Lung infections · 4

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Pathogenesis of lower respiratory tract infections due to *Chlamydia*, *Mycoplasma*, *Legionella* and viruses

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Acute infection of the lower respiratory tract comprises bronchitis, bronchiolitis, and pneumonia. From a clinical point of view it may be difficult to distinguish these disease entities and one infection may progress into another. The most common pathogens causing these infections are the primary respiratory viruses (respiratory syncytial virus (RSV), influenza virus, adenoviruses, parainfluenza virus, and rhinovirus[1 2]), *Mycoplasma pneumoniae*,[3] and *Chlamydia* species.[4–6] *Legionella* may cause pneumonia and non-pneumonic upper respiratory tract infection and approximately 85% of c ases are caused by *L pneumophila*. Long lasting sequelae such as bronchiectasis, lung fibrosis, and decreased lung function are seen after lower respiratory tract infections[7–10] and it has been debated whether respiratory tract infection can cause chronic bronchial asthma.[6 11–13]

Acute bronchitis and bronchiolitis

Acute bronchitis is an inflammatory condition of the bronchi often caused by infectious agents, although in many cases no aetiology can be established.[14 15] It shares many pathological and clinical features with bronchiolitis, and the same agents may induce both conditions. Most cases of acute bronchitis of known aetiology are due to respiratory viruses such as influenza virus, adenovirus, RSV, rhinovirus, and coronavirus,[1 2 16] and a few are caused by *M pneumoniae*, *Bordetella pertussis* and *C pneumoniae*.[4 5 15 17] *Legionella* infections limited to the bronchial tree are not described.

ADHERENCE OF PATHOGENS

The pathogenesis has not been studied for all agents, but the transmission of disease is thought to occur through droplet spread from an infected person. After inhalation the infectious agent may adhere to different receptors such as acid containing glycoproteins or the adhesion molecule ICAM-1 on respiratory epithelial cells.[18 19] The infectious chlamydial particle is the elementary body that attaches itself to and enters a susceptible cell where it changes to the larger metabolically active reticulate body.[20] Viable chlamydiae may be present at the site of infection and induce an inflammatory response.[20] *M pneumoniae* attaches to ciliated epithelial cells by a specialised terminal organelle.[18] Metabolic and ultrastructural alterations in the affected cell are seen and these result in epithelial cell damage and ciliostasis. Some epithelial cell lines produce cytokines when stimulated with other bacteria such as *Escherichia coli*,[21] and epithelial cells might therefore play a more active role in the mucosal immune response after extracellular bacterial infection. In acute respiratory viral diseases a number of different inflammatory mediators such as kinins and cytokines have also been demonstrated. In some infections such as influenza extensive infiltrations with polymorphonuclear leucocytes (PMN), oedema, and degeneration of epithelial cells are seen,[22] whereas in others such as rhinovirus infection the cytopathic effects are either absent or minor in degree.[23]

BRONCHITIS AND BRONCHIAL HYPERREACTIVITY

The cardinal symptom of acute bronchitis is cough, while wheezing occurs in 10–90% of cases.[6 14 15 24 25] Transient bronchial hyperreactivity has been found several weeks after influenza A infection in subjects with no previous history of bronchospasm,[25] and in 40 patients with acute bronchitis and without pre-existing pulmonary disease wheezing was reported in 62%.[14] A reduction in forced expiratory volume in one second (FEV_1) and peak expiratory flow (PEF) was found during the acute illness, and 37% had bronchial hyperreactivity measured by histamine challenge testing six weeks later.[14] In patients with bronchial asthma[26 27] it has been shown that acute exacerbations of wheezing and decreased PEF were associated with respiratory tract infections caused by rhinoviruses, coronaviruses, influenza virus, RSV, parainfluenza virus, and *Chlamydia* in 80–85% of cases. Thus, in both asthmatic and non-asthmatic patients pulmonary symptoms and changes in airway function occur during and after viral respiratory illness.[14 25] This may be due to cholinergic hyperresponsiveness or immunological reactions.[14 28–30]

Chlamydia pneumoniae can cause prolonged acute bronchitis with wheezing[6 15 31 32] and Hahn and coworkers[6] found that nine (47%) of 19 patients with acute *C pneumoniae* infection had bronchospasm during their respiratory illness. They also found that 29% of 71 adults

