THE CLINICAL SPECTRUM OF DISEASE IN ADULTS

2

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2.1 INTRODUCTION

Since the various viruses are discussed in detail in other chapters, this is an overview of the clinical findings associated with respiratory viruses, a re-look at the role bacteria play in respiratory infections, viral respiratory infections in patients with airways damaged by tobacco smoke or other toxic chemicals, previous chronic infection, antibody deficiency, or inherited disease, and pneumonia due to viruses usually restricted to the upper airways in patients with severe immunodeficiency.

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2.2 COMMON COLDS

What is condescendingly described as the common cold has proven to be a complex melange of symptoms, agents and therapeutic challenges. Indeed, this medical syndrome has become a symbol for the limits of scientific competence: '...but you can't cure the common cold'. Nevertheless, the five decades since World War II have witnessed a very large expansion of what is known about colds. Previous to that time a great deal of effort had resulted in a few small steps forward. There was increasing assurance that filterable agents rather than bacteria were primarily involved [12]. Colds may indeed be common, the average adult experiencing two to four episodes a year, but the investigations over this period have revealed literally a world of viral agents. Causes for colds encompass both DNA and RNA viruses, membrane-bound as well as unenveloped. Beyond this there is a small group of tantalizing illnesses for which no agent can be detected, some of them having a glimmer of evidence that they are transmissible, and some whose explanation in terms of infectivity continues to elude the most vigorous attempts at definition.

2.2.1 SYMPTOMATOLOGY

The hallmark of a cold is nasal discharge and obstruction. This can vary considerably in degree, however. Some colds qualify as 'dry' because there is very little discharge whereas

others are truly 'streaming'. Sneezing is a harbinger of increased inflammation in nasal passages and may be associated with infection as much as allergy. Some viral upper respiratory infections begin with a sore throat. When the patient is examined all that can be seen is the cobble stoning produced by hyperplastic lymphatic tissue on the posterior pharyngeal wall. Subsequently nasal obstruction and streaming begin. Hoarseness is not uncommonly associated with a cold and, of course, this can be either the initial symptom or the symptom which dominates the entire illness.

Sir William Osler's description of a cold still deserves mention: '... the patient feels indisposed, perhaps chilly, has slight headache, and sneezes frequent .... There is usually a slight fever .... At first the mucus membrane of the nose is swollen, 'stuffed up', and the patient has to breathe through the mouth. A thin, clear irritating secretion flows, and makes the edges of the nostrils sore .... Usually, within thirty-six hours the nasal secretion becomes turbid and more profuse, the swelling of mucosa subsides ... and gradually, within four or five days the symptoms disappear'.

Useful distinctions are observed in the symptoms produced by the different agents causing colds. Clinical studies of rhinovirus infections show that after a period of incubation that varies from 2–6 days, a sore throat occurs, followed by cough 2 days later [1]. The most constant measure of the severity of a rhinovirus infection is the amount of nasal discharge. In volunteers at the Common Cold Unit a wet cold might cause the use of up to 26 paper handkerchiefs on the worst day. However, the amount of discharge is highly variable and some colds are stuffy and relatively dry. The amount of nasal discharge varies throughout the day in a diurnal fashion: discharge is greatest during the morning and tapers through the day with a slight increase during the late evening [15]. When cough frequency was assessed by tape recording, a diurnal variation in frequency was also observed [9]. Here, coughs were more frequent between noon and 6:00 p.m. and less frequent between midnight and 6:00 a.m. There was marked variability in the frequency of coughing between patients; many patients coughed as often as 300 to 400 times in a 6-hour period and occasional patients coughed as many as 800 to 1300 times. The median range was between 12 and 377 for a 6-hour period. Patients were not aware of a variation in cough frequency throughout the day.

Constitutional symptoms can be associated with all agents causing colds. Fever, chills, malaise and myalgia, along with a deep cough are the hallmark of influenza, but can occur in varying degrees with the other agents. Fever is not common in rhinovirus infection, but a few patients complain of chills and myalgias. Rhinoviruses are isolated from some patients presenting with clinical syndromes more severe than a cold: children with bronchitis or bronchopneumonia, adults with fever and laryngitis plus nasal discharge. Contrariwise, nasal stuffiness may be a small part of the illness or acknowledged only on direct questioning in patients with influenza. Virus strains associated with a particular set of symptoms when isolated from one individual do not necessarily produce the same set of symptoms when experimentally inoculated into a volunteer [18].

