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Respiratory Complications of Pregnancy

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The pregnant woman is susceptible to a variety of respiratory complications. When a pregnant patient presents with an abnormal chest x-ray or a pulmonary complaint, an understanding of the pathophysiology of pregnancy will guide the clinician in establishing a diagnosis. Pregnancy brings about many changes to a woman's body. One of the more intriguing is a decrease in the T helper cells, resulting in a state of relative immunosuppression. Despite this, the prevalence of infectious pneumonia is not increased in pregnancy. Complications from pneumonia, however, are increased in the pregnant host. Most notably are increases in both mortality related to influenza infection and the risk for dissemination of coccidioidomycosis.

Other physiologic changes predispose the pregnant woman to certain disease processes. Hypercoagulability associated with pregnancy results in a marked increase in the incidence of thromboembolic disease. Although rare, pregnancy is also associated with other embolic phenomena including amniotic fluid embolism, air embolism, and trophoblastic embolism. Because of the increases in intravascular volume and cardiac output that occur in pregnancy, women with underlying structural heart disease will frequently present for the first time or have an exacerbation of their disease. This is especially true of mitral stenosis. Peripartum cardiomyopathy also can occur, and for the majority of patients, the heart remains damaged for life. Finally, although uncommon, lymphangioleiomyomatosis will often present or become exacerbated during pregnancy. Patients with this disorder need to be counseled concerning the increased risk associated with pregnancy. This paper reviews the various respiratory complications associated with pregnancy.

Target Audience: Obstetricians & Gynecologists, Family Physicians

Learning Objectives: After completion of this article, the reader will be able to review the changes in respiratory mechanics that occur during pregnancy, to list the various causes of pulmonary infections during pregnancy, and to describe the noninfectious causes of pulmonary complications during pregnancy.

Numerous mechanical, immunologic, biochemical, and hemodynamic changes occur during pregnancy. These physiologic alterations although protective to the fetus, often leave the mother more vulnerable to medical mishaps. Pregnant women are more vulnerable to a variety of infections, have a marked increase in thromboembolic disease, are susceptible to exacerbations of underlying immunologic disease, and develop heart failure more frequently than nonpregnant individuals of comparable age. For these reasons, the etiology of respiratory complications in this population has a broad differential. The evaluation and management of pulmonary disease in the pregnant patient requires knowledge of both the physiology and pathophysiology of pregnancy. We will review the many respiratory complications associated with pregnancy (Table 1).

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Table 1. Causes of pulmonary infiltrations during pregnancy

Infections
Bacterial
Viral
Tuberculosis
Pneumocystis
Fungal
Aspiration
Immunologic diseases
Wegeners granulomatosis
Systemic lupus erythematosis
Pulmonary emboli
Thrombotic
Air
Amniotic fluid
Trophoblastic
Cardiogenic pulmonary edema
Peripartum cardiomyopathy
Mitral Stenosis
Malignancy
Acute respiratory distress syndrome
Interstitial lung disease

RESPIRATORY MECHANICS

It is not difficult to imagine that the gravid uterus would affect respiratory mechanics. The enlarging uterus causes the diaphragm to rise by 4 cm and increases the transverse diameter of the chest by 2 cm. Additionally, the subcostal angle increases from approximately 68.5 degrees in early pregnancy to 103.5 degrees in late pregnancy (1). Despite these changes in the position of the diaphragm and the configuration of the thoracic cage, diaphragmatic motion is not impaired. By the second half of the pregnancy, there also are changes in the various lung volumes. Decreases in both expiratory reserve volume and residual volume result in a 9.5% to 25% decrease in functional residual capacity (2, 3). Total lung capacity also is diminished slightly at term (2).

In addition to these anatomic changes, pregnancy-induced biochemical changes also affect respiratory mechanics. Serum progesterone concentrations progressively increase throughout the course of pregnancy (4, 5). The rise in progesterone stimulates the respiratory centers in the brain resulting in hyperventilation and a sense of dyspnea. A respiratory alkalosis is universally present with partial pressure of CO_2 routinely falling to approximately 30 mm Hg (5).

