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LOWER RESPIRATORY TRACT INFECTIONS IN ELDERLY PATIENTS WITH ASTHMA

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Infection plays a significant role in the morbidity and mortality of the elderly. One population in which infection has not been adequately studied is the elderly asthmatic. This article examines the problems of lower respiratory tract infections in elderly asthmatics in the context of their host defenses, the severity of infection, and their risk of infection with specific organisms. The role of infection in the pathogenesis of asthma and consideration of prophylaxis and therapy are presented.

DEMOGRAPHICS

Bronchial asthma is not generally considered to be a disease of the elderly. Population surveys, however, show that the prevalence of asthma in the elderly ranges from 2.4% to 12.2%.[18, 45, 48, 154] In a study comparing late-onset asthma and long-standing disease in nonsmoking elderly asthmatics, Braman et al[19] noted that 48% of patients developed asthma after 65 years of age. In a review of 10 population studies, Enright et al[45] found the prevalence of asthma to range from 2.4% to 6.6%. Banerjee et al[8] noted that 61% of randomly selected geriatric day-hospital patients exhibited airflow obstruction on pulmonary function testing. Of those with airflow obstruction 41.2% demonstrated greater than 15% improvement in peak expiratory flow rate following inhalation

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of 200 μg of salmeterol. In addition to chronic asthma, the incidence of new cases after 60 years of age appears to remain relatively constant, ranging from two to six cases per thousand.[18, 21, 22, 39] Advances in technology, nutrition, and medicine have set the stage for profound increases in the geriatric populations, such that the over-85 age group is the fastest growing segment of society in North America.[28] Based on current trends, by the year 2020, the over-65 and over-75 age groups will constitute 22% and 14.2% of the populations in the industrialized nations.[30] Thus we can anticipate a sustained increase in geriatric asthmatics requiring care. The principles of managing asthma in elderly patients differ little from those of treating younger patients. The impaired excretion of drugs by the kidney and liver, however, and greater likelihood of comorbid diseases and adverse drug–drug interactions make the management of asthma in elderly patients complex.[178, 196]

Infection-related mortality in the elderly is three- to 20-fold higher for given diseases compared with younger patients.[66, 178] Pneumonia-associated mortality in the elderly ranges from 5.9% to 32.9%, accounting for 89% of all pneumonia and influenza deaths in the United States between 1979 and 1992,[29, 60, 62, 83, 111, 125] and with influenza is the fifth leading cause of death in patients over 65 years of age.[29] A recent 2-year prospective observational study of independent elderly individuals reported that 54% of those older than 65 years of age had respiratory tract infections, of which bronchitis, pneumonia, and influenza constituted 42% of the total respiratory infections.[158] The severity of lower respiratory tract infections is a function of host susceptibility, the virulence of the infecting agent, and the extent of disease at the start of therapy.

HOST DEFENSES

Normal Lung Defenses

Resistance to microbial invasion of the lower respiratory tract is multifactorial and complex. The respiratory tract immune system is composed of both specific and nonspecific defense mechanisms that consist of a variety of anatomic, neurologic, cellular, and humoral mechanisms. The integrity of these mechanisms, pathogen virulence and the size of the bacterial inoculum play key roles in colonization and subsequent infection of the lower respiratory tract. A variety of conditions contributing to alveolar fluid accumulation place the host at an increased risk of pneumonia. Diminishing host defenses increase the vulnerability of elderly asthmatic patients to more protracted and debilitating consequences of lung infections. Increased vulnerability may also reflect the increased prevalence of diseases associated with fluid retention, such as cardiac, renal, or liver failure, swallowing disorders, altered consciousness, deconditioning due to a sedentary lifestyle, or adverse effects of malnutrition, immunosuppression, or malignancy. Harford and Hara[87]

demonstrated the harmful effects of increased lung water on the survival of mice with experimental pneumonia. A 15-fold increase in mortality was described in mice inoculated with endobroncheal bacteria, following endobronchial infusion of saline or serum. Effective phagocytosis cannot occur under these conditions in the absence of opsonic antibodies. Disease-related pulmonary dysfunctions associated with an increased frequency of lower respiratory tract infection are as follows[41]:

Disorders of Swallowing or Coughing
- Advanced age, debilitation, trauma, surgery
- Altered consciousness, seizure disorder
- Neurologic or neuromuscular disorder (esophageal disorders)
- Severe underlying disease

Disorders of Mucociliary Defenses
- Chronic bronchitis, bronchiectasis, viral infection, ciliary-dysfunction syndromes
- Exposure to irritants, alcohol, anesthesia, cold

Alveolar Fluid Accumulation
- Burns, trauma, acute respiratory distress syndrome
- Congestive heart failure, nephrosis, cirrhosis
- Viral, mycoplasmal, or bacterial infection

Altered Alveolar Macrophage Function
- Irritants, viral infection, uremia

Impaired Phagocytosis or Bacterial Clearance
- Asplenic or dysplenic states
- Comorbid disease (acquired immunodeficiency syndrome, diabetes mellitus, hypogammaglobulinemia, sickle, cell disease, malnutrition, immunosuppression)

The Immunosenescence of Aging

The immune decline of elderly patients is best considered an immunosenescence as opposed to an immunodeficiency state.[74] Numerous age-related in vitro immune deficiencies have been demonstrated in the elderly[77]:

Structural/Neurologic Deficiencies
- Homogeneous increase in air spaces
- Loss of airway elastic recoil
- Impairments of cough reflex
- Decreased mucociliary clearance

B-Cell Deficiencies
- Decreased immunoglobulin production
- Decreased antibody binding avidity
- Increased circulating autoantibodies
- Increased incidence of benign monoclonal gammopathies (BMG)
- Association of BMG with multiple myeloma, amyloidosis, malignant lymphoproliferative processes

T-Cell Deficiencies
Proliferative responses
Decreased mitogenic response to plant lectins
Decreased mixed lymphocytic response
Decreased proliferative response to OKT3 stimulation
Fewer responsive T cells
Responsive T cells fail to divide normally when stimulated
Cytokine/receptor expression
Decreased response to interleukin (IL)-2
Decreased IL-2 production
Decreased expression of IL-2 receptors
Decreased production of T-cell growth factors
Decreased response to T-cell growth factors
Thymic involution