Where predominating symptoms are pain around the eyes and discomfort over the bridge of the nose and in the face, some patients complain that instead of a cold, they have sinusitis. A study using magnetic resonance imaging (MRI) detected abnormalities in the ethmoid or antral sinuses associated with acute experimental rhinovirus infection [19]. All subjects were young adults between the ages of 18 and 40 years. Sinus involvement was associated with increased levels of nasal secretion. Three subjects had mucosal thickening and one an air–fluid level. One had right ethmoid thickening, one bilateral ethmoid

thickening, one right antral thickening and one right antral fluid. Three additional subjects had right antral thickening on a pre-challenge MRI. Three of the four subjects had a follow-up MRI done 37 days after challenge. This showed that the sinuses had returned to normal. No antimicrobial treatment was given. There is, therefore, an overlap between the signs and symptoms of viral colds and those of what is usually presumed to be acute bacterial sinusitis.

2.2.2 PHYSIOLOGY

Physiological measurements in volunteers experimentally infected with coronavirus 229E showed increases in nasal airway resistance and mean nasal mucosal temperature whether or not there was clinical evidence of infection [3]. Mean ear temperature (recorded near the drum by a probe) also increased in both the clinically and subclinically infected groups. Blood flow in the nasal mucosa, measured by the ^{133}Xe washout method, increased in the clinically infected group only. Nasal airway resistance and blood flow correlated with the severity of the symptoms. Increase in secretion followed the changes in the other parameters.

2.2.3 THE ROLE OF BACTERIA

The evolution of the thick, turbid nasal discharge from one that is clear and thin is not necessarily associated with the presence of pathogenic bacteria [24]. More than half of 55 volunteers developed purulent discharge during the course of a naturally acquired cold. Despite repeated sampling, however, only 16% became colonized with *Staphylococcus aureus, Haemophilus influenzae, Streptococcus pneumoniae* or β-haemolytic streptococci. Light and scanning microscopy of nasal biopsies from 29 student volunteers with naturally acquired colds showed sloughing of epithelial cells, but preservation of the epithelial lining and structurally normal cell borders. The nasal epithelium of infected and normal individuals could not be distinguished by light microscopy in biopsies taken at 2 and 14 days after the onset of symptoms. The epithelium and lamina propria showed an increase in the number of neutrophils by the second day of illness. The acute stage was also characterized by an increase in the extravasation of erythrocytes [23]. In none of these studies, however, was the infecting virus identified. Colds are, therefore, associated with non-destructive infection of the nasal epithelium with subsequent polymorphonuclear leucocyte infiltration and exudation even in the absence of complicating bacterial colonization.

2.2.4 AGENTS ASSOCIATED WITH COLDS

Using sensitive tissue and organ culture methods, agents can be cultivated from two-thirds to three-quarters of adults with colds [10,20]. Rhinoviruses are the single most common type of agent, accounting for 40–50% of isolates. Organ cultures enhance the recovery of rhinoviruses. Beyond the identification of agents that are clearly rhinoviruses, however, lie additional agents which can be established as chloroform stable by means of further testing in human volunteers. It is not completely clear whether these replicate in any *in vitro* system, but it is possible that they represent a further group of rhinoviruses causing a proportion of those colds from which no agent is routinely recoverable.

Coronaviruses cause approximately one-fifth of colds, although their identification in survey studies is very laborious. However, when organ and tissue culture-negative specimens were subsequently passaged in human volunteers, only one additional agent was found to be chloroform sensitive and capable of belonging to this group [10]. It is likely that coronaviruses cause colds less frequently than rhinoviruses, but are still deserving of the term 'common'. Infections with influenza and parainfluenza viruses, respiratory syncytial virus and adenoviruses are also associated

with cold syndromes. However, the frequency with which they produce common colds relative to rhinoviruses and coronaviruses is highly variable and depends upon the year in question. Influenza A and B viruses may be responsible for up to 10% of respiratory illness in epidemic years. Parainfluenza viruses, adenoviruses and respiratory syncytial virus share about 10% of the burden of illness in adults.

2.3 VIRAL PNEUMONIA

The viruses which have concerned us in causing illness of the upper respiratory tract may on occasion also involve the lower respiratory tract. The viruses most likely to produce these effects in adults are influenza, parainfluenza, respiratory syncytial (RS) virus and adenoviruses. The occurrence of severe pneumonia in immunosuppressed adults is a special case to be considered in more detail below. However, viral pneumonia occurs even in previously healthy adults. Marrie, Durant and Yates [11] prospectively surveyed 719 cases of both community-acquired and nursing home originating pneumonia over a 5-year period. Viruses were the cause in 72 cases (10%). No aetiology was apparent in 47%. Influenza A and B viruses were responsible for 57 of these, parainfluenza 3 for 18 cases and parainfluenza 1 and 2 for seven cases.

