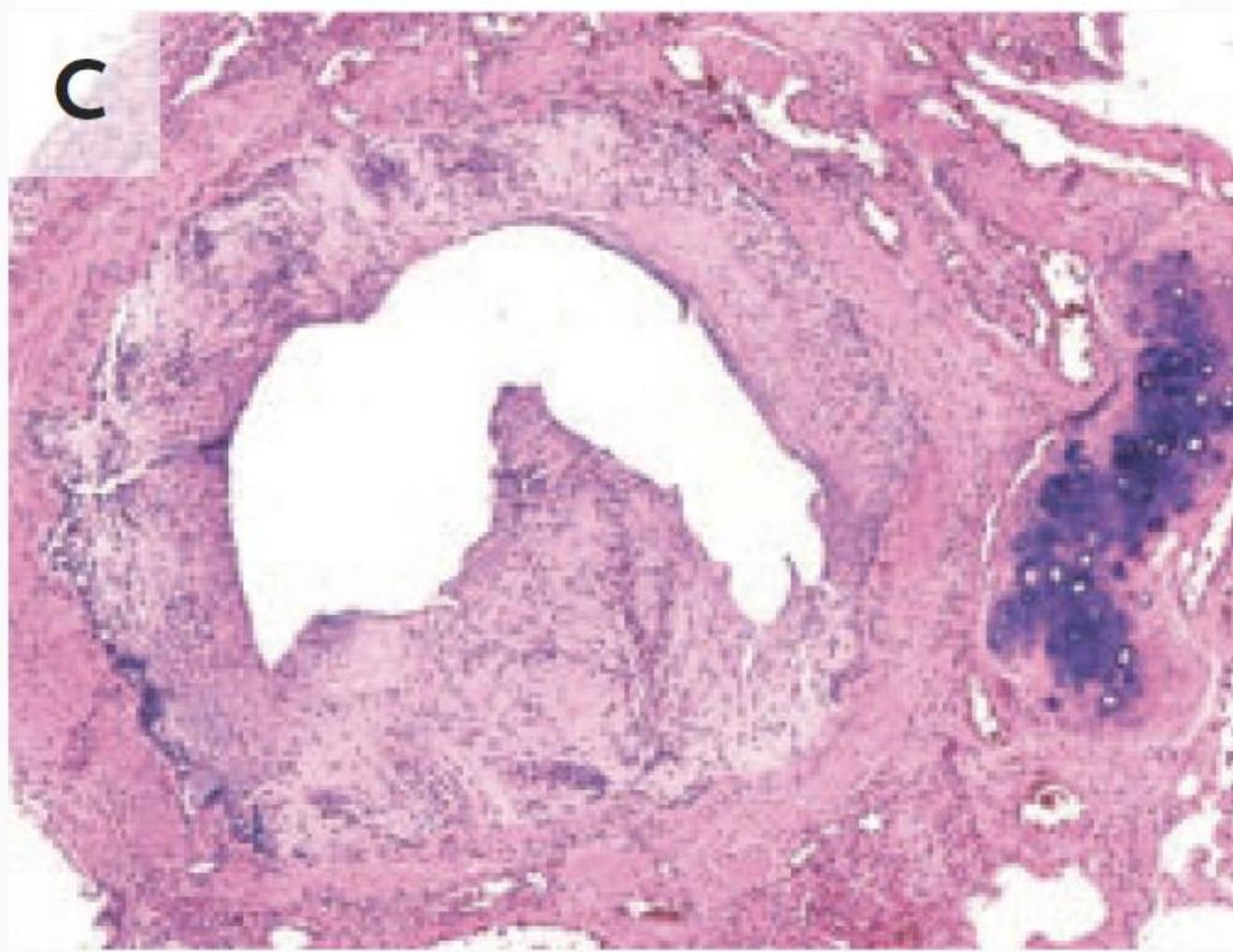
- However, patients with rapid onset asthma exacerbations may more commonly report **sensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs)**
 - . Rapid-onset asthma exacerbations do not appear to be due to anaphylaxis, although that diagnosis must be considered given the rapidity of the deterioration