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with *C pneumoniae* antibody titres above 32 had or developed asthmatic bronchitis after a respiratory illness compared with only 7% of a matched control group. In another study[33] *C pneumoniae* could be isolated from the nasopharynx of 11% of asthmatic children with an acute episode of wheezing but in only 4.9% of a control group. Thus, infection with *C pneumoniae* can trigger acute episodes of wheezing in asthmatic children and Allegra and coworkers[34] found a similar association in adults. *C pneumoniae* infection may predispose to bronchospasm during subsequent infections with other respiratory pathogens, or a prolonged infection and exposure to *C pneumoniae* may explain a protracted illness.[32] Similar to findings in some viral respiratory tract infections with wheezing,[29 30] specific IgE antibodies could be demonstrated in *C pneumoniae* infection.[35] IgE antibodies were detected by an immunoblotting technique in 85% of 14 asthmatic children aged 5–15 years with culture proven *C pneumoniae* respiratory infection and also in 18–22% of culture negative asthmatics and asymptomatic children.[35] Antibodies to a 98 kD protein that seem to be *C pneumoniae* specific were most commonly recognised.[36] Some serum samples also reacted with epitopes present in *C trachomatis*, but the pattern of reactivity was different with the two species.[35] These findings suggest that type 1 allergy may be implicated in the pathogenesis of *C pneumoniae* infection. The role of *C trachomatis* as a respiratory pathogen after the neonatal period is controversial. *C trachomatis* was isolated from pharyngeal swabs in seven of 20 children with wheezing[37] and serological evidence of acute infection with *C trachomatis* was found in 19.2% of Argentinian children aged 1–18 months with acute lower respiratory tract infection.[38] On the other hand, *C trachomatis* could not be isolated from 48 children newly admitted to an asthma clinic in the UK,[39] and Hahn and coworkers[6] did not find any correlation between *C trachomatis* antibody titres and wheezing in children and adults with lower respiratory tract infection. Thus, the role of *C trachomatis* and *C psittaci* in bronchitis and wheezing is still undetermined and further studies are needed.

Mycoplasma pneumoniae infection may result in bronchitis about 30 times more often than it causes pneumonia[17] and it may be accompanied by paroxysmal cough, probably related to the cilial dysfunction, and by wheezing.[1 11 15] In children with "wheezing associated respiratory illness" *M pneumoniae* was isolated in 3% of infants aged 0–2 years and in 52% of schoolchildren aged 9–15 years.[1] In another study *M pneumoniae* was cultured from 25% of asthmatics aged 0–31 years during a period with wheezing and in only 5% of subjects without asthma,[40] but no association between wheezing and isolation of *M pneumoniae* could be found in a Japanese study.[41] Based on serological tests, Seggev and coworkers[42] concluded that *M pneumoniae* infection could cause exacerbation of asthma but this finding could not be confirmed by other workers.[40] IgE antibodies to *M pneumoniae* have been detected in a few patients[43] and it has been suggested that they have a possible role in the pathogenesis. However, it should be borne in mind that antibodies could result from stimulation with cross reacting antigens and that a number of different antibodies are found in patients with *M pneumoniae* infection.[44]

BRONCHIOLITIS

Bronchiolitis is an acute infection of the small bronchi and bronchioles in children below the age of 2–3 years. Some authors may include older children and use the term "wheezing associated respiratory infection".[1] RSV is the major cause of bronchiolitis, accounting for 45–75% of the cases, while parainfluenza virus is responsible for 15–30%. Rhinovirus, adenovirus, and influenza virus have each been isolated in 3–10% and *M pneumoniae* has been found in a small percentage.[1 2 30] Serological evidence of *C trachomatis* and *C pneumoniae* infection in bronchiolitis has been described in a few cases.[38] *Legionella* species may cause inflammation in bronchioles in connection with pneumonia,[45] but a clinical syndrome of bronchiolitis due to these bacteria has not been reported.