Yet despite their acceptance and teleologic attractiveness, these deficiencies' causal relationships to clinical infections are unclear.[4, 12, 72, 77, 152, 161] Chandra[30] noted that in previously healthy individuals, the presence of anergy, lymphopenia, or both was associated with 1-year survival rates of 72%, 58%, and 45%, respectively. In a 16-year longitudinal study of healthy elderly men, decreased absolute lympocyte counts were noted within 3 years of death.[12] The leukopenia, however, was not age dependent and in both of these studies might have served as a marker of more severe comorbid disease(s). In predominately healthy patients with a mean age of 82 years, a normal inflammatory response to pneumonia was noted, as measured by appropriate rise in C-reactive protein, leukocytosis, and a neutrophil degranulation product, plasma neutrophil elastase α-1-antiproteinase complex.[4] In addition, despite having measurably lower numbers of cytotoxic T lymphocytes at baseline, elderly patients were able to mount an adequate response following inactivated influenza A virus vaccination.[152] These results support the notion that the healthy elderly are still able to mount an adequate immune response to pneumonia. Nasopharyngeal colonization with gram-negative bacteria has been reported to increase in elderly patients, but few studies have looked at the elderly living independently within the community.[49, 50, 181, 185] It is likely that the high rates of colonization are more representative of comorbid illnesses and therapy, in addition to the milieu in which these patients reside. The elderly have an increased incidence of bacteremia, urinary tract infection, diverticulitis, pneumonia, infective endocarditis, disseminated fungal infection, and reactivation of tuberculosis.[36, 161] Although immune dysfunction probably plays a role in these infections, the increased susceptibility of the elderly to infection may in part represent a synergistic effect of comorbid illnesses, nutritional status,[134, 161] and age-dependent organ dysfunction.[36, 178]

Nutrition In the Elderly

Saltzman and Peterson[161] noted a 41% to 85% prevalence of protein-calorie malnutrition while reviewing immunodeficiency in the elderly.

Impaired T-cell responsiveness and anergy are known immunologic sequelae of malnutrition and may contribute to the immune dysfunction of the elderly.[111, 161] The provision of nutritional, vitamin, and trace element supplementation for 8 weeks resulted in improved skin test response, increased T-lymphocyte numbers, and responses to mitogen.[31] Zinc may be especially important. Animal studies involving zinc-deficient mice have demonstrated reversible thymic involution and T-cell dysfunction with adequate zinc replacement.[56, 64] These studies have relevance in the elderly because the prevalence of deficient zinc intake and measurable zinc deficiency are 24% and 14%, respectively.[30] In a randomized controlled trial in institutionalized elderly, the administration of 220 mg of zinc sulfate twice daily resulted in increased numbers of circulating T lymphocytes, enhanced delayed cutaneous hypersensitivity, and immunoglobulin G response to tetanus vaccine.[42] Four randomized, double-blind, placebo-controlled trials involving zinc administration for the common cold have demonstrated a decrease in symptoms when compared with placebo.[3, 43, 71, 137] Four additional randomized controlled trials failed to document any clinical improvement with administration of zinc gluconate for the common cold, and in addition found no change in viral shedding.[40, 54, 173, 190] There are numerous proposed mechanisms by which zinc might exert some antimicrobial action,[137] but its clinical role has yet to be worked out. The precise role of vitamin replacement is not established, but clearly adequate caloric and nutritional support are important in the elderly.

Asthma and the Host Immune System

Chronic obstructive lung disease is a predisposing factor for pneumonia in the elderly, but asthma is not generally considered a significant independent risk.[51, 61, 133] Koivula et al,[108] however, in a population-based study of individuals more than 60 years of age in Finland, noted the prevalence of asthma to be 3.5%.[108] When compared with those patients who did not develop pneumonia, the adjusted relative risk for contracting pneumonia in asthmatics was 4.2 (95% confidence interval [CI], range 3.3–5.4), suggesting that asthma itself may predispose patients to develop infection. The presence of lung disease and bronchial asthma did not increase the risk of death. Postulated mechanisms by which asthma causes host immune system dysfunction have been reviewed (Table 1).[10, 25, 27, 84, 85, 97, 98, 117, 148, 149] In addition, mucociliary transport may be slowed by as much as 72% during an acute exacerbation.[130] Multiple authors have described impaired mucociliary transport in asthmatic patients.[10, 25, 97, 105, 117, 149] In addition, hypogammaglobulinemia was 4.8 times more likely to be identified in unselected asthmatics than in the normal population.[85] Of note, 10 of the 12 patients with hypogammaglobulinemia received a cumulative prednisone dose (or its equivalent) of $\geq$ 5 mg/day for at least 2 years. Because asthma in the elderly is less likely to be responsive to conservative therapy, more elderly asthmatics

Table 1. POSTULATED IMMUNE IMPAIRMENTS ASSOCIATED WITH ASTHMA

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Adapted from Drach FS, Bryant RE: Spotting the pneumococci in today's pneumonia milieu. J Respir Dis(14)2:198–216, 1993; with permission.

will be at risk of suffering the combined immune-altering effects of age, comorbidity, and immunosuppression.[18] In a survey of consecutive geriatric asthmatic patients in their pulmonary practice, Braman et al[19] noted that 22 of 25 patients more than 70 years of age required oral steroids in addition to inhaled corticosteroids, highlighting the potential clinical significance of iatrogenic immune deficiencies. The previously described immune host defense dysfunction may be significant, but may be less important than the combined effects of comorbid disease(s). Asthmatic patients more than 65 years of age have been shown to have six- to 10-fold higher mortality than younger patients, partially attributable to complicating illnesses and therapies, but in addition attributable to delays in presentation, increased noncompliance with medications, poor nutrition, and isolated living situations that predispose them to poorer outcomes.[18, 34, 151, 162]

PNEUMONIA IN ELDERLY ASTHMATICS

The Effects of Age

The separate effects of age and comorbid disease on the susceptibility of the elderly to infection are complex. Many studies have attempted to identify historical, clinical, and laboratory parameters by which physicians could appropriately stratify patients with pneumonia with respect to their need for hospitalization and intensive care.[17, 54, 61, 83, 120, 143] Farr et al[54] reviewed prognostic factors obtained by history that have been associated with death from pneumonia, and they identified 18 studies that showed an association between older age and death. Nine of the studies found an association using univariate analysis, and two studies found an association using multivariate analysis.[20, 37] In a recent study evaluating the utility of radiographic presentation of community-acquired pneumonia, the overall mortality rate of patients 65 years of age or older was 10.2% as compared with the 1.8% mortality rate of patients 45 to 64 years of age, further highlighting the risk of age and infection.[83] In a metaanalysis, Fine et al[62] noted 14 cohort studies that evaluated the

association of age and mortality, with a mean age difference in survivors versus nonsurvivors of 7.8 years. In the same study, logistic regression analysis performed on 85 cases noted an odds ratio of 1.05 (95% CI, range 1.01–1.09) of death for each 10-year increment in mean patient age. Although this metaanalysis found age to be significantly associated with death, the weight of comorbid illness was not addressed. Studies by Esposito et al,[46] Black et al,[17] and Lipsky et al,[120] which corrected for comorbid factors, found that age was not a significant risk factor for mortality. Using retrospectively derived prognostic parameters, Black et al[17] noted that ambulatory elderly patients were more likely to be admitted with pneumonia than younger patients. When a multivariate analysis was performed controlling for comorbid conditions, age was no longer predictive.[17] In a retrospective case control study, Lipsky et al[120] noted dementia, seizure disorders, and institutionalization to be associated with acquiring pneumococcal infections. In the same study, age was not significantly associated with pneumococcal pneumonia when corrected for comorbidities. These observations support the overriding importance of an individual's physiologic status as a determinant for initiating invasive life-saving medical therapy.