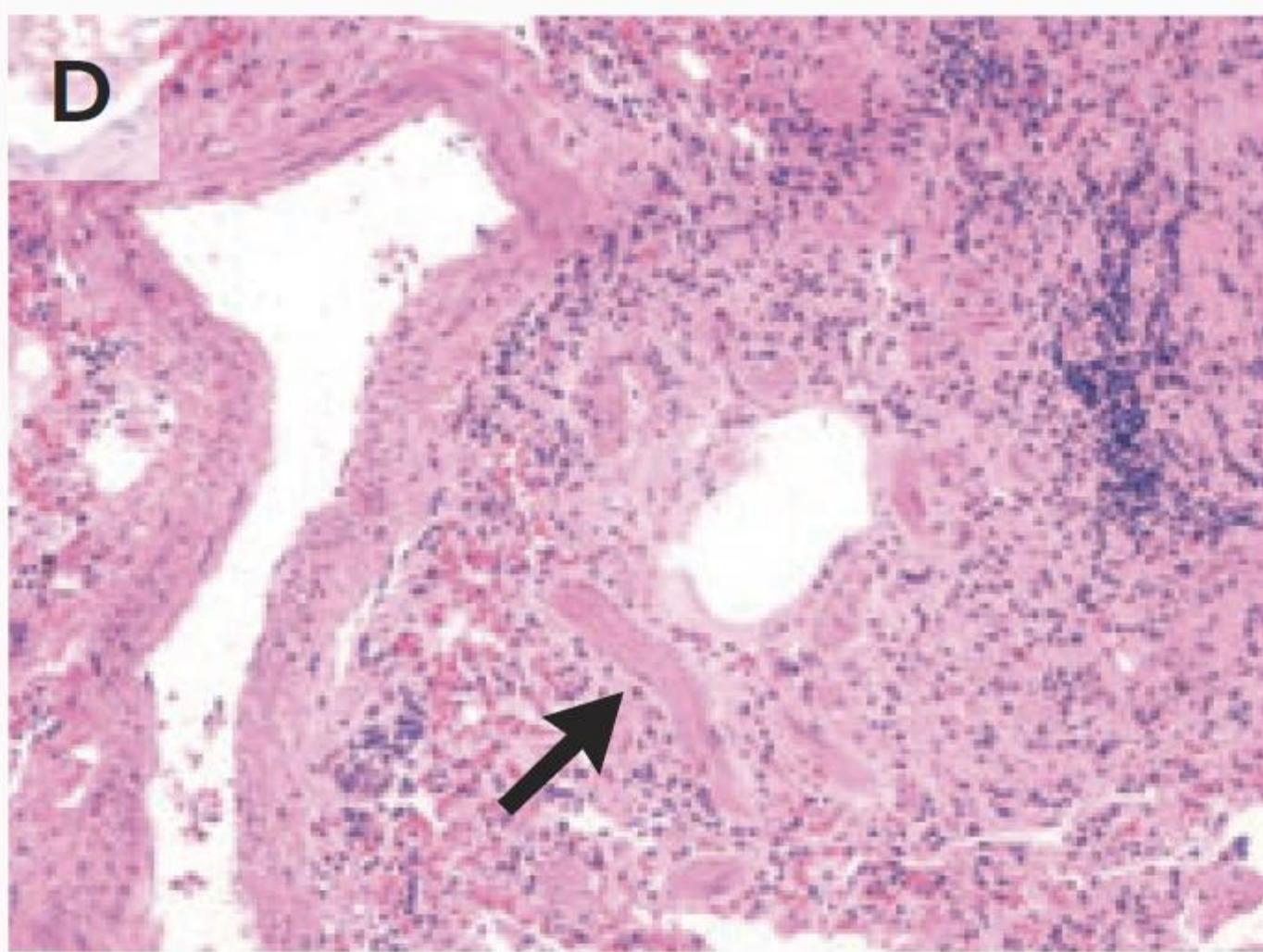
The right lung is hyperinflated in this gross photograph taken before the lung was removed from the body (Panel A)