RSV may initially replicate in the epithelium of the upper respiratory airways and it then subsequently spreads downwards along the epithelium of the respiratory tract, mostly by cell to cell transfer. The bronchiolar epithelium is colonised by virus and necrosis may occur. Peribronchial inflammation with predominantly mononuclear cells and oedema is seen. Thick plugs composed of cell debris and fibrin are found, and they may lead to partial obstruction of the bronchioles, resulting in air trapping.[46] This obstruction is probably the most important feature of acute bronchiolitis. The pathological process may progress and involve the alveolar walls leading to interstitial pneumonia. During recovery the bronchiolar epithelium regenerates within a few days. The elastic and muscular tissues are not damaged and the bronchial tree should recover completely.[46]

In RSV bronchiolitis the pathogenesis of the inflammatory process may involve an abnormal immunological response. Children vaccinated against RSV with a formalin inactivated vaccine developed an antibody response without acquiring protective immunity, and when natural RSV infection occurred the vaccinated subjects developed a disease of increased severity.[47] The vaccine not only failed to offer protection but also induced an exaggerated response to naturally occurring infection. RSV contains two surface glycoproteins—an attachment protein (G), and a fusion protein (F)—against which neutralising antibodies are usually directed.[47 48] Infants immunised with the formalin inactivated RSV vaccine developed a high titre of antibodies to the F glycoprotein and a poor response to the G protein, whereas older children developed high levels of antibodies to both proteins. However, in both groups the level of neutralising antibodies was lower than that obtained after natural RSV infection.[48] Thus formalin

treatment appeared to alter the epitopes of the glycoproteins in a way that resulted in production of non-neutralising antibodies. After natural RSV infection of vaccinated subjects the non-neutralising antibodies might have reacted with the virus antigens and elicited a local Arthus reaction in the bronchioles or alveoli, resulting in enhancement of pulmonary pathology.[48] Studies of mice primed with single RSV proteins have shown that the G protein induces a strong specific antibody response but a weak specific IL-2 release from T lymphocytes. The F protein, on the other hand, is a potent stimulator of T helper cells.[49 50] Mouse T cell lines primed with various RSV proteins, cultured in vivo and injected into RSV infected mice, revealed that the most severe illness was seen in mice receiving G specific cells whereas F specific cells caused only minimal enhancement of the disease. It has also been found that mice sensitised with G protein developed eosinophilic efflux into the bronchi, whereas mice sensitised with F protein developed PMN efflux.[49 50] Different RSV proteins may therefore stimulate different subsets of T helper lymphocytes.[49 51] The G protein may stimulate Th2 cells which produce IL-4 and IL-5 and may lead to IgE production and eosinophilic chemotaxis. Although these findings should be interpreted cautiously, they might explain some of the pathological findings in patients with bronchiolitis in whom IgE, histamine, and eosinophilic cationic protein can be found in respiratory secretions.[29 52] Leukotriene C_4 (LTC_4) was detected in nasopharyngeal secretions in the acute phase of RSV bronchiolitis and it may be released from mast cells by an IgE mediated mechanism.[53] The amount of histamine and IgE antibodies to RSV and parainfluenza virus in nasopharyngeal secretions correlated with the severity of the disease and with recurrent wheezing.[29 30 54] It is therefore possible that local stimulation of Th2 helper lymphocytes (rather than Th1 lymphocytes) by RSV or other infectious agents may lead to or augment the risk of developing bronchiolitis with wheezing.

BRONCHIAL ASTHMA AND INFECTION

After acute bronchitis increased airway reactivity to inhaled histamine which could be blocked by atropine was demonstrated.[14 25 28] This cholinergic hyperresponsiveness may be a consequence of epithelial damage by respiratory pathogens with exposure and sensitisation of sensory fibres.[55] However, the finding of specific IgE antibodies to RSV, parainfluenza virus, mycoplasma, and *C pneumoniae*[29 30 35 43] might suggest that type 1 allergy plays a role in bronchospasm and wheezing, although specific IgE antibodies have also been found in non-respiratory viral infections.[56] In infants with RSV bronchiolitis during the first year of life one study[13] showed that 23% had developed asthma—defined as three episodes of bronchial obstruction—at the age of three years compared with 9% in a control group. It was also found that the children recovering from bronchiolitis developed IgE antibodies to other antigens more often than control children.[13] It is therefore possible that respiratory infection might stimulate Th2 cells and elicit IgE mediated bronchial asthma.[27 49 50]