Because adult experience with RS virus is almost entirely due to re-infection, it is often presumed that these infections are clinically mild. Routine testing for RS virus in 2400 patients admitted to hospital with pneumonia in Sweden revealed 73 whose clinical diagnosis had been considered to be RS virus pneumonitis [21]. Diagnosis was based upon detection of RS virus in nasopharyngeal aspirates or a four-fold rise is specific antibody titre or the presence of anti-RS virus IgM serum antibody was present. Altogether, 36 patients had documented RS virus infection together with clinical signs of pneumonia and infiltrates on chest X-ray. Of these, 16 had distressed respiration, a preponderance being exacerbation of underlying obstructive lung disease.

Ruben and Nguyen [14] reviewed the subject of RS virus pneumonia occurring in adults and noted that 44% had respiratory distress. The clinical features are not specific and knowledge of an RS virus outbreak in the community might suggest the diagnosis.

Adenoviruses are some of the most frequent causes of lower respiratory tract disease in adults. These infections can be clinically severe, and even fatal in immunosuppressed bone marrow transplant (BMT) patients. There is usually an upper respiratory prodrome for 4 to 7 days preceding presentation with pneumonia.

2.4 RESPIRATORY VIRAL INFECTIONS IN CHRONIC LUNG DISORDERS

Stenhouse showed in a controlled, prospective study that rhinovirus infection was more likely to be associated with acute lower respiratory tract symptoms even while it was less common in patients with bronchitis than in a comparison group [17]. Virus infections are associated with approximately one-third of exacerbations of chronic obstructive pulmonary disease [4]. Rhinoviruses were found in 2.7% of stored, frozen, sputum specimens from episodes of exacerbation, in contrast to 0.55% of remission interval sputum specimens. Single-agent antibody titre rises to viruses (influenza A and B, parainfluenza virus types 1, 2 and 3, RS virus, adenoviruses, coronaviruses) or *M. pneumoniae* in 24.7% of exacerbations and in 13.8% of remission specimens. Coronavirus and influenza virus A were more often associated with exacerbations than remissions. In this study virus infection was not consistently associated with worsening of respiratory function. One-third of all isolations occurred during a period when there was no compromise of respiratory status. Titre rises to *M. pneumoniae* occurred in association with titre rises to one or more respiratory viruses. A low recovery rate

for rhinoviruses may have been due to the extended period of frozen storage.

Smith *et al.* [16] found rhinoviruses, influenza viruses, parainfluenza viruses and coronaviruses significantly associated with acute respiratory illness in patients with chronic obstructive pulmonary disease (COPD). There were 272 detections in 1030 follow-up intervals over an 8-year period. Fifty-three of the 272 infections studied were due to influenza viruses A and B, 17 of which were of the 'influenzal-type' clinical syndrome; 56 of the 272 infections were due to rhinoviruses, only one of which was an 'influenzal-type' syndrome. Patients with an influenzal-type clinical syndrome were most likely to have viruses detected (28.9%). Illnesses with cough and sputum were next most likely (20%). Illnesses confined to the upper respiratory tract were least likely (11.4%). Between 40% and 80% of the acute respiratory illness in COPD patients had no discernible aetiology, a proportion similar to the rest of the population. In this study there was no evidence that patients with COPD were more susceptible to virus infections. However, patients with COPD were more likely to develop increased cough and lower respiratory tract symptoms during rhinovirus infections than were normal subjects or those with mild COPD.

Considerable evidence has accumulated to show that cold viruses are associated with exacerbations of asthma in adults as well as children. The prevalence with which viruses can be identified in such attacks is lower than in children, but there is a correlation between the frequency of virus detection and the severity of the illness. Increases in the frequency of asthma during winter months correlate with the prevalence of common cold viruses during those periods [2]. The exposure of patients with chronic chest disease to other individuals with colds can result in the development of respiratory symptoms and exacerbation of the underlying illness [25]. In patients with asthma, 34% of the exposures resulted in symptoms. Lower respiratory tract involvement persisted for up to 33 days in some patients. It was possible to identify a viral pathogen in one-third of the exposure episodes; rhinoviruses, coronaviruses and respiratory syncytial virus were implicated. Paranasal sinus infection commonly coexists with asthma in adults. In a study where radiographically abnormal sinuses were aspirated and cultured, one-third had viruses detected where the lavage fluid obtained was abnormal [13].

