Tobias Welte
Diagnosis and treatment of community acquired pneumonia – the German perspective
Summary

Current concepts of diagnosis and treatment of CAP are risk stratified and adapted to the national resistances of important pathogens. Thorough surveillance systems have to be implemented in all countries.
The risk of patients can be assessed reliably with a limited number of clinical data (CRB-65 score). Extended microbiological and laboratory diagnosis is recommended for hospitaliszed patients only. Outpatient treatment can be performed with classic antibiotics like amoxicillin or doxycyclin. Macrolides are only an alternative in these patients. In the hospital, treatment has to be adapted to the severity of the disease. Further studies concerning the duration of treatment and advantageous combinations are necessary.
Recommendations for treatment of CAP have to be adapted to the quickly changing epidemiology and have to be updated every 2 to 3 years.

Reinhard Marre
Detection of respiratory bacterial pathogens
Summary

Microbiology of community acquired pneumonia often is based on indirect or precarious evidence. Time and effort to detect a respiratory pathogen often is not sufficiently related to its usefulness in guiding therapy. If sputa are accepted by the laboratory for microbiologic studies (Gram stain, culture), they should fulfill quality criteria such as high number of leukocytes and low number of squamous epithelial cells. Complementary tests such as antigen detection assays are useful adjuncts for diagnosing pneumococcal and *Legionella* pneumonia. Nucleic amplification tests help to overcome the problems in detecting *Chlamydia pneumoniae*, *Legionella* and *Mycoplasma pneumoniae*.

Walter Hampl and Thomas Mertens
Viral pathogens and epidemiology, detection, therapy and resistance
Summary

Worldwide Community acquired pneumonia (CAP) is one of the most frequent infectious diseases and a leading cause of death. Several studies have shown that a pathogen could be identified only in 50 to 60% of all patients, although in children < 6 month infectious agents can be detected in about 90%. Viral infections are most frequent in children < 2 years (80%), whereas bacterial infections increase with age.
RSV, influenzaviruses, rhinoviruses, parainfluenzaviruses and adenoviruses are the most common viruses associated with CAP in children. Among adenoviruses a predominance of adenovirus 7 has been reported in several countries with emergence of highly pathogenic variants with significant lethality in young children. Many childhood respiratory infections are caused by more than one pathogen and up to 30% mixed viral / bacterial infections can be observed. CAP in immunocompetent adults is rare, whereas persons with underlaying diseases have an increased incidence of CAP. In the elderly, RSV, influenzaviruses, parainfluenzaviruses and less frequent adenoviruses are predominant viruses causing pneumonia. Less frequently associated with CAP are the newly discovered human metapneumovirus and the coronaviruses NL63 and HKU1. Hantaviruses, involved in the

hantavirus pulmonary syndrome, belong to the emerging pathogens to date in north, middle and south america.
For optimum diagnosis the whole spectrum of potential respiratory viral agents should be included and multiple diagnostic techniques have to be used.
In view of the high relevance of influenza virus for CAP influenza vaccination is highly advisable for prevention of CAP, especially in high-risk groups.

Mathias W.R. Pletz, Lesley McGee and Tobias Welte
Resistance in *Streptococcus pneumoniae*
Summary

Streptococcus pneumoniae is a leading cause of community-acquired lower respiratory tract infections, sinusitis, meningitis, and bloodstream infections. Pneumococci are Gram positive, encapsulated bacteria and exhibit more than 90 different capsular serotypes.
Resistance to penicillin in clinical isolates was reported anecdotally as early as 1965, but was not considered a major concern until the mid-1990s. In the 1990s, there was a tremendous global increase in resistance to penicillins and this led to the increased use of macrolides and tetracyclines to treat infections. After several years, the resistance rates to these antibiotics began to increase as well. Currently, fluoroquinolones are used most frequently to treat community-acquired respiratory infections in adults and resistance rates globally are still low.
Pneumococci are naturally competent bacteria and frequently acquire resistance by intraspecies or interspecies gene transfer. Resistance to β-lactams is due to the acquisition of different mutations within the pencillin-binding proteins that have been demonstrated to originate from the less pathogenic viridans streptococci. Other mechanisms of antibiotic resistance include enzymes and efflux pumps on mobile genetic elements (e.g. *erm* and *mef*), or resistance arising through spontaneous mutations. Clinical studies show that resistance, particularly to penicillins, is not always related to clinical failure.
The global increase in resistance rates in pneumococci is in part due to the spread of a limited number of highly sucessful multiresistant pneumococcal clones. Isolates belonging to a specific clone, defined by sequence types according to multilocus sequencing, often exhibit the same serotype. However, capsular switching due to genetic rearrangements within the same clone has been observed. The recently introduced seven-valent conjugated pneumococcal vaccine has been shown to decrease disease and carrier rates of the included serotypes. Since some of the multiresistant clones exhibit vaccine serotypes, resistance rates to penicillin, macrolides and fluoroquinolones have been decreasing since the introduction of this vaccine.