The Effect Of Asthma

The precise relationships between infection and asthma are unclear. As previously mentioned, Koivula et al[108] showed that elderly asthmatics have an increased risk of pneumonia when compared with the general age-matched population, suggesting that asthma per se may predispose elderly patients to pneumonia. Although this is a tenable hypothesis it is unclear whether comorbid illness or therapy with corticosteroids might have prevented detection of the separate effects of asthma as a risk factor for pneumonia. More extensive work has gone into trying to elucidate the mechanism by which infections may affect the risk of or perpetuate the course of asthma. Similarly it is not totally clear whether asthmatic patients have a different incidence or worsened prognosis with viral, bacterial, or combined infection.

Many studies have evaluated the role of preceding viral infection in the development of airway hyperresponsiveness in children. The role of infection in the pathogenesis of asthma and its exacerbations in adults continues to be controversial. Few studies have separated bronchial asthma from chronic obstructive pulmonary disease, hence there are few if any clinical data demonstrating whether asthma predisposes one to develop respiratory tract infections. In the only study addressing bronchial asthma as an independent comorbidity, Koivula et al[108] noted bronchial asthma to be second only to alcoholism as a risk for pneumonia. This study, involving elderly independent Finns, showed that asthmatics had an adjusted relative risk for pneumonia and hospitalization of 4.2 (95% CI, range 3.3–5.4) and 6.0 (95% CI, range 4.1–9.0), respectively, when compared with the remainder of the population. This

increased risk remained statistically significant after a multivariate analysis for all significant comorbidities. There is a need for further studies in this area.

Bacterial Infections and Asthma

Bacterial infections have a minimal or inapparent role in asthma exacerbations except for the recently described association of *Chlamydia pneumoniae* and the development of asthma.[80] In a study involving young asthmatics, McIntosh et al[129] found no difference in the bacterial isolation rates of pneumococcus, *Hemophilus influenzae,* β-hemolytic streptococci, *Staphylococci aureus,* or enteric bacteria when looking at symptomatic versus asymptomatic asthmatics. Several studies have suggested a possible role of *Mycoplasma pneumoniae* in the development of asthma exacerbations. In a study involving 77 wheezing asthmatics, from 8 months to 31 years of age, Gil et al[70] were able to isolate *M. pneumoniae* in 24.7% of subjects compared with 5.7% of controls. Several studies have associated *Mycoplasma* sp with asthma, but its clinical importance is still uncertain.[13, 94, 164, 182] In a study in adults, Hudgel et al[93] confirmed these results, finding no difference in bacterial isolation rates when comparing symptomatic versus asymptomatic asthmatics. In addition, Berman et al[14] using transtracheal biopsy, did not correlate bacterial isolation with exacerbations when comparing symptomatic versus asymptomatic asthmatics. Studies looking at antimicrobial therapy for acute exacerbations of asthma have found no difference in outcomes between those who received antibiotics and controls.[13, 92, 168] Exclusive of secondarily infected upper respiratory infection, bacterial infection appears to play a minimal role in asthma exacerbations and therefore antimicrobials are seldom indicated.

Chlamydia Pneumoniae and Asthma

C. pneumoniae causes a number of respiratory and nonrespiratory inflammatory conditions.[73] The seroprevalence in the population ranges from 30% to 50%, with about 50% positivity in older patients.[73] In a prospective study involving 365 Wisconsin outpatients, Hahn et al[80] assessed the association of *C. pneumoniae* infection with wheezing, asthmatic bronchitis, and adult-onset asthma. In the prospective phase, three (11%) of 27 patients with pneumonia and 16 (4.7%) of patients with bronchitis had positive serology for *C. pneumoniae.* Of these 19 infected patients, three (16%) had wheezing with their acute infection, and six (32%) developed bronchospasm during the ensuing 6 months. After controlling for confounding variables, a *C. pneumoniae* titer of 1:16 or more was associated with an odds ratio of 2.1 (95% CI, range 1.1–4.2) for developing wheezing. In the matched control phase of the study, 29.6% of *C. pneumoniae*–positive patients compared with 7% of controls were diagnosed with asthma, with an odds ratio of 7.2 (95% CI, range

2.2–23.4). This finding was further substantiated by demonstrating a dose–response relationship between titers and the presence of wheezing. *C. pneumoniae* titers of 1:16 and 1:128 or more were associated with odds ratios for wheezing of 1.2 (not significant) and 3.5 (significant), respectively. Eighty percent of patients diagnosed with asthma following their illness had a *C. pneumoniae* titer of more than or equal to 1:64, and of these six (75%) developed chronic asthma following bronchitis, and one (12.5%) following pneumonia. Asthmatic bronchitis was more likely to occur in older reinfected patients, raising the question whether *C. pneumoniae* might have exerted an immune-mediated effect on the lung.[73, 80]

In a follow-up study composed of asthmatics with and without chronic obstructive pulmonary disease (COPD), Hahn and Golubjatnikov[81] reported 100% *C. pneumoniae* seroreactivity in asthmatics, 80% seroreactivity in asthmatic bronchitis patients without antecedent asthma, and 52.8% seroreactivity in patients with nonwheezing respiratory illness. Additional studies have had similar results associating *C. pneumoniae* with asthma.[5, 79–81, 150] A recent community-based open-label treatment trial involving asthmatic patients with a mean *C. pneumoniae* titer of 1:128 showed significant improvement in 54% of patients after 4 weeks of varying antimicrobial treatments (doxycycline, azithromycin, or erythromycin), as reflected by improvement in forced expiratory volume in 1 second (FEV_1) and symptoms.[79] Nonresponders were more likely to be receiving inhaled corticosteroids, to have a lower mean FEV_1/forced vital capacity (FVC) ratio at baseline, and to have a significantly longer history of asthma symptoms prior to treatment. This is an interesting study, but it is hampered by the lack of a control arm and the association of significant impairment of pulmonary function tests prior to testing in the nonresponder arm. Grayston[74] found the incidence of wheezing and asthma to be no higher in *C. pneumoniae* than *M. pneumoniae* or viral respiratory disease (respiratory syncytial virus [RSV], influenza A and B, and adenovirus). This recent recognition of the association of *C. pneumoniae* with asthma is yet another linkage of infection to an inflammatory condition. The exact implications of the *Chlamydia*-asthma association are yet to be defined and further study is needed to characterize improved diagnostic and therapeutic options available to clinicians.