CONCLUSION

Acute bronchitis may result in decreased lung function in both asthmatic and non-asthmatic patients.[14 25 27] The abnormalities usually resolve after several weeks or months but some cases only resolved after eradication of a chlamydial infection.[35 37] There have been no long term follow up studies to show that acute bronchitis may elicit chronic bronchial asthma. RSV bronchiolitis in infants has been associated with development of asthma and sensitisation to common allergens during the subsequent two years. However, these infants also had a heredity for atopy and asthma.[13] This was not found in other studies[12] and it cannot be ruled out that the infants who develop severe RSV infection are those with a predisposition for atopy and asthma. It is also possible that pulmonary infection early in life may have a deleterious effect on the developing respiratory system, although the bronchioles seem to recover completely.[46] Thus, it is not possible to determine whether respiratory tract infections can lead to chronic bronchial asthma, but it has been shown that they may increase the rate of other chronic respiratory diseases later in life.[9 57] Early treatment might ameliorate the acute symptoms and may reduce the persistent wheezing. Patients with acute bronchitis may benefit from inhaled β_2 agonists.[14] Nebulised budesonide decreases the severity of laryngotracheobronchitis caused by parainfluenza virus[58] and may also have an effect in other respiratory tract infections.

Pneumonia

The aetiology of community acquired pneumonia has usually been studied in hospital inpatients and pneumococci have been the predominant micro-organisms with viruses, *Chlamydia*, *Mycoplasma*, and *Legionella* causing less than 25% of cases.[59 60] However, in less severe cases seen in outpatient clinics viruses, *M pneumoniae*, and *C pneumoniae* may dominate.[61 62]

VIRAL PNEUMONIA

Infection with the usual respiratory viruses seems to spread downwards from the larger bronchi to the bronchioles and alveoli and this may explain why these infections often start with symptoms of bronchitis. All primary respiratory viruses cause similar pathological changes in the lower airways and lungs.[46] Inflammation of bronchioles and alveolar parenchyma with foci of necrosis is seen and many alveoli are lined with thick hyaline membranes which may compromise air diffusion.[46] As in bronchitis and bronchiolitis, changes in airway reactivity may persist for weeks or months after viral pneumonia.

CHLAMYDIAL PNEUMONIA

Chlamydial pneumonia may be caused by all three human pathogenic species. Newborn infants may be infected with *C trachomatis*

during delivery and develop pneumonia with dry cough and wheezing 4–6 weeks later.[17] *C trachomatis* may also cause lower respiratory tract infection after the neonatal period since serological evidence of recent or acute *C trachomatis* infection was found in 20% of 89 children aged 1–18 months with pneumonia.[38] It is uncertain how the infection is acquired by these children, but persistent unrecognised infection might be a possibility.[20] *C trachomatis* infection has also been reported in adults with pneumonia.[63] However, previous serological tests have been less specific and it is possible that some of these cases were due to other species.

Ornithosis is a systemic infection often accompanied by pneumonia.[17] It is caused by *C psittaci* which is common in birds and some domestic animals. Infection is spread to man from infected birds by the respiratory route, either by direct contact or by aerosolisation of infectious discharge or dust. The agent is spread haematogenously from the respiratory tract to other sites, including the lungs. The trachea and bronchi become inflamed and the inflammation spreads to the bronchioles and alveolar walls. Unlike most viral pneumonias, chlamydial pneumonia results mainly in an intra-alveolar inflammatory response and, to a lesser extent, in interstitial inflammation.

Primary infection with *C pneumoniae* in young people usually causes mild pneumonia accompanied by upper respiratory tract infection.[4 62] Adults are more severely affected[31 64] and an immunological pathogenesis due to repeated infections has been suggested. *C pneumoniae* and *C psittaci* infections have been associated with extrapulmonary manifestations[31 65–67] that may be caused by haematogenous spread or immunological mechanisms. *C psittaci* has been cultured from blood in patients with endocarditis[66] whereas other complications such as glomerulonephritis,[67] reactive arthritis, or erythema nodosum[31 65] may be immunologically mediated, though no study has so far reported deposition of chlamydial antigen in the lesions. In immune guinea pigs a genus specific 57 kD chlamydial protein can elicit a delayed hypersensitivity reaction,[68] supporting the assumption that immune reactions play a role in the pathogenesis of chlamydial infections.