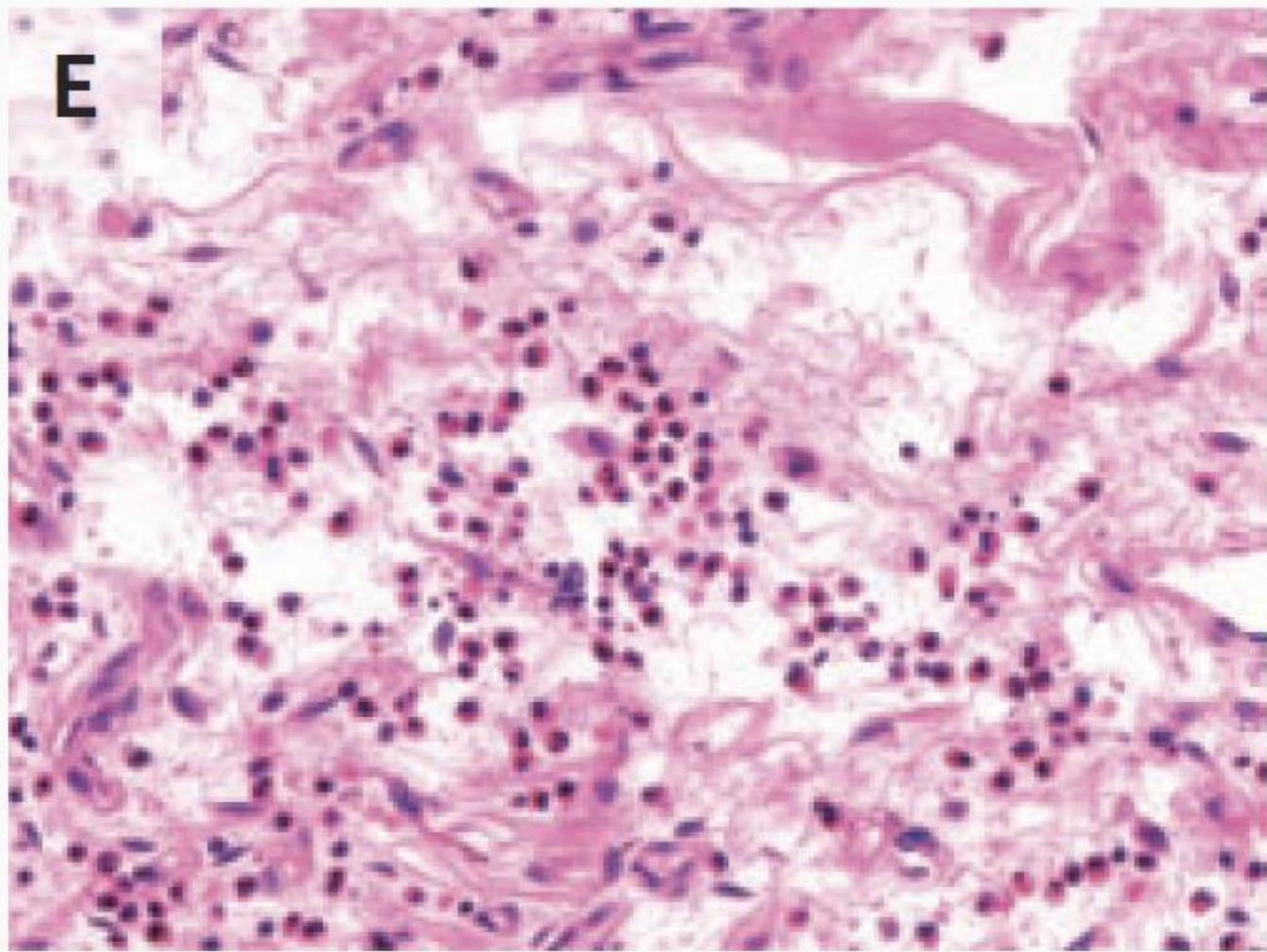
a depressed polygonal lobule (arrow) contrasts with the hyperinflated adjacent lung. Mediastinal emphysema is present (Panel B) with bubbles of air in the pericardial fat (arrows).