PULMONARY INFECTIONS

Pregnancy is considered a state of relative immunosuppression. Studies have shown a decrease in cell-mediated immunity in pregnant women. Maternal lymphocytes obtained during the second and third trimester exhibit a decreased proliferative response to both soluble antigens and allogenic lymphocytes (6, 7). A decrease in helper T cells during early pregnancy results in a lowering of the helper/suppressor ratio causing decreased antibody production (8, 9). Polymorphonuclear leukocytes have also been shown to have a decreased chemotactic response during pregnancy (10). Maternal serum not only hinders the lymphocyte proliferative response to alloantigens, but also impedes the release of lymphokine macrophage inhibitory factor in response to allogeneic cells (11–13). Altered levels of hormones such as progesterone, β-human chorionic gonadotropin, α-fetoprotein, and cortisol may contribute to immunosuppression as well (14). Fetal lymphocytes can also suppress the mother's T lymphocyte proliferation and thus inhibit the maternal immune response (15).

Despite this immunosuppression, the prevalence of pneumonia in pregnancy is only between 0.04% and 1%; a rate of infection that surprisingly is not different from that in the nonpregnant individual. Although the incidence of pneumonia during pregnancy does not seem to be increased, complications associated with pneumonia are frequently more common (Table 2). Before antibiotics, the mortality rate of pneumonia associated with pregnancy was quite high; however, since the advent of antibiotics, mortality has decreased (16). In 1939, Finland and Dub-

Table 2. Pneumonia in pregnancy

Infections	Prevalence	Maternal Mortality
Community-acquired pneumonia	No change	No change
Influenza	No change	Increased
Varicella pneumonia	? Increased	No change
Measles	?	No change
Tuberculosis	No change	No change
Pneumocystis	?	? Increased
Coccidiodomycosis	No change	Increased dissemination more frequent
Blastomycosis	No change	?
Cryptococcus	?	?

?, questionable.

lin (17) reported a 32% maternal mortality rate in 212 women. By 1994, Richey and colleagues (18) noted a maternal mortality of only 3% in 71 women. The most frequent causes of pneumonia occurring antepartum are bacterial, viral, and aspiration.

The organisms causing pneumonia in pregnant women are similar to those found in the nonpregnant host. *Streptococcus pneumonia* is the most common pathogen encountered in pregnancy and accounts for 30% to 50% of all pneumonias in this population (16). Other common bacterial pathogens include *Haemophilus influenzae*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*. *Mycoplasma pneumoniae* is the most frequent cause of atypical pneumonia. *M. pneumoniae* has been identified in 11% of antepartum pneumonia, which is similar to the prevalence in the nonpregnant population (18). Mortality from *Mycoplasma* is rare and the recovery generally occurs 10 to 14 days after the onset of symptoms. *Legionella* accounts for 5% of antepartum pneumonia with a mortality rate as high as 20% (18, 19).

Type A influenza, a frequent cause of viral pneumonia, is associated with a greater mortality in women who are pregnant than those who are not pregnant. In 1918, Harris (20) noted that 50% of 1350 cases of influenza in pregnant women were complicated by pneumonia with an overall mortality rate of 27%. During the third trimester, however, mortality climbed to 61%. In the 1957 influenza epidemic in Holland, 11 of the 1230 fatalities were in women who were pregnant. That same year in England, 12 of 103 deaths due to influenza occurred in the pregnant population (21). In New York, 10% of deaths caused by influenza occurred in women who were pregnant (22). Because of this high mortality, polyvalent vaccine should be administered to all pregnant patients if an impending influenza outbreak is predicted.

Varicella pneumonia may occur in up to 20% of adults with varicella infection (23). Pneumonia develops 3 to 6 days after the vesicular eruption. The chest x-ray typically shows a diffuse nodular pattern. Although in the past it had been suggested that there was an association between varicella pneumonia and pregnancy, modern series have not been able to confirm such a relationship. Paryani and Arvin (24) reported a 9.3% incidence of varicella pneumonia in the pregnant population, although Baren et al. (25) documented only a 3.6% incidence. These numbers certainly are lower than previous reports in the nonpregnant host (16% in a series of Army recruits) (23, 25, 26). It is also unclear whether the course of pneumonia in the pregnant host is more severe than in nonpregnant adults. Treatment of varicella pneumonia with acyclovir has been suggested to reduce the mortality from as high as 45% to approximately 14% (27, 28). This is a rate comparable with the mortality found in the nonpregnant population (27, 28). At present, if varicella pneumonia is suspected in pregnancy, it seems prudent to admit the patient to the hospital for observation and treat with acyclovir.