Hans-Dieter Klenk
Influenza
Summary

Influenza-A-viruses have a wide host range and occur with a wide spectrum of variants defined by 16 HA and 9 NA subtypes. All of these subtypes occur in birds, whereas only some of them have so far been observed in man, pig, horse, and a number of other mammals. In contrast, influenza-B and C-viruses occur only with man, and there are no subtypes of these viruses. Influenza-A-viruses occasionally can be transmitted from aquatic birds, their natural reservoir, to terrestrial birds and mammals. On rare occasions, they adapt to the new species and establish thus new virus lineages. Adaptation requires multiple mutations and it may involve gene reassortment after co-infection with another virus. By these mechanisms,

viruses with new surface glycoproteins and therefore a distinct change in antigenicity are generated. If a new virus with such an antigenic shift occurs in man, it causes a pandemic. Antigenic drift, unlike antigenic shift, is characterized by slight changes in antigenicity resulting from successive mutations in HA and NA. Antigenic drift is responsible for the annual human epidemics. It occurs not only with influenza-A-viruses, but also with influenza-B-viruses. Influenza is a highly contagious disease that is transmitted by aerosols. Virus replication occurs in airway epithelia and reaches its peak 2-3 days after infection. Symptoms typically include high fever, chills, headache, sore throat, dry cough, myalgias, anorexia, and malaise. Complications include primary viral pneumonia, secondary bacterial pneumonia or combined bacterial and viral pneumonia. Serious complications of influenza most often occur in people 65 years of age and older, in the very young, and in those of any age with underlying chronic cardiac, pulmonary, or metabolic disease. Vaccination is the most potent instrument for influenza control. Prime candidates for vaccination are persons at risk for complications and individuals who might transmit influenza to such persons. Inactivated vaccines obtained from infected chicken embryos are most commonly used. Neuraminidase inhibitors are the influenza antivirals of choice. Application is limited to a relatively small time window shortly before or after infection.

Matthias Krüll and Norbert Suttorp
Pathogenesis of *Chlamydophila pneumoniae* infections – epidemiology, immunity, cell biology, virulence factors
Summary

Chlamydophila (Chlamydia) pneumoniae, a Gram-negative obligate intracellular bacterium, is a widespread respiratory pathogen causing sinusitis, pharyngitis, bronchitis and pneumonia. Repetitive or chronic persistent infections have been associated with an increased risk for asthma, chronic obstructive pulmonary disease (COPD) or vascular lesions. Although the genome of *C. pneumoniae* has been sequenced completely this information has not led yet to an understanding of the mechanisms of infection and target cell activation nor to the identification of potential chlamydial virulence factors. In this review we will give an overview on the pathogenesis of *C. pneumoniae*-induced acute and chronic infections.

Dina M. Bitar, Marina Santic, Yousef Abu Kwaik and Maëlle Molmeret
The Legionnaires' disease and its agent *Legionella pneumophila*
Abstract

Legionella pneumophila, the agent responsible for Legionnaire's disease, is a facultative intracellular pathogen that can replicate within protozoan and macrophages. Protozoa is considered to play a central role in the pathogenesis and ecology of L. pneumophila. In humans, L. pneumophila reaches the lungs, where it ingested in alveolar macrophages. Unlike phagosomes containing inert particles or avirulent bacteria, the L. pneumophila-containing vacuoles avoid fusion with lysosomes, recruiting rough endoplasmic reticulum (RER) and mitochondria. The formation of this specialized vacuole is directed by the type IV secretion system encoded by the dot/icm genes in mammalian and protozoan cells. The dot/icm genes are also required for macropinocytosis in A/J mice macrophages, up-regulation of phagocytosis in human-derived macrophages, induction of apoptosis in macrophages and pore formation-mediated cytotoxicity. Killing of mammalian cells by L. pneumophila has been proposed to occur through induction of apoptosis during the early stages of the infection, via the activation of caspase-3. A rapid induction of necrosis by L. pneumophila also occurs upon

entry into the post-exponential phase of growth within both macrophages and protozoa, when the bacteria become cytotoxic. Before the lysis of the mammalian or protozoan plasma membrane, the bacteria egress into cytoplasm. In vivo, the clearance of Legionella from the lungs depends on the host production of IFN- γ in A/J mice, while in BALB/c mice IFN-γ is not produced. Intracellular replication of L. pneumophila is inhibited in IFN-γ-activated mouse and human primary macrophages, which is associated with the maturation of the LCP into a phagolysosome. Both antigen-specific humoral and cell mediated immune responses are induced during Legionella infection. Although Legionella specific antibodies are produced during human or murin infection, acquired cell-mediated immune response is believed to play a stronger role in Legionella clearance. Both macrophages and DCs are able to present microbial antigens on major histocompatibility (MHC) class I and class II molecules, which stimulate antigen specific T cell response. Identification of antigens and determination of vesicular trafficking mechanisms involved in processing and presentation remain to be understood in greater details.