A small bronchus is filled with mucus and sloughed epithelial cells (Panel C, hematoxylin and eosin).



A terminal bronchiole (Panel D, hematoxylin and eosin) contains hypertrophic smooth muscle (arrow).



Numerous eosinophils are present in the pulmonary interstitium (Panel E, hematoxylin and eosin).

Identifying high risk patients

- ▶ Two elements of the clinical history are most useful in assessing risk for a future fatal or near-fatal asthma exacerbation in an individual patient.

- Recent history of **poorly controlled asthma** - Recent history of poor or only partial control of asthma symptoms indicates increased risk. While no single symptom is predictive of an impending severe attack, **increases in dyspnea and wheezing, frequency of nocturnal awakenings, use of short-acting, beta-adrenergic agonist rescue medications, and increased diurnal variability in peak expiratory flow rate (PEFR)** all indicate a pattern of poor or partial control of asthma.

- Hospitalization or emergency care visits in the past year, current or recent use of oral glucocorticoids, and lack of treatment with inhaled glucocorticoids are all indicative of poorly controlled asthma and should alert the physician to increased risk of asthma-related death.

- Prior history of near-fatal asthma - Any past history of a prior near-fatal asthma exacerbation requiring endotracheal intubation and mechanical ventilation or a history of a prior intensive care unit admission for asthma should alert the clinician to the patient's propensity and high risk for near-fatal or fatal asthma exacerbations.

- Although a previous history of mechanical ventilation is high among patients being evaluated for near-fatal or fatal attacks, the lack of such prior history in an individual patient does not rule out the possibility of a potentially fatal attack and should not be reassuring to the clinician assessing risk.

Minor risk factor

- Sensitivity to aeroallergens - After adjusting for age and lung function (FEV1), patients with non-allergic asthma have a higher risk of mortality than patients with allergic asthma (relative risk 1.9)
However, aeroallergen exposure, particularly due to pet ownership, is associated with episodes of near fatal and fatal asthma in sensitized individuals

- Food allergy - A history of food allergy in a patient with asthma may be a significant risk factor for asthma-related death. Importantly, deaths can occur in patients with a history of only mild prior reactions to a specific food.

- **Aspirin exacerbated respiratory disease (AERD)** - For patients with AERD, exposure to aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclooxygenase (COX)-1 can result in severe and potentially fatal asthma exacerbations .
Patients with AERD should avoid aspirin and NSAIDs , unless they have been desensitized to aspirin.

- Exercise - Exercise is an uncommon cause of fatal asthma but certain features have been observed in association with fatal events. In an eight year period in the United States, 61 episodes of fatal asthma were identified that were precipitated by exercise .
Most subjects were White males between the ages of 10 and 14.
Basketball and **track** were the most common sports associated with fatal asthma. The level of asthma control of these individuals prior to participation in exercise was not reported.

- Illicit drug use - **Cocaine** and **heroin** usage is a frequent trigger for severe acute asthma exacerbations: both are associated with a higher rate of intubation, and cocaine use is associated with a longer ICU length of stay
In a retrospective study of hospital admissions for asthma in patients age 16 and older, 27.6 percent were cocaine users and 30.9 percent were heroin users .

- Intubation and ICU admission were over 10 times more frequent among users compared with nonusers, even after controlling for cigarette smoking. Several mechanisms contribute to the adverse effect that cocaine and heroin have on asthma: direct thermal injury from smoking the drugs, IgE mediated allergy to cocaine, direct bronchoconstriction by cocaine, and an irritant effect on respiratory epithelium from cocaine or insufflated heroin.

- **Menstruation** - An increased frequency of near-fatal asthma episodes at the time of menstruation has been reported.