Rubeola is associated with pneumonia in 3.5% to 50% of infected patients (29). During the Greenland measles epidemic, there was a 10% mortality rate for women who were pregnant compared with 7% for the control group (29). Maternal measles can cause spontaneous abortion and preterm delivery. Pregnant women with measles must be observed closely for the development of complications such as otitis media, hepatitis, encephalitis, and pneumonia. If secondary bacterial infections develop, they should be treated promptly with antibiotics (29).

Although up to 0.1% of pregnant women residing in endemic areas are infected with tuberculosis, studies have shown neither an increased risk of developing active tuberculosis (TB) nor more aggressive disease during pregnancy (30). There, however, may be a small increase in the occurrence of toxemia, vaginal bleeding, and more difficult labor in women with tuberculosis (31). Once active disease is excluded, prophylaxis is recommended for pregnant women who have had conversion of their purified protein derivative (PPD) within 2 years of pregnancy and women who live with or are in close contact with a person with active disease. In the case of active tuberculosis, the recommended therapy is isoniazid (INH) and rifampin initially, plus ethambutol if INH resistance is likely, for at least 9 months. Pyridoxine should be added to decrease the incidence of INH-associated peripheral neuropathy (32). The impact of TB on maternal mortality and morbidity seems appears to be similar to that of nonpregnant patients (32).

In North American and European surveys, approximately 0.1% to 0.3% of pregnant women are infected with human immunodeficiency virus (HIV) and these rates are 10 to 20 times higher in some inner-city areas. In fact, changes in the demographics of HIV infection have made women and children one of the fastest growing groups of newly infected patients (33, 34). Longer survival rates also mean more women infected with HIV are becoming pregnant. Similar to nonpregnant patients, pneumocystis and tuberculosis are the most frequently encountered HIV-related pulmonary complication encountered during pregnancy (34). Other pulmonary diseases

such as fungal infections, cytomegalovirus, lymphoma, and Kaposi's sarcoma only rarely have been reported in pregnant women with HIV (34). The clinical presentation of HIV-associated pneumonia typically is not altered by pregnancy. Except for issues related to potential fetal effects, the diagnostic work-up and management of pulmonary infiltrates in pregnant patients with HIV are similar to those in the nonpregnant patient (34). To prevent any delay in diagnosis and treatment, it is necessary for the clinician caring for women who are pregnant to maintain a high degree of suspicion.

Although initially it had been suggested that there was both a markedly increased risk of dissemination and a very high mortality of coccidioidomycosis during pregnancy, more recent data suggest that this had been overstated (35). In fact, many pregnant women have favorable outcomes without drug treatment. The risk for dissemination, although not as great as previously described, is, however, two- to three-fold higher than that reported in women who are not pregnant. If dissemination occurs, treatment with amphotericin B is recommended. In endemic regions, it is important to promptly recognize coccidioidomycosis during pregnancy. Unlike coccidioidomycosis, *Blastomycosis* is rare and does not seem to be increased by pregnancy (36, 37).

Cryptococcal pneumonia can occasionally occur in the absence of any identifiable immunodeficiency state. Ely et al. (38) reported four pregnant women who developed cryptococcal pneumonia. At the present time, however, it is uncertain whether there is an association between cryptococcus and pregnancy. After a careful discussion of the risks and benefits, treatment may be withheld from those patients who have limited nodular or unilobar pulmonary disease without evidence of dissemination, hypoxemia, or other signs of clinical instability. Close follow-up of these patients is necessary. Serial determinations of the serum cryptococcal antigen titer may provide a useful method for monitoring the status of the infection (38). In the case of moderate to severe pneumonia or dissemination, treatment with amphotericin B is warranted (38). Amphotericin B has been widely used without evidence of teratogenicity (38). The use of fluconazole as a primary therapy should be discouraged because of the possibility of fetal malformation.