Rhinovirus was administered experimentally to a group of 21 adult patients with asthma. In four of these patients histamine responsiveness was increased and forced expiratory volume (FEV_1) was significantly reduced subsequent to infection [6]. None of a group of volunteers without asthma showed such changes, even though they developed symptomatic colds after inoculation. It is possible that viruses other than rhinoviruses are more apt to be associated with airway hyperresponsiveness and likely that adults are less susceptible than children. Nevertheless, virus infection did trigger wheezing in some adult patients with asthma under well-controlled conditions.

2.5 RESPIRATORY VIRAL INFECTIONS IN IMMUNOCOMPROMISED ADULTS

Influenza, parainfluenza, respiratory syncytial and adenoviruses have all been shown to cause serious lower respiratory illness in immunocompromised adults. The main subjects for systematic study have been patients about to undergo or who have undergone BMT. For example, severe RS virus disease was reported in 11 immunocompromised adults [5]. Six had had BMT, four organ transplantation, and one T-cell lymphoma. Patients presented with fever, cough, rhinorrhoea, nasal congestion and otalgia. Chest radiography showed diffuse interstitial pneumonia; there was also radiographic evidence of sinusitis. Half of the BMT patients died while 36% of all the patients died.

In a larger series of 74 BMT patients from March 1987 to April 1988, there were eight cases of acute lung injury due to RS virus. In all cases there were initial upper respiratory tract symptoms (cough) followed by evidence of lower respiratory tract involvement. Six of eight patients had pulmonary infiltrates on chest X-ray. Six of the eight cases became ill before engraftment (<10 days after BMT) of whom four had severe diffuse pneumonia and died despite treatment with ribavirin. Six of the eight patients had abnormal sinus radiographs and went on to have drainage procedures. Autopsy findings in all patients who died showed organizing diffuse alveolar damage, with lung disease being the predominant contributor to death. This was also true clinically, three of the patients dying of respiratory failure, while one died of refractory hypotension after 3 days on the ventilator. Failure of lung repair occurred even though there was evidence that the treatment had eliminated the virus from the lower respiratory tract in three of the four patients who died. It was suggested that the chemotherapy and radiation treatment given before BMT rendered the patients incapable of generating a normal reparative response [8].

The role of engraftment in susceptibility to severe RS virus infection was evaluated in 31 of 199 BMT patients who developed RS virus infection over a period of 3 months, beginning January, 1990 [7]. Eighteen patients developed pneumonia, of whom 14 died. Pneumonia was more common in patients who became ill before engraftment had occurred. Early therapy with ribavirin was thought to be helpful in patients with pneumonia. Seventeen of 18 pneumonia patients were positive on broncheoalveolar lavage (BAL) for RS virus. The other patient had an endotracheal tube aspirate that was positive. Eleven of 14 pre-engraftment patients developed pneumonia and seven of 17 post-engraftment patients did so. One patient with *Pneumocystis carinii* pneumonia who had been ill for some weeks had a superinfection with RS virus. Two other patients had both RS virus and CMV in BAL specimens. Fourteen of 18 pneumonia patients had diffuse, bilateral infiltrates. Autopsy histology showed diffuse alveolar damage. RS virus was able to be detected by immunofluorescence staining in bronchiolar and alveolar epithelium and in cells sloughed into alveolar air spaces. Patients dying of pneumonia shed RS virus from 11 to 22 days. Nine of 11 pre-engraftment pneumonia patients died as compared with five of seven post-engraftment pneumonia patients, not a meaningful difference. Ribavirin treatment was not given to five patients who died of pneumonia, and on autopsy three of these had high rates of RS virus positivity, (>35% of cells per high-power field (HPF) positive for RS virus). Two patients receiving ribavirin for RS virus pneumonia who died had <5% of cells positive for RS virus. Pre-engraftment patients are more highly immunosuppressed. Survival appears to depend on confining RS virus infection to the upper respiratory tract.

An outbreak of parainfluenza type 3 in a renal transplant unit was associated with an increase in the frequency of acute allograft rejection during the period of infection [22]. Some 27 patients, of whom 12 were adults, were found to have developed parainfluenza infection between 1974 and 1990. One-third of the patients with lower respiratory tract involvement developed respiratory failure and all died. Ribavirin was given by aerosol but evidently it was not helpful. During the 1991–1992 influenza epidemic season, 25% of adult BMT patients at the MD Anderson Cancer Center had acute respiratory symptoms with influenza A infection confirmed by culture. Two-thirds of these patients had lower respiratory tract disease. Some 10% of adults with leukaemia with acute respiratory symptoms had influenza A viruses; of these infections, 75% were complicated by pneumonia. During the epidemic, 20% of all pneumonia and nosocomial respiratory infections were associated with influenza A viruses.

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