Viral Infection and Airway Hyperresponsiveness

In children, viral respiratory tract infections have been shown to play a significant role in the development of acute asthma, as well as contributing to the pathogenesis of airway hyperresponsiveness. Epidemiologic studies in children have established a convincing link between antecedent viral respiratory tract infection and acute asthma exacerbations, and as potential causative agent in the pathogenic process of airway hyperresponsiveness.[118, 172] Table 2 summarizes proposed patho-

Table 2. PROPOSED MECHANISMS OF VIRAL-INDUCED AIRWAY HYPERREACTIVITY

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Adapted from Gyetko MR, Toew GB: Immunology of the aging lung. Clin Chest Med 14:379–391, 1933; with permission.

genic mechanisms by which viral infections exacerbate pre-existing asthma, as well as cause airway hyperreactivity. Viral infections have been shown to decrease peak flow rates[75, 171] and induce airway epithelial damage, thereby potentially increasing antigenic exposure in the host,[113, 117, 159] which may result in increased airway reactivity in normal or genetically predisposed hosts.[75, 82, 116] Viral infections and influenza vaccination have been shown to cause nonspecific bronchial hyperresponsiveness in asthmatics.[99, 153] Hence, although clinical and experimental evidence support a causal link between neonatal and childhood RSV infections and bronchiolitis, and subsequent asthma, there is conflicting evidence that this occurs in adults.[118, 172, 175, 177, 180]

Epidemiologic studies have addressed the possible role of viral infection in asthma exacerbations. Pattemore et al[146] reviewed the epidemiology of viral illness and asthma and noted four studies in children that identified significantly elevated virus isolation rates in symptomatic asthmatics, compared with asymptomatic asthmatics.[91, 93, 100, 132] Rhinoviruses have been associated with the majority of cases of virus-mediated infective asthma, with RSV, parainfluenza, adenovirus, influenza virus, and coronavirus comprising the remainder.[11, 101, 135, 146] Lemanske et al[116] induced rhinovirus infections in 10 adults allergic to ragweed, noting increased airway reactivity to both allergen and histamine provocation. In addition, eight of 10 patients experienced a greater than 15% decline in FEV_1 within 6 hours of the antigen challenge. In a longitudinal study of adult asthmatics 19 to 46 years of age, Nicholson et al[141] identified nonbacterial pathogens in 44% of asthma exacerbations associated with cold symptoms. Twenty-four percent of laboratory-confirmed infections were associated with significant airflow obstruction. In this study, viral pathogens accounted for 93% of all infections, of which rhinovirus and coronavirus accounted for the majority. In children identification rates during exacerbation have approached 20% to 60%.[26, 91, 100, 129, 131] Viral respiratory tract infections are likely to play a role in adult exacerbations but to a lesser extent. Viral identification rates during exacerbation in adults range between 10% and 19%.[11, 93, 94, 146] Minor et al[131] and Hudgel et al[93] noted that viral isolation rates in adults were significantly lower than rates in children (10% to 13% versus 40% to 60%).[93, 94, 129] In a small

prospective study involving adult asthmatics 15 to 59 years of age, Beasley et al[11] reported an overall viral isolation rate of 10%, which increased to 36% in association with severe asthma exacerbations (FEV_1 < 60% or peak expiratory flow rate < 40%). Sixty percent of viral respiratory tract infections were associated with an acute asthma exacerbation. In a study of 253 exacerbations in 67 asthmatics, Kava[106] found that 25% of asthma exacerbations were associated with symptomatic respiratory tract infections, and 55% of respiratory tract infections were associated with an asthma exacerbation. In the same study, viral-associated asthma exacerbations had a more protracted course then did exacerbations unassociated with a viral illness, or an uncomplicated viral respiratory tract infection: 11.4 days versus 8.1 days versus 4.9 days, respectively. Although the isolation rates in adults are significantly lower than those in children, these studies support the notion that viruses contribute to exacerbation of bronchial hyperreactivity in adults as well as children.

All studies have not reported an association between antecedent viral infections and asthma. Tarlo et al[180] isolated virus in only 3% of adults with asthma exacerbations presenting with symptoms of an upper respiratory tract infection, a rate identical to the isolation rate of asymptomatic individuals. Similarly, Sokhandan et al[175] obtained nasal swabs for viral isolation from 33 of 35 adults during asthma exacerbations that necessitated emergency room evaluation. In total, 55.9% of patients had symptoms consistent with an upper respiratory tract infection, yet by immunofluorescence, culture, or complement fixation testing, none of these had evidence of viral infection. Sokhandan and coworkers rationalized that despite expecting a higher isolation rate in emergency room presentations, as compared with the rates noted in ambulatory clinics, this lower rate raised significant questions about the role of viral infections in adult asthma exacerbations. Hence, there are solid yet conflicting data concerning viral-mediated exacerbation of asthma in adults, with little specific data in the elderly.

Aspergillus In Elderly Asthmatics

Aspergillus can affect the asthmatic host by several pathologic mechanisms. It may cause a profound allergic reaction in atopic individuals with preexisting bronchial asthma, it may coexist by colonizing the respiratory mucosa, or it may progress to more severe invasive aspergillosis. Allergic bronchopulmonary aspergillosis (ABPA) is the most common allergic bronchopulmonary mycosis. It is characterized by fever, malaise, sputum production with brown mucous plugs, pulmonary eosinophilia, a significant allergic response in the bronchi and skin, and proximal bronchiectasis, in the setting of established asthma or another chronic lung disease such as cystic fibrosis.[103, 187] The clinical course varies from mild asthma exacerbations to severe pulmonary fibrosis following years of repeated inflammatory episodes. In 1952, Hinson et al[90] first described ABPA syndrome in three patients with

recurrent asthma, peripheral eosinophilia, fever, sputum production, and abnormal chest radiographs.[187] *Aspergillus fumigatus* later grew out of sputum culture. This association of *A. fumigatus* and ABPA has subsequently been well documented. Although *A. fumigatus* is responsible for the majority of cases, the syndrome may occasionally be caused by other *Aspergillus* spp, as well as other fungi.[147] Additional diagnostic considerations for *A. fumigatus*–negative patients with a compatible clinical syndrome are *Pseudoallescheria boydii, Candida albicans, Curvularia lunata, Rhizopus* spp., *Helminthosporium* spp, *Penicillium* spp, *Stemphylium* spp, *Torulopsis glabrata, Bipolaris* spp, *hawaiiensis,* and *Fusarium vasinfectum.*[7] No formal studies have evaluated the prevalence of ABPA in the elderly. In a recent study of asthmatics preselected for having positive immediate *A. fumigatus* skin tests, however, 28% of patients fulfilled clinical criteria for ABPA.[163] Of these episodes, 36% had proximal bronchiectasis on radiographic interpretation. In this study, the over-60 age group accounted for 24% of the study population, yet was responsible for 39% of ABPA diagnoses. In addition, 46% of the over-60 patients had a diagnosis of ABPA during the study, compared with only 18% of patients younger than 60 years of age. This preliminary information highlights the potential clinical significance of ABPA in the elderly population, hence enforcing our need to consider ABPA in patient evaluation.