Because of the triad of decreased gastroesophageal sphincter tone, delayed gastric emptying, and elevated intraabdominal pressure, pregnant women, especially at term, are at high risk for aspiration pneumonitis (14). Prevention is the mainstay of therapy. Aspiration usually results in an immediate chemical pneumonitis secondary to the gastric acidity. Within 24 to 72 hours, bacterial superinfection may supervene. The use of steroids remains controversial and cannot be recommended. Antibiotics should be administered if a bacterial infection is suspected.

NONINFECTIOUS PNEUMONIA

Carrington et al. (39) described chronic eosinophilic pneumonia in 1969. This disease is characterized by fever, dyspnea, weight loss, and night sweats associated with diffuse pulmonary infiltrates as well as both pulmonary and peripheral blood eosinophilia. There are only three reported cases of eosinophilic pneumonia in pregnancy (40–42). Treatment is with corticosteroids. Davies et al. (43) reported a case of recurrent postpartum eosinophilic pneumonia. He postulated that changes in circulating glucocorticoids during the puerperium might have been responsible for the relapse.

WEGENER'S GRANULOMATOSIS

Wegener's granulomatosis is a rare necrotizing granulomatous vasculitis involving the upper and lower respiratory tracts, with or without glomerulonephritis. When this disease occurs in pregnancy, it may have a more virulent course and may require more aggressive treatment (44). Currently, the accepted treatment for active Wegener's is a combination of cyclophosphamide and corticosteroids. Cyclophosphamide is known to cause fetal malformations including facial and musculoskeletal deformities as well as spontaneous abortions especially during the first trimester of pregnancy. Treatment with cyclophosphamide during the second and third trimesters is much safer than during the first trimester, although rare cases of fetal pancytopenia and impaired growth have been reported (44).

SYSTEMIC LUPUS ERYTHEMATOSUS

The major effect of pregnancy on systemic lupus erythematosus (SLE) is an increase in the risk of exacerbations, especially in the puerperium (45). The more active the disease is before conception, the more likely an exacerbation will occur. There is no evidence suggesting an increase of pulmonary lupus-related complications during pregnancy. SLE, however, is associated with the presence of antiphospholipid antibodies (APAs) (45). The APAs of the IgG and IgM class are known to produce thrombosis. The clinical consequences of this in the pregnant host are

recurrent, unexplained fetal death, intrauterine growth retardation, early severe preeclampsia, and vascular thrombosis with an increased incidence of pulmonary emboli (46).

PULMONARY EMBOLI

Pregnancy is associated with a five-fold increase in risk for venous thromboembolic disease (47). Factors II, VII, and X and fibrin are increased and protein S levels are decreased. Furthermore, pregnancy inhibits the fibrinolytic system especially during the third trimester (48). In addition to these changes in the coagulation pathways, venous stasis plays an important role in the development of venous thrombosis during pregnancy. The gravid uterus compresses the venous outflow from the lower extremities thus giving rise to stasis. Clinically, this translates into venous thrombosis with a striking predilection to involve the left leg more commonly than the right leg (48). This likely is related to an exaggeration of the compressive effect of the iliac arteries on the left iliac vein leading to more venous stasis on the left than on the right. Traditionally it has been said that venous thromboembolism occurs mostly during the third trimester and immediate postpartum period. More recent studies show that the majority of episodes occur antenatally and are divided equally during all trimesters (48).

Almost unique to pregnancy is the risk for thrombosis of the ovarian veins, which most frequently happens in the postpartum period (49). The pathogenesis of this disorder is thought to be associated with an infection, cesarean delivery, and a prothrombic tendency. The cardinal signs of this thrombosis include leukocytosis, fever, and right lower-quadrant abdominal pain. Quick recognition of this complication is important because of their associated risk of pulmonary embolism. Fortunately, modern imaging techniques enable this diagnosis to be made easily (49).

Other factors associated with an increased risk of thromboembolic disease include prolonged bed rest, instrumentation or cesarean delivery, hemorrhage, sepsis, multiparity, and increased maternal age (50). Venous thrombosis occurs with a frequency of 0.5 to 3 per 1000 deliveries. When untreated, as many as 24% of patients with deep venous thrombosis will develop pulmonary embolism (51). The mortality associated with pulmonary embolism is approximately 15% (51). Anticoagulating pregnant patients who have deep vein thrombosis lowers the risk of pulmonary embolism to 4.5% and mortality decreases to less than 1% (52).