Sven Hammerschmidt, Gavin K. Paterson, Simone Bergmann and Timothy J. Mitchell
Pathogenesis of *Streptococcus pneumoniae* infections: adaptive immunity, innate immunity, cell biology, virulence factors
Summary

During past decades the intense study of the infection process of *Streptococcus pneumoniae* has elucidated multifaceted interactions of the human pathogenic bacterium with the host. A broad spectrum of pneumococcal virulence factors, which are adapted successfully to different host niches, is involved either predominantly in nasopharyngeal colonization or subsequently in dissemination and transmigration of host tissue barriers. The severe course of infections becomes manifest in invasive diseases like pneumonia, meningitis and septicaemia. To escape the risk of increasing antibiotic resistance and to combat the threat of pneumococcal infections pneumococcal vaccines have been developed. The carrier protein of the current available heptavalent vaccine is not derived from pneumococci therefore it is thought to substitute this carrier by a highly conserved and immunogenic pneumococcal-specific protein. *S. pneumoniae* is a versatile microorganism and has evolved numerous successful strategies to colonize its host and to evade host defence mechanisms. In this report we discuss the bacterial repertoire of virulence factors and provide insights into the surface protein variability. In addition, we show the impact of these virulence factors on interactions with host components, including cellular receptors and how the function of these proteins contributes to colonization and virulence of *S. pneumonaie*. The non-invasive and invasive infections are accompanied by immune responses of both the innate and adaptive immune system. These two systems operate in concert to combat infections, but pneumococci have developed highly sophisticated mechanisms to subvert the host immune system. We introduce pattern recognition receptors that recognize specific structures of pneumococci and stimulate thereby host defence mechanisms.

Ken B. Waites, Jerry W. Simecka, Deborah F. Talkington and T. Prescott Atkinson
Pathogenesis of *Mycoplasma pneumoniae* infections: adaptive immunity, innate immunity, cell biology, and virulence factors
Summary

Mycoplasmas represent the smallest self-replicating organisms. They are unique among bacteria in that they lack a cell wall and require sterols for growth. The limited metabolic and

biosynthetic activities of mycoplasmas have complicated development of accurate means for laboratory detection and hampered understanding of their roles as human pathogens. Mycoplasma pneumoniae was first identified and characterized in the 1960s and shown to be common cause of upper and lower respiratory disease in children and adults. Serious infections requiring hospitalization, while rare, occur in persons of all age groups, and may affect multiple organ systems. Severity of disease appears to be related to the degree to which the host immune response reacts to the infection. Extrapulmonary complications involving all of the major organ systems can occur in association with M. pneumoniae infection as a result of direct invasion and/or autoimmune response. Evidence is accumulating for this organism's contributory role in chronic lung conditions such as asthma. Serology has been the most common means for laboratory detection of M. pneumoniae infection due to the slow growth that makes culture impractical. Newer diagnostic methods utilizing nucleic acid amplification offer the advantages for rapid detection and are likely to become increasingly important in the future, but these techniques have not achieved widespread utilization thus far due to the lack of commercially sold products and non-standardized methodology. Management of M. pneumoniae infections can usually be achieved with macrolides, ketolides, tetracyclines, or fluoroquinolones. As more is learned about pathogenesis and immune response elicited by M. pneumoniae, improved methods for diagnosis and prevention of disease due to this organism are anticipated.

Pablo D. Becker and Carlos A. Guzmán

Community-acquired pneumonia: paving the way towards new vaccination concepts

Summary

Despite the availability of antimicrobial agents and vaccines, community-acquired pneumonia remains a serious problem. Severe forms tend to occur in very young children and among the elderly, since their immune competence is eroded by immaturity and immune senescence, respectively. The main etiologic agents differ according to patient age and geographic area. Streptococcus pneumoniae, Haemophilus influenzae, respiratory syncytial virus (RSV) and parainfluenza virus type 3 (PIV-3) are the most important pathogens in children, whereas influenza viruses are the leading cause of fatal pneumonia in the elderly. Effective vaccines are available against some of these organisms. However, there are still many agents against which vaccines are not available or the existent ones are suboptimal. To tackle this problem, empiric approaches are being now systematically replaced by rational vaccine design. This is facilitated by the growing knowledge in the fields of immunology, microbial pathogenesis and host response to infection, as well as by the availability of sophisticated strategies for antigen selection, potent immune modulators and efficient antigen delivery systems. Thus, a new generation of vaccines with improved safety and efficacy profiles against old and new agents is emerging. In this chapter, an overview is provided about currently available and new vaccination concepts.

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