MYCOPLASMAL PNEUMONIA

After inhalation of infected material, *M pneumoniae* binds to respiratory epithelial cells and induces inflammation.[11 18] Locally produced secretory IgA may inhibit the binding to respiratory epithelium, and these antibodies seem to play a greater role than serum antibodies in the protection against repeated mycoplasmal infections.[69] In fatal cases of mycoplasmal pneumonia micro-organisms are rarely demonstrated in lung tissue and corticosteroids have had some beneficial effects in severe cases.[70 71] In immunocompromised patients with severe mycoplasmal infection the chest radiographic changes were minimal or absent.[72] This could be explained by decreased immunological reactivity in these patients, and it would therefore support the assumption that immunological mechanisms play a pathogenic role. Several extrapulmonary complications occur in mycoplasmal infection[11] and there is evidence to suggest that immune mechanisms, rather than direct infection, may also be responsible for these manifestations. Thus, *M pneumoniae* is seldom isolated from clinical specimens, apart from nasopharyngeal secretions. *M pneumoniae* may act as a polyclonal activator of lymphocytes[73] and autoantibodies to various tissues and immune complexes have been demonstrated in a high proportion of patients.[44 74] This might contribute to injury to extrapulmonary organs, although antibodies are also found in patients without extrapulmonary manifestations.[44] Altered immune function induced by *M pneumoniae* may facilitate infection with other micro-organisms and explain why co-infection with other bacteria or viruses may result in severe disease.[75]

LEGIONELLA PNEUMONIA

Legionella pneumonia is most often caused by *L pneumophila* and the prevailing mode of transmission is probably by direct inhalation of aerosols containing micro-organisms.[76] Aspiration of oropharyngeal content contaminated with legionellae[77] seems unlikely since oropharyngeal colonisation is rare.[78]

The histopathological lesions of Legionnaires' disease are predominantly located in alveolar ducts and alveoli which contain a mixture of PMNs and macrophages with fibrin and cell debris. Leucocytes predominate in the early phase of infection followed by macrophages in the later phase.[45] Abscess formation, indicating that the bacterium may produce irreversible damage, has been reported.[45 79] Once the bacteria have entered the respiratory tract they will normally be cleared by the mucociliary system.[79 80] However, the *Legionella* bacterium has several cell associated and extracellular factors that may help to establish infection.[81] They possess flagella and fimbria that may mediate adherence to lung cell surfaces[82] but this process may be inhibited by *Legionella* antibodies in bronchial secretions. The micro-organisms can evade this neutralisation by antibodies by producing proteases that may degrade both IgG and secretory IgA in the secretions[83] and another legionella protease may inhibit the neutrophil chemotaxis and thus facilitate infection.[84] Cell mediated immunity also plays an important role in the defence against legionella infection[85] and, in accordance with this, legionella pneumonia occurs more commonly in immunocompromised patients. Several bacterial virulence factors may help to invade cells, multiply intracellularly, and cause cell damage.[81] The mode of action of many of these factors is not known and they may vary in different strains. The macrophage infectivity potentiator (Mip) is a basic protein with a molecular weight of 24 kD and it has been shown that *L pneumophila* strains defective in this factor exhibit reduced infectivity in cell cultures and that reintroduction of the Mip gene restores virulence.[81 86] Some component of *L pneumophila* such as

Mip or cytotoxin[87 88] affects the respiratory burst of phagocytes during infection and this suppression may contribute to the intracellular survival of the bacteria.[89] On the other hand, enhanced generation of toxic oxygen radicals might also be involved in the pulmonary damage seen in Legionnaires' disease, and lung fibrosis has been described as a sequel of this illness.[10] Legionellosis can be dominated by a diversity of extrapulmonary manifestations, probably due to haematogenous spread of bacteria following infection of the lungs. Renal failure, hypotension, and respiratory failure have been reported[90 91] and these complications do not seem to be immunologically mediated.[45]

CONCLUSION

Lower respiratory tract infection may be followed by long term sequelae and a direct link between acute respiratory tract infection in early infancy and development of chronic bronchitis and emphysema in adults has been established.[9] Interstitial lung fibrosis has been reported after influenza pneumonia[8] and Legionnaires' disease,[10] as well as bronchiectasis and abnormal lung function tests after adenovirus pneumonia.[7 92] Symptoms recurring and persisting for years have been described in patients with ornithosis.[93] The occurrence of symptoms was related to a delay in the initiation of antibiotic therapy and to high antibody titres to chlamydial group antigens, which might suggest continued chlamydial infection.[32 93] Thus acute pneumonia can lead to chronic pulmonary disease and it is a theoretical possibility that early antimicrobial treatment might prevent this.

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