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 rhinoviruses), *Mycoplasma pneumoniae,* and *Chlamydia* species. *Legionella* may cause pneumonia and non-pneumonic upper respiratory tract infection and approximately 85% of cases are caused by *L. pneumophila.* Long lasting sequelae such as bronchiectasis, lung fibrosis, and decreased lung function are seen after lower respiratory tract infections and it has been debated whether respiratory tract infection can cause chronic bronchial asthma.

**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. 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, and a few are caused by *M. pneumoniae,* *Bordetella pertussis* and *C. pneumoniae.* *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. 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. Viable chlamydia may be present at the site of infection and induce an inflammatory response. *M. pneumoniae* attaches to ciliated epithelial cells by a specialised terminal organelle. 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,* 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, whereas in others such as rhinovirus infection the cytopathic effects are either absent or minor in degree.

BRONCHITIS AND BRONCHIAL HYPERREACTIVITY

The cardinal symptom of acute bronchitis is cough, while wheezing occurs in 10–90% of cases. It has been found that 29% of 71 adults had bronchospasm during their respiratory illness, whereas in others such as rhinovirus infection the cytopathic effects are either absent or minor in degree.
with *C pneumoniae* antibody titres above 32 had developed asthmatic bronchitis after a respiratory illness compared with only 7% of a matched control group. In another study* 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 Allegre and coworkers 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. Similar to findings in some viral respiratory tract infections with wheezing, specific IgE antibodies could be demonstrated in *C pneumoniae* infection. 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 in 18–22% of culture negative asthmatics. Antibodies to a 98 kD protein that seem to be *C pneumoniae* specific were most commonly recognised. Some serum samples also reacted with epitopes present in *C trachomatis*, but the pattern of reactivity was different with the two species. 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 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. On the other hand, *C trachomatis* could not be isolated from 48 children newly admitted to an asthma clinic in the UK, and Hahn and coworkers 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 and it may be accompanied by paroxysmal cough, probably related to the ciliary dysfunction, and by wheezing. 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. 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, but no association between wheezing and isolation of *M pneumoniae* could be found in a Japanese study. Based on serological tests, Seggev and coworkers concluded that *M pneumoniae* infection could cause exacerbation of asthma but this finding could not be confirmed by other workers. IgE antibodies to *M pneumoniae* have been detected in a few patients 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.

**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”. 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. Serological evidence of *C trachomatis* and *C pneumoniae* infection in bronchiolitis has been described in a few cases. *Legionella* species may cause inflammation in bronchioles in connection with pneumonia, 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. 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 bronchiolar tree should recover completely.

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. 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. 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. 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.49 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 Th1 helper cells.49 50 Mouse IgE mediated mechanism.53 The amount of non-neutralising antibodies might have reacted with mast cells by an IgE mediated mechanism.53 However, the finding of specific IgE antibodies to RSV, parainfluenza virus58 and may also have an effect in other respiratory tract infections.

CONCLUSION
Acute bronchitis may result in decreased lung function in both asthmatic and non-asthmatic patients.14 21 27 The abnormalities usually resolve after several weeks or months but some cases only resolved after eradication of a chlamydial infection.39 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 studies12 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.55 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.5 57 Early treatment might ameliorate the acute symptoms and may reduce the persistent wheezing. Patients with acute bronchitis may benefit from inhaled β2 agonists.14 Nebulised budesonide decreases the severity of laryngotracheobronchitis caused by parainfluenza virus35 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.30 40 However, in less severe cases seen in outpatient clinics viruses, M pneumoniae, and C pneumoniae may dominate.41 42

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.16 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.16 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.26 C trachomatis
infection has also been reported in adults with
pneumonia.40 However, previous serological
tests have been less specific and it is possible
that some of these cases were due to other spe-
cies.