Summary

In summary, infection clearly has a significant role in asthma. Although the evidence linking viral infection to asthma exacerbations and pathogenesis is convincing in children, it is less convincing in adults. The epidemiologic studies reviewed did not focus on the elderly population, hence we are required to extrapolate the above association of virus-mediated airway hyperresponsiveness in children and younger adults to consideration of the elderly patient. This area needs more work. At one time bacterial infections were considered a likely cause of asthmatic exacerbations; however, except for the recently proposed association of *C. pneumoniae* and asthma, and to a lesser degree *M. pneumoniae,* bacteria are considered to play a minor role in recurrent episodes of airway hyperresponsiveness in children and adults alike. Methodologic limitations of easily identifying infective agents causing lower respiratory tract infections severely limits progress in this area.

Perhaps the most important insight into the role of prior respiratory viral infection in secondary bronchial reactivity is provided by study of prior viral infections in patients with sinusitis or otitis media.[88, 170] The very elegant studies available from the examination of cultures, antigen detection, or serologic confirmation of middle ear or sinus aspiration specimens have shown a clear association between primary viral and secondary bacterial infection of the sinuses or middle ear.[2, 69, 76, 86] Unlike the normally sterile milieu of the sinuses and middle ear, the lower

respiratory tract lies distal to the heavily colonized oropharynx, thus impairing more precise microbiologic assessment.[16, 47] Clarification of the exact relationship between viral, bacterial, or combined infection in the asthmatic awaits a better assessment of microbial infection that can bypass contamination from the oropharynx. Considering the multitude of infectious agents and the expense and methodologic complexity of defining infections of the nose, oropharynx, lung, and gastrointestinal tract, it is amazing that we know as much as we do.

MANAGEMENT OF INFECTION

Prevention and Prophylaxis

Waning immunity is cited as a potentially correctable host defense defect in the elderly.[109] Despite the availability of vaccines for viral influenza, and *Streptococcus pneumoniae,* these important protective measures are often omitted. The viral influenza vaccine should be given each year in the late fall. The pneumococcal vaccine is especially important because it protects against invasive pneumococcal infection and its current formulation includes antigens from multidrug-resistant strains that would be more difficult to treat with antibiotics. Unfortunately, severely ill patients, those with comorbid diseases, and the immunocompromised elderly are substantially less likely to respond to this or other vaccines. Pneumococcal immunization is usually given at or about 65 years of age, but it should be given at a younger age to patients with cardiac, pulmonary, renal, or hepatic disease that would increase their susceptibility to invasive pneumococcal disease.[55, 138, 139] There is controversy over the desirability of repeated vaccination. Dermal reactivity to reimmunization is seldom a problem in those more than 65 years of age, however, and the elderly without comorbid disease show no statistical impairment of immunologic responsiveness to the vaccine.[139, 140] Five-year efficacy in immunocompetent 65- to 74-year-olds was 71% and in 75- to 84-year-olds was 67%.[167] Considering that data and conceding that definitive studies with elderly asthmatics are unlikely to become available, it seems prudent to provide pneumococcal immunization to elderly asthmatic patients on the basis of their other underlying disease(s) (i.e., cardiovascular disorders, chronic pulmonary diseases, renal failure, alcoholism, or hematopoietic malignancies), to begin before 65 years of age in the most vulnerable patients with comorbid disease, and to consider repeating immunization at approximately 5- to 7-year intervals. Better vaccines and better instruments for testing their efficacy in the elderly are needed.

If elderly patients with asthma are at greater risk of serious sequelae from viral infections then measures likely to reduce the risk of viral infection should be beneficial.[108] Societal practices also contribute to enhanced respiratory infection in the elderly. Vulnerable patients are

grouped together in nursing homes and often subjected to affectionate and effusive reunions with families, children, grandchildren, and other carriers of infectious microbes that can then be circulated rapidly among the susceptible residents. Adults have approximately four viral infections per year and children average six to eight per year;[76] thus, it is wise for grandparents and great-grandparents to avoid contact with children likely to have active viral infection, a logical but often unacceptable choice. Rhinoviral illness is often transmitted by infectious nasopharyngeal secretions and, therefore, is potentially amenable to reduction by barrier precautions, frequent hand washing, and returning babies to their parents if they need attention for their runny noses.[114]

The lay press has suggested that improved handwashing practices in nursery schools can reduce colds in the home by nearly 50%.[183, 188] This thesis is given credibility by studies documenting the transmissibility of viruses on fomites and the hands of volunteers, the frequency with which children and adults pick their noses or rub their eyes, and the infectivity of viruses inoculated onto the nasal mucosa or conjunctiva.[76, 89, 123] Thus appropriate attention to handwashing, disposal of soiled tissues, and interruption of the transmission of infected nasopharyngeal secretions should benefit the elderly. The common sense benefits from covering the mouth during a cough were recognized to reduce risks of transmission of tuberculosis in the 1960s,[155] and are also applicable to reduce transmission of certain viral infections. We need to document and expand our repertoire of ways of interrupting transmission of viral infections to our elderly and infirm patients. Risks of respiratory infection can also be associated with vocational or recreational exposures. Geographic and exposure risk factors associated with respiratory disease that are not host-specific for asthmatic patients are shown in Table 3.

It seems prudent to advise physicians caring for vulnerable elderly asthmatics to help prevent fluid retention secondary to cardiac, renal, or liver failure. Those at risk of aspiration due to hiatal herniae, gastroesophageal reflux, or presbyesophageal or other swallowing disorders should have thoughtful evaluation and advice as to precautions for eating, sleeping, and safe swallowing techniques.

Table 3. ENVIRONMENTAL AND ZOONOTIC EXPOSURES

Exposure	Pathogen
Birds (farm, pets, wild, tame, domestic, foreign)	*Chlamydia psittaci*
Parturient animals (sheep, goats, cows, cats)	*Coxiella burnetii*
Cave exploration, chicken or starling roosts, excavation in histoplasmosis areas	*Histoplasma capsulatum*
Dust storms or ground exposure in coccidioidomycosis areas	*Coccidioides immitis*
Ground squirrels, rodents, or burrows in Southwestern US desert	*Yersinia pestis*
Contaminated water and plumbing	*Legionella pneumophila*

Diagnostic Assessment

As discussed previously, asthmatic patients with respiratory disease usually have asthma that is not linked to bacterial infection and is not helped by antibiotics. Sputum purulence can be associated with eosinophil-rich exudates or with viral infection that confounds diagnostic assessment. Likewise, criteria for assessing the severity and need for hospitalization for an asthma attack are well defined and distinct from diagnostic assessment and criteria for hospitalization for pneumonia. This article addresses issues relevant to lower respiratory tract infection in elderly patients who happen to have asthma. In most instances concomitant asthma will have little effect on the most common bacterial causes of pneumonia in that group. In rare instances protracted therapy with high doses of corticosteroids may reactivate tuberculosis or opportunistic fungal or nocardia infections. Likewise *Pneumocystis carinii* infection can complicate high-dose corticosteroid therapy in relatively normal hosts. It is well to keep these situations in mind, but they are extremely rare (Table 4).

