BOGDAN NEAMTU[1], IOANA MATACUTA[2], SVETLANA HADJU[3]

ETIOPATHOGENESIS OF ACUTE COMMUNITY ACQUIRED PNEUMONIA

[1] *Faculty of Medicine, Lucian Blaga University Sibiu, Romania*
[2] *Faculty of Medicine, Lucian Blaga University Sibiu, Romania*
[3] *State Medical and Pharmaceutical University„Nicolae Testemiţanu", IMSP Mother and Child Institute, National Epileptology Center*

ABSTRACT

Acute community pneumonia etiology is related to age and immune system status. Certain age groups (neonates, infants, ante-preschools, preschoolers, schoolchildren, adolescents, patients with severe immunosuppression) reveal particular aspects in immune defense mechanisms (macrophages, neutrophils, lymphocytes and eosinophils) and nonimmune responses (aerodynamic filtration of inhaled particle size, shape, electrostatic charge, cough reflex, mucociliary clearance, lysozyme, complement, defensine). Firstly, this review tackles the main mechanisms involved in airway permeability, alveolar ventilation and perfusion impairments, gas exchange and cellular metabolism alterations affecting vital tissues and organs. Then, the focus is on the age related pathogens interaction with the host defence systems, in different age groups.

EPIDEMIOLOGY

According to UNICEF, pediatric pneumonia accounts for 3.0 million deaths annually with a peak in the developing countries. The severe outcome is primarily related to co-morbidities such as chronic pulmonary diseases, congenital heart diseases and immunosuppression. However, community pneumonia is one of the most frequent morbidity causes in industrialised countries.

BACKGROUND

Lower respiratory tract infections are the leading causes of death worldwide. In the developing countries, this diagnosis is usually based on supporting the radiological examination although WHO admits the clinical criteria. A pneumonic process is either a consequence of direct infection of the pulmonary parenchyma or is the local septic complication of an extrapulmonary or systemic infectious process. Pneumonia associates different mechanisms' impairments involving airway permeability, ventilation and alveolar perfusion. Eventually, gas exchange and cellular metabolism in vital tissues and organs are altered.

PATOPHYSIOLOGY

In pneumonia, the infectious agent overcomes immune and nonimmune mechanisms. Lysozyme, complement, defensines, macrophages, neutrophils, eosinophils, mastocytes and lymphocytes interplay in the immune mechanisms (innate and adaptive). The aerodynamic filtration of inhaled particle size, electrostatic charge, cough reflex, mucociliary clearance intervene in the nonimmune processes of clearance.

Respiratory tract defense mechanisms

Systemic and respiratory defense mechanisms are either nonspecific against any invasive agent or specific for different antigenic determinants. In the fetus and newborn, many of the mechanisms are compromised with breaks and the consequent impairment of structure and lung function. (1)

Non-specific mechanisms include glottis, vocal cords, mucociliary apparatus, airway secretions, migratory and fixed phagocytes, non-specific antimicrobial proteins, opsonins.

The associated reflexes of upper airways anatomical structures(CRS)limit the particles entry. Epithelial cells in trachea and bronchi present a coordinated movement that tends to remove the particles and mucus from distal respiratory structures and alveoli.

Airways' secretions provide a physical barrier diminishing epithelial adherence and subsequent microorganisms invasion. Fibronectin and other proteins bind microbes facilitating phagocytes