Ornithosis is a systemic infection often
accompanied by pneumonia.7 They 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
affected63 64 and an immunological pathogen-
esis due to repeated infections has been
suggested. C pneumoniae and C psittaci infec-
tions have been associated with extrapulmo-
nary manifestations65 66 67 that may be caused by
haematogenous spread or immunological
mechanisms68 69 that may be caused by
repeated infections. C psittaci has been cultured from
blood in patients with endocarditis66 whereas
other complications such as
glomerulonephritis,67 reactive arthritis, or ery-
thematos nodosum69 70 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 hyper-
sensitivity reaction,71 supporting the assum-
ton that immune reactions play a role in the
pathogenesis of chlamydial infections.

MYCOPLASMAL PNEUMONIA

After inhalation of infected material, M pneu-
moniae binds to respiratory epithelial cells and
induces inflammation.72 73 Locally produced
secretory IgA may inhibit the binding to respi-
atory epithelium, and these antibodies seem
to play a greater role than serum antibodies in the
protection against repeated mycoplasmal
infections.74 In fatal cases of mycoplasmal
pneumonia micro-organisms are rarely demon-
strated in lung tissue and corticosteroids have
had some beneficial effects in severe cases.75 76
In immunocompromised patients with severe
mycoplasmal pneumonia the chest radiographic
changes were minimal or absent.77 This could
be explained by decreased immunological
reactivity in these patients, and it would there-
fore support the assumption that immuno-
genital mechanisms play a pathogenic role. Several
extrapulmonary complications occur in myco-
plasmal infection19 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
lymphocytes78 and autoantibodies to various
tissues and immune complexes have been
demonstrated in a high proportion of patients.79
80 This might contribute to injury to
extrapulmonary organs, although antibodies
are also found in patients without extrapulmo-
nary manifestations81 82. Altered immune func-
tion 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.73

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.83 Aspira-
tion of oropharyngeal content contaminated with
legionella pneumophila is unlikely since orophar-
yngeal colonisation is rare.84

The histopathological lesions of Legion-
nae’ disease are predominantly located in
alveolar ducts and alveoli which contain a mix-
ture of PMNs and macrophages with fibrin and
cell debris. Leucocytes predominate in the
early phase of infection followed by macro-
phages in the later phase.85 Abscess formation,
indicating that the bacterium may produce
irreversible damage, has been reported.86 87
Once the bacteria have entered the respiratory
tract they will normally be cleared by the
mucociliary system.88 89 However, the Legionella
bacterium has several cell associated and extra-
cellular factors that may help to establish
infection.81 They possess flagella and fimbria
that may mediate adherence to lung cell
surfaces89 but this process may be inhibited by
Legionella antibodies in bronchial secretions.
The micro-organisms can evade this neutrali-
sation by antibodies by producing proteases
that may degrade both IgG and secretory IgA
in the secretions4 but 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 infection86 and, in
accordance with this, legionella pneumonia
occurs more commonly in immunocompro-
mised patients. Several bacterial virulence fac-
tors may help to invade cells, multiply intracel-
ularly, and cause cell damage.80 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 reintroduc-
tion of the Mip gene restores virulence.81 85
Some component of L pneumophila such as
Mip or cytotoxin affects the respiratory burst of phagocytes during infection and this suppression may contribute to the intracellular survival of the bacteria. 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. 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 and these complications do not seem to be immunologically mediated.

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. Interstitial lung fibrosis has been reported after influenza pneumonia and Legionnaires’ disease, as well as bronchiectasis and abnormal lung function tests after adenovirus pneumonia. Symptoms recurring and persisting for years have been described in patients with ornithosis. 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. Thus acute pneumonia can lead to chronic pulmonary disease and it is a theoretical possibility that early antimicrobial treatment might prevent this.

5 Falck G, Heyman L, Gnarpe J, et al. Suppression may contribute to the intracellular 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. 1 Henderson FW, Clyde WA, Collier AM, et al. The etiologic and epidemiologic spectrum of bronchiolitis in pediatric practice. J Pediatr 1979;85:183–90.
5 Falck G, Heyman L, Gnarpe J, et al. Suppression may contribute to the intracellular infection. 32 93

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