- ▶ **Respiratory virus infection** - In one series, evidence of respiratory viral infection, particularly picornavirus and adenovirus, was found in 59 percent of patients presenting to a hospital with near fatal asthma exacerbations .
- ▶ Are people with asthma at increased risk of COVID-19, or severe COVID-19?
- ▶ People with asthma do not appear to be at increased risk of acquiring COVID-19, and systematic reviews have not shown an increased risk of severe COVID-19 in people with well-controlled, mild-to-moderate asthma

- ▶ Are people with asthma at increased risk of COVID-19-related death?
- ▶ Overall, studies to date indicate that people with well-controlled asthma are not at increased risk of COVID-19-related death (Williamson, Nature 2020; Liu et al JACI IP 2021) and in one meta-analysis, mortality appeared to be lower than in people without asthma (Hou, JACI IP 2021).
- ▶ However, the risk of COVID-19 death was increased in people who had recently needed OCS for their asthma (Williamson, Nature 2020; Shi, Lancet RM 2022) and in hospitalized patients with severe asthma (Bloom, Lancet RM 2021).

- ▶ **Smoking and vaping** - Current smoke exposure is predictive of acute care need for asthma, and both in-hospital and post-hospital mortality are increased in smokers who require mechanical ventilation for asthma
Use of electronic nicotine delivery systems for vaping has not been definitively linked to fatal or near-fatal exacerbations of asthma per se, but asthmatics may represent a population especially vulnerable to the adverse effects of vaping.

- **Vaping** has been associated with an increased number of days absent from school for asthma symptoms among high school students in South Korea, and second hand exposure to vaping aerosols was associated with increased self-reported asthma attacks in the 2016 Florida Youth Tobacco Survey.

- Other factors - Other features associated with fatal and near fatal asthma, particularly slow onset fatal asthma, include: long duration of asthma, systemic glucocorticoid dependence, non-adherence to therapy, poor asthma control, psychosocial problems and less adaptive personality, delay in obtaining medical care, older age, and comorbid conditions

- Objective measures

Several studies have observed that a low forced expiratory volume in one second (**FEV1**) is associated with an increased risk of asthma exacerbations and the lower the FEV1, the greater the risk .

- In addition, **air trapping** and hyperinflation are associated with an increased frequency of serious asthma exacerbations. As an example, in a prospective study of severe or difficult to control asthma, postbronchodilator forced vital capacity (FVC) less than 70 percent was a predictor of asthma related emergency department visits and hospitalization.



- Despite these associations, patients with subsequent fatal or near fatal asthma may have entirely normal baseline spirometry.

- **Poor perception of dyspnea**

Other clinical or physiological features that have been noted in some asthmatics with a history of near-fatal asthma are reduced chemosensitivity to hypoxia, a poor perception of airway obstruction, a blunted perception of dyspnea, and difficulty communicating symptoms .

- These phenomena could be important in explaining, at least in part, the apparent delays these patients sometimes have in seeking medical attention during an asthma exacerbation.

- Only one-third of asthma mortalities in the United States in the year 2000 occurred in hospitalized patients, suggesting that many patients who ultimately die from asthma must either fail to seek medical attention during the hours or days of increased symptoms, or have a course of deterioration that is too rapid to reach hospital care in time, or are not appropriately hospitalized upon presentation.

- Therefore, efforts to decrease mortality from asthma have focused on educating patients to recognize the symptoms of an attack early and to follow an appropriate action plan that includes prompt medical evaluation.

- For patients who are at high risk of fatal asthma we prescribe **prednisone** (or equivalent) for the patient to keep on hand and start as advised by a prednisone-based action plan.

- Efforts to modify risk factors for fatal and near fatal asthma include: **avoidance of asthma triggers** such as aeroallergens, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs); **consideration of aspirin desensitization** in aspirin sensitive patients; **adherence to use of inhaled glucocorticoids**; **smoking and vaping cessation**; **appropriate treatment of exercise-induced bronchoconstriction**; and **avoidance of illicit drugs**.

- Patients with severe asthma should undergo evaluation for therapy with a **biologic agent** to reduce exacerbations.

- Use of objective measures such as peak expiratory flow rate, forced expiratory volume in one second (FEV1), and forced vital capacity (FVC) can be an important component of assessing asthma control and the severity of an acute exacerbation.