The incidence of amniotic fluid embolism has been reported to be between 1:8000 and 1:80,000 live births (53, 54). Although 90% of cases have been associated with labor and delivery, 10% can precede the onset of labor. Mortality may be as high as 86% (55). The first description of amniotic fluid embolism syndrome was made by Steiner and Lushbaugh (53) in 1941. The syndrome is characterized by the sudden onset of dyspnea, cyanosis, and hypotension quickly followed by cardiorespiratory arrest (55). If the initial phase is survived, up to 70% of the patients will develop noncardiogenic pulmonary edema (56). Diagnosis is often one of exclusion and primarily made on clinical grounds. Finding fetal material, especially squamous cells, in the maternal circulation is, however, diagnostic. Treatment is supportive and delivery should be expedited.

Obstetric and gynecologic operative procedures are well known to cause air embolism. In 1850, the first fatal case of air embolism was seen in pregnancy (57). Air embolism is more common than was once believed, especially in patients undergoing a cesarean delivery. Malinow et al. (58) found that venous air embolism occurs in as many as 52% of patients during a cesarean delivery. The large retroplacental sinusoids act as conduits for air entry into the circulatory system, especially if the patient is placed in the Trendelenburg position. The placenta is then well above the heart, and there exists a gradient for the potential entry of air into the circulation (59). Although most cases of air embolism are asymptomatic and often go undetected, they can result in significant and dire complications. A major consequence of venous air embolism is obstruction of the right ventricle and the pulmonary arterioles. Turbulence promotes increased fibrin deposition, clot formation, and increased platelet aggregation. In the lung, there is release of histamine and serotonin leading to pulmonary vasoconstriction and increased capillary permeability. This results in pulmonary hypertension and pulmonary edema (60). The diagnosis can be established with echocardiography or computerized tomography.

In obstetrical/gynecological surgeries, flooding the surgical field with saline decreases and prevents further entrainment of air (61). Hyperbaric oxygen therapy may be beneficial, especially if the patient has cerebral and/or cardiac symptoms. This therapy should be instituted early because a delay of more than 5 hours is associated with reduced chances of a full recovery. Hyperbaric oxygen may benefit the

patient by decreasing the bubble size, thus relieving the obstruction and improving oxygen delivery to the tissues.

Trophoblastic disease arises from the fetal chorion, which produces human chorionic gonadotropin. Trophoblastic embolism usually occurs during evacuation of a molar pregnancy or during hysterectomy for an invasive mole (62). This process is usually self-limiting and results in pulmonary edema, preeclampsia, anemia, and coagulopathy. The clinical course is short, with gradual improvement after 48 hours and complete resolution in 72 hours. Trophoblastic embolism should be a part of the differential diagnosis in those patients that develop postoperative acute respiratory distress (62).

ASTHMA

Because there are approximately 10 to 12 million women with asthma in the United States, asthma complicating a pregnancy is a very common occurrence (63). The effects of pregnancy on asthma have been quite variable. The disease status in pregnancy is affected by the severity of the disease before pregnancy. Asthma is associated with a wide array of complications including preterm labor, low birth weight, perinatal mortality, hyperemesis gravidarum, preeclampsia, chronic hypertension, and complicated labor (46). The management of asthma in the pregnant woman is the same as that for the nonpregnant woman. Because 10% of women with asthma will have an attack during labor, it is imperative that asthma medications be continued into labor and the postpartum period (63).

PULMONARY EDEMA

Dilated cardiomyopathy and mitral stenosis are two cardiac conditions that may lead to respiratory failure in a pregnant woman. Peripartum cardiomyopathy occurs in 1 of 1300 to 4000 pregnancies, with an overall mortality rate of 25% to 50% (64). This disorder rarely occurs before 36 weeks of gestation and can present as late as 6 months postpartum. However, it usually occurs in the peripartum period. Echocardiography typically reveals global hypokinesis. One third of the patients will progress to end-stage cardiac failure, another third will continue to have permanent cardiac dysfunction, and the remaining third will recover cardiac function (46). Because death frequently results from a mural thrombus in the left ventricle, when there is significant ventricular dilation, anticoagulation with heparin should be instituted (65). Risk factors for peripartum cardiomyopathy include multiparity, older age, black race, twin gestation, and preeclampsia. Some believe there is a risk of recurrence of the cardiomyopathy with each successive pregnancy. The etiology of peripartum cardiomyopathy remains unknown. Endomyocardial biopsies have, in some cases, suggested myocarditis. In those patients who do not improve, treatment with intravenous immunoglobulin (Ig) might be beneficial although this use has not been approved by the U.S. Food and Drug Administration. Patients refractory to therapy should be considered for cardiac transplantation (66).