Diagnosis of respiratory infection in the elderly is based on the statistical probability of a specific infection considering host vulnerability, epidemiologic risks, and clinical presentation. Therapy is based on the clinical clues, laboratory evaluation, and the assessment of the severity of the patient's illness.

The cause of community-acquired pneumonia varies with the patient's age, comorbid disease, disability, and exposure to infectious agents. Pneumonia is generally attributed to *S. pneumoniae* (20% to 60%), *H. influenzae* (3% to 10%), gram-negative bacilli (3% to 10%), *S. aureus* (3% to 5%), legionella (2% to 8%), *C. pneumoniae* (4% to 6%), viral pneumonia (2% to 15%), and aspiration (6% to 10%).[9, 51, 112, 126] The cause of pneumonia is unknown in 20% to 30% of patients and the frequency of combined infection is probably higher than recognized. Kauppinen and coworkers suggested mixed infection may occur in more than a third of patients hospitalized with *C. pneumoniae*.[104] Lieberman and coworkers[119] reported age-specific etiologic data for pneumonia. Patients

Table 4. PULMONARY INFECTIONS RELATED TO CORTICOSTEROID THERAPY

Organism	Reference(s)
Aspergillus pneumonia	35, 156
Candida spp	156
Cytomegalovirus	156
Invasive aspergillosis	145, 194
Legionella spp	1
Mucormycosis	176
Pneumocystis carinii	1, 157, 165
Strongyloides stercoralis	102
Tuberculosis	166, 191
Varicella pneumonia	32, 136, 191

more than 65 years of age had pneumococcal pneumonia (46% to 57%), *H. influenzae* (4%), *M. pneumoniae* (4% to 13%), legionella (8% to 15%), and *C. pneumoniae* (24% to 28%). The latter statistic is comparable to figures cited by Grayston,[73] who noted an increased incidence of *C. pneumoniae* in the elderly. This finding has special relevance to the elderly asthmatic patient, who might be expected to have a higher likelihood of worsening asthma and a more prolonged illness after a *C. pneumoniae* infection.

Criteria For Hospitalization

There have been a series of elegant studies documenting risk factors associated with severe pneumonia and a bad prognosis.[20, 61, 62, 142] The features of the history, physical examination, or laboratory assessment associated with severe pneumonia that requires hospitalization and often admission to an intensive care unit are as follows:

History
- Age more than 65 years
- Comorbidity (COPD, diabetes mellitus, malignancy, immunodeficiency, fluid retention from heart, liver, or renal disease)
- Hospitalization within prior year
- Postsplenectomy
- Chronic alcoholism, malnutrition, immunosuppression

Physical Examination
- Respiration more than 30 breaths per minute
- Shock (blood pressure $\leq$ 90/60 mm Hg)
- Temperature greater than 101°F
- Altered consciousness or confusion
- Extrapulmonary signs of disease; meningitis, endocarditis, arthritis

Laboratory Findings
- White blood cell count less than 4000/mm^3 or more than 30,000/mm^3; more than 5% bands
- Significant elevation in bands
- $Pa_{O_2} \leq 60$ mm Hg or $Pa_{CO_2} \geq 50$ mm Hg on room air
- Elevated creatinine or BUN
- Hematocrit less than 30%, Hgb less than 9 g/dL
- Acidosis, disseminated intravascular coagulation, prolonged prothrombin time or partial thromboplastin time, thrombocytopenia
- Lobar pneumonia, multiple lobe pneumonia, cavitation, effusions, empyema, or rapid radiographic progression
- *S. aureus*, gram-negative bacilli, aspiration, or polymicrobic origin

Labored breathing, inability to mobilize secretions, and a rapidly progressive course necessitate evaluation for intubation and ventilatory assistance. Sicker and more vulnerable patients require more aggressive

diagnostic work-up, including bronchoscopy, aspiration of parapneumonic effusions, and monitored assessment in an intensive care unit. A clinical prediction rule for 30-day mortality in patients with community-acquired pneumonia has recently been studied.[58] A weighted point system, based on the number of adverse indicators, can be applied to calculate the patient's mortality risk group.[58, 60] This work is a significant advance and provides an improved structure for testing treatment decisions in patients with pneumonia.

Additional contributions have been made regarding indicators of mild disease that permit ambulatory treatment of patients with pneumonia.[52, 58, 59, 189] Criteria supporting the appropriateness of outpatient therapy include youth, lack of comorbid diseases, and absence of features indicating severe infection or an especially virulent pathogen:

Normal Host
- Age less than 50 years who can and will take medication dependably (and will communicate if disease worsens)
- Lacks host defense defects associated with cardiac, renal, or liver failure, cerebrovascular disease, debility due to malignancy, chronic lung disease, immunosuppression, or nursing home residence

Objective Features Suggesting Mild Disease
- Historical and Physical Findings
  - Nonprogressive clinical course
  - Normotensive, normothermic, alert, and oriented patient with normal respiratory rate, pulse less than 125, and no signs of extrapulmonic sepsis
- Laboratory Findings
  - Normal oxygenation, acid–base balance and hemoglobin levels
  - Postintervention PEFR or FEV_1 greater than 50% of baseline values
  - Normal platelet, white blood cell, and differential leukocyte count
  - Normal renal function and coagulation values
  - Minimal bronchopneumonia without pleural effusion, cavitation, or empyema
  - Probability of low-risk pathogens

The authors[58] emphasized that clinical judgment should supersede their guidelines and that broader applications await further testing. Interestingly, bronchial asthma was not associated with an adverse prognosis.[58]

Suggestions for antimicrobial therapy of patients requiring hospitalization for community-acquired pneumonia have been nicely summarized by the recent works of the American Thoracic Society and Bartlett and Mundy.[9, 142] Empiric therapy of elderly patients requiring hospitalization for pneumonia usually includes cephalosporins to treat pneumococcal or *Hemophilus* strains, and macrolides with or without rifampin for Legionella. Patients at risk of gram-negative bacillary, staphylococcal, or aspiration pneumonia are treated with regimens shown in Table 5.

Table 5. RECOMMENDED TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA IN THE ELDERLY

Suspected Pathogen	First Choice	Alternatives
Streptococcus pneumoniae	Ceftriaxone/Cefotaxime*†	Vancomycin Macrolides‡ Cefuroxime
Hemophilus influenzae	Ceftriaxone/Cefotaxime†	β-lactamase inhibitor combinations§ Parenteral fluoroquinolones‖ Azithromycin
Aerobic gram-negative bacilli	Cephalosporins as above with or without aminoglycoside‖	Imipenem/meropenem**†††‡‡ Parenteral fluoroquinolones
Staphylococcus aureus	Nafcillin	Cefazolin/Cefuroxime Vancomycin for methacillin-resistent *Staphylococcus aureus*
Polymicrobic anaerobic	Clindamycin plus cefotaxime	β-lactamase inhibitor combinations§
Legionella pneumophila	Parenteral erythromycin-azithromycin‡‡§§‖‖¶¶[110, 122]	Rifampin Parenteral fluoroquinolones
Mycoplasma pneumoniae (rare)	Macrolides¶¶[110]	Doxycycline Levofloxacin***
Chlamydia pneumoniae	Macrolides¶¶[110]	Doxycycline Levofloxacin***
Chlamydia psittaci or *Coxiella burnetii*	Doxycycline	Azithromycin Levofloxacin***

Hypotensive or critically ill patients should also receive vancomycin.

*Severely ill patients require broader coverage according to risk of specific diseases. Similarly, patients with risk of multiple pathogens like legionella, mycoplasma, or *C. pneumoniae* plus concomitant bacterial disease will require erythromycin, another macrolide, doxycycline, or a parenteral fluoroquinolone in addition to specific coverage for *S. pneumoniae* or other bacteria likely to be present. Antipneumococcal coverage is always necessary because of the frequency of pneumococcal pneumonia. Multidrug-resistant pneumococcal pneumonia can probably be treated adequately with high-dose cephalosporins but patients at risk of concomitant endocarditis, meningitis, or endophthalmitis may require concomitant parenteral vancomycin, meropenem, or rifampin.

†Erythromycin, azithromycin, or clarithromycin.

‡β-lactamase inhibitor combination: ampicillin-sulbactam, ticarcillin-clavulanate, piperacillin-tazobactam.

§Parenteral fluoroquinolones: ciprofloxacin, levofloxacin, Trovofloxacin.

‖Aminoglycoside or parenteral fluoroquinolone is added to ceftriaxone or cefotaxime.

¶Imipenem or meropenem is indicated for severely ill immunocompromised patients with risk of nosocomial infection.

**Patients with comorbid disease are diagnosed and treated according to risks of specific diseases or complications of organ failure. Patients with AIDS, neutropenia, and leukemia or organ transplants require evaluation for opportunistic infections. Severely ill patients require more invasive diagnostic studies.

††Patients with gram-negative bacillary pneumonia caused by *Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter* or *Serratia* spp should receive two antibiotics effective against the suspected pathogen (usually a β-lactam plus an aminoglycoside or parenteral ciprofloxacin (depending on renal dysfunction or prior antibiotic therapy).

‡‡Patients with organ failure or shock should receive two agents effective against the primary pathogen plus therapy for intracellular pathogens like *Legionella* spp, *M. pneumoniae*, or *C. pneumoniae.*

§§Victor Yu, MD, personal communication, April 1997.

‖‖Patients with pneumonia and prominent wheezing or exacerbations of asthma during infection should have treatment that includes coverage for *C. pneumoniae* while that diagnosis is being confirmed.

¶¶Young, overtly healthy patients with minimal bronchopneumonia infiltrates and no indicators of serious disease can be treated with macrolides as outpatients.

***Only to be used in the elderly, nonmenstruating patient.

Hypotensive patients with organ failure or fulminant infection receive broadly based empiric therapy until diagnostic studies permit institution of pathogen-specific therapy. Patients with multidrug-resistant pathogens are an increasing problem; their therapy must be individualized.

Of equal importance is the rapidly progressive pneumonia that may occur with bacteremia or with infection caused by *S. pyogenes*, plague, primary viral influenza, or staphylococcal pneumonia complicating viral influenza. Primary fungal pneumonia with blastomycosis, histoplasmosis, coccidioidomycosis, or cryptococcosis rarely causes fulminant infection.[126] Perhaps the most common fulminant pneumonia in the elderly is bacteremic pneumococcal pneumonia, which may present abruptly with shock in the absence of cough or sputum production.

Inpatient Management

Penicillin-resistant pneumococcal infection has become a widespread problem in the United States.[6, 127] In many areas of the country, 20% to 30% of strains will have intermediate to high-level resistance to penicillin and, therefore, penicillin is no longer the drug of choice for the primary treatment of suspected pneumococcal pneumonia.[9, 20, 112, 142, 169] Pneumococcal pneumonia caused by strains with intermediate penicillin sensitivities of 0.1 to less than 1.0 μg/mL can be treated with cephalosporins like ceftriaxone (1 to 2 g/day), or cefotaxime (3 to 6 g/day). Patients with meningitis or fulminant pneumococcal infection should be treated with vancomycin plus cefotaxime or ceftriaxone until sensitivity data become available. It is important to remember that ceftizoxime is 10- to 100-fold less active than cefotaxime or ceftriaxone against penicillin-resistant pneumococci.[78] It has been suggested that cefotaxime dosage can be increased to 12 to 24 g daily to treat critically ill patients with marginally sensitive pneumococci.[184] The applicability of this approach requires further study.

Outpatient Management

Elderly asthmatic patients with pneumonia are usually hospitalized because they are at greater risk of serious infection. The need for admission is based on the evidence of the severity of their infectious disease, and the severity of their asthma. Patients who are overtly well, who have indicators of mild disease, and who are clinically stable, however, may be treated as outpatients and followed carefully.[58] Although an algorithmic approach to triaging the elderly patient may give a sense of false security, the "healthy" elderly patient with posttreatment FEV_1 or peak expiratory flow rate (PEFR) greater than 60% of previous best or of predicted may be considered for outpatient management.[15] Eligibility for ambulatory care requires a cooperative and dependable patient with an adequate support system to verify that the patient is taking and

retaining medicines (i.e., not vomiting them up) and responding to ambulatory antibiotic therapy.

Oral antibiotics for the elderly asthmatic patient with pneumonia must provide adequate coverage for *S. pneumoniae* and *H. influenzae.*[9] Broader-spectrum oral antibiotics like ampicillin-clavulanate, cefuroxime, or azithromycin meet this need. Alternative combination therapy with 1 g of parenteral ceftraxione and oral macrolide therapy provides substantial coverage until the patient's course and treatment can be reviewed the next day. Although oral fluoroquinolone treatment of pneumococcal pneumonia has been considered controversial in the past, the newer agent levofloxacin may be an acceptable alternative as experience is gained with its use.[57, 122] *M. pneumoniae* or *C. pneumoniae* can be treated with macrolides, doxycycline, or the fluoroquinolones cited previously.

Atypical pneumonia in the elderly asthmatic patient is less likely to be due to *M. pneumoniae,* but is often caused by *C. pneumoniae.*[119] The latter infection may exacerbate prior respiratory disease in the asthmatic patient or cause pneumonia presenting with new-onset asthma.[79, 106] The disease usually moves slowly through family members, causing complaints of pharyngitis, sinusitis, dry and poorly productive cough, headache, and malaise. The disease may cause a persistent illness with chronic circulating immune complexes that enhance atherosclerotic disease in elderly patients.[160] While the magnitude and frequency of that phenomena are being clarified scientifically, it seems prudent to initiate therapy early in the course of illness because of the potential benefits of shortening the duration of infection, ameliorating effects of asthma, and reducing risk of vascular disease.

Uncomplicated pneumonia caused by *S. pneumoniae, H. influenzae,* or *M. pneumoniae* usually can be treated adequately in 7 to 10 days. *C. pneumoniae* generally is treated for 5 days with azithromycin or 10 to 14 days with other agents. Legionella pneumonia in the compromised patient may require 21 days of treatment.[142]

There has been some concern over the use of fluoroquinolones as primary treatment of respiratory tract disease.[186] Fluoroquinolones are contraindicated in pregnancy and therefore should not be used in sexually active women whose risk of pregnancy is uncertain. Ciprofloxacin is known to impair clearance of theophylline and can only be used with close monitoring of theophylline blood level,[115, 186] and sparfloxacin has an increased risk of photosensitivity. Levofloxacin and sparfloxacin do not affect theophylline metabolism but greater experience is required to demonstrate their efficacy as alternatives to parenteral therapy for elderly asthmatics with pneumonia.

The new fluoroquinolones are less active than ciprofloxacin against *Pseudomonas aeruginosa* and most fastidious gram-negative aerobic bacilli.[186] Ciprofloxacin is the fluoroquinolone of choice against these pathogens[63] and is used in conjunction with another effective parenteral agent in hospitalized patients. As a class, the fluoroquinolones lack dependable efficacy against *Stenotrophomonas* and *Nocardia* spp. The fluoroquinolones

have no antiviral or antifungal activity and should not be used as single-drug therapy for mycobacterial infection. The place of the new fluoroquinolones for treatment of polymicrobial anaerobic infection or fulminant pneumonia is not established. The breadth of the spectrum of activity of the fluoroquinolones has been responsible for their widespread misuse. Enthusiasm for their use has obscured the fact that their overuse increases the risk of emergence of fluoroquinolone resistance, thereby jeopardizing the future of even better fluoroquinolones currently under development.

We need to reiterate the importance of defining the most likely microbial cause(s) of pneumonia prior to selecting an antibiotic to eradicate the pathogen causing infection. Focusing on the patient's risk of infection and the pathogen(s) causing it makes it easier to identify appropriate diagnostic studies and to remain alert to errors of diagnosis and treatment.

Therapy of Viral Infection

Viral respiratory diseases of elderly asthmatic patients are essentially the same as those of other patients of comparable age or debility. Illness from viral influenza A can be ameliorated by early treatment with either amantadine or rimantidine.[121, 135] Amantadine is primarily excreted by the kidneys, so the dose should be adjusted to reflect reduced renal function in the elderly.[23] The ordinary amantadine dose of 100 mg twice daily is usually adjusted to 100 mg daily in the elderly or renally impaired patient. Rimantidine is excreted primarily by the liver, so its dosage need not be adjusted for renal dysfunction.

Patients with fulminant influenza A, influenza B, or respiratory syncytial viral (RSV) infection have been successfully treated with inhalational ribavirin.[107, 121, 128] This experience has been largely limited to severely ill patients requiring ventilatory assistance in an intensive care unit or patients with unusually severe host defense defects owing to liver, lung, or bone marrow transplantation, women in the third trimester of pregnancy, and a few very sick patients with ostensibly normal host defenses.[49, 193] The experience of RSV pneumonia in bone marrow transplant recipients suggests that treatment within the first 4 days of illness, prior to onset of clear-cut respiratory insufficiency, is required to modify the nearly 100% mortality seen in such patients.[193] Treatment can be given as an 18-hour inhalation procedure or as a higher-dose treatment given four times daily. Current experience suggests that concomitant intravenous gamma globulin administration is helpful in bone marrow transplant patients with RSV pneumonia.[49, 193] Although elderly patients are known to be at increased risk of severe RSV, influenza A, or influenza B infection, most elderly patients with those infections will go undiagnosed, and will not receive ribavirin therapy. Ribavirin therapy should be thought of as a potentially useful therapeutic alternative

for critically ill elderly patients whose course suggests RSV or influenza A or B infection.

Likewise, patients with primary herpes simplex, pneumonia, chickenpox pneumonia, or cytomegaloviral pneumonia can benefit from appropriate antiviral therapy with acyclovir, gancyclovir, or foscarnate. These illnesses are rare in the elderly asthmatic patient but need to be considered in the context of concomitant illness such as leukemia, lymphoma, and acquired immunodeficiency syndrome.[135, 195]

Therapy for Fungal-Mediated Hypersensitivity

ABPA may occur as a complication of asthma or cystic fibrosis. Patients usually require protracted therapy with prednisone, and their disease often relapses when the prednisone dose is reduced. Treatment with antifungal agents has been limited by the inability of current antimicrobials to eradicate aspergillus from bronchopulmonary tissues. At least three nonrandomized studies, however, have demonstrated a benefit from oral itraconazole therapy coupled with steroid therapy,[38, 67, 144] as reflected by reduction in serum immunoglobulin E, eosinophilia, and improvement in FEV_1 during therapy with itraconazole.[38, 124] These studies support an adjunctive role for itraconazole that may permit reduction, or rarely cessation, of prednisone ABPA therapy. Controlled trials are needed to document the validity of this contention. Likewise, evaluation of newer, more potent therapy for aspergillus pulmonary infection is badly needed.

CONCLUSION

In conclusion, asthma is underrecognized in the geriatric population and has some special considerations. Although data are lacking in the elderly, epidemiologic studies in younger age groups strongly suggest the causative and provocative roles of infection in asthma. Future evaluation must be performed to better characterize what role viral and bacterial infections have in the geriatric population. As the role of *C. pneumoniae* and other infections in asthma is better defined, more specific therapy may be possible. The normal lung defense mechanisms decline with age, but clinical disease and therapeutic strategies are more dependent on organ dysfunction and underlying comorbid diseases. Thus assessment and specific therapy are dependent on an individual's physiologic health rather than chronologic age. For now, selection of therapy should be based on host vulnerability, the epidemiologic risk of infection, the severity of the patient's infection, and the virulence of potential pathogens. Although conceding the importance of antimicrobial therapy once infection occurs, one must continue to stress the importance of good hygiene, adequate nutrition, proper surveillance of the patient's

asthma, and more vigilant use of vaccines to prevent infection in asthmatic patients.

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