In contrast to peripartum cardiomyopathy, which presents late in pregnancy, heart failure from underlying structural disease usually presents during the second trimester when the hemodynamic changes of pregnancy are the greatest (65). The physiologic changes of pregnancy, which include increases in blood volume, cardiac output and heart rate, all contribute to the exacerbation of cardiac failure in patients with structural heart disease (65). Up to 25% of women with mitral stenosis present for the first time during pregnancy with pulmonary edema resulting from congestive heart failure (65).

MALIGNANCY

With the recent increase in cigarette smoking among women, lung cancer in women of reproductive age can be expected to increase. Maternal malignancies in general only occur in 0.1% of pregnancies (68). The few cases of lung cancer diagnosed during pregnancy seem to be more aggressive and fatal. Whether the cancer itself is more aggressive or whether there is a delay in diagnoses and treatment is unknown. On the other hand, lung cancer does not seem to have a negative effect on the fetus. Delivery should occur as soon as the fetal lung has reached full maturity so as to provide prompt and appropriate treatment to the mother (68).

ACUTE RESPIRATORY DISTRESS SYNDROME

Acute respiratory distress syndrome (ARDS) has been noted to occur in about 0.2% to 0.3% of pregnancies. Associated conditions are numerous and include sepsis, aspiration, blood transfusion reactions, disseminated intravascular coagulation, sickle cell disease, chorioamnionitis, amniotic fluid embolism, pregnancy-induced hypertension, and tocolytic agents. The mortality rate has ranged from 10.5% to

43% (67). The three most common obstetrical causes of acute respiratory distress syndrome are chorioamnionitis, amniotic fluid embolus, and trophoblastic embolus. The three most common nonobstetrical causes of acute respiratory distress syndrome in the pregnant woman are pneumonia, sepsis, and aspiration (67).

INTERSTITIAL LUNG DISEASE

We recently treated a young woman entering her third trimester who presented with worsening dyspnea and pulmonary infiltrates (69). An extensive evaluation, including an echocardiogram, pulmonary angiogram, and bronchoscopy, was not revealing. An open-lung biopsy revealed respiratory bronchiolitis-associated interstitial lung disease. Treatment with steroids resulted in a prompt improvement in symptoms and clearing of the chest x-ray. It is unclear whether this entity is in any way related to pregnancy. Respiratory bronchiolitis, which is considered to be an early form of desquamative interstitial pneumonitis, is associated with a long history of smoking. This disease typically improves with the cessation of smoking and steroids (70).

Another interstitial lung disease that can present or be exacerbated by pregnancy is lymphangioleiomyomatosis (LAM). LAM is a rare entity of unknown etiology. Most of our knowledge comes from case reports. The disease is confined to women with an average age at presentation of 34 years. It is characterized by its progressive nature, usually terminating in respiratory failure requiring lung transplantation. Common to it are progressive dyspnea, recurrent pneumothorax, and hemoptysis and chylothorax (71). Pathologically, there is a diffuse involvement of the lungs by varied size cysts, from millimeters to centimeters, and a characteristic lack of a granulomatous component (71). There is evidence suggesting that the exogenous administration of estrogens and pregnancy may exacerbate the disease, whereas the use of antiestrogen therapy and oophorectomy have proven useful in many instances. Although the overall management of this disease is not the scope of this article, during pregnancy, primarily supportive measures are advised. Other complications such as pneumothorax and symptomatic chylous effusions may require anywhere from simple chest tube drainage to surgery. Perhaps the most important message is to make sure that women with LAM be warned of the risks involved with pregnancy before they become pregnant (71).

In summary, respiratory complications are not unusual in pregnancy. The obstetrician, pulmonologist, and primary care physician need to be aware of the physiologic changes that occur during pregnancy. With this knowledge an organized approach to the diagnosis of respiratory disease can be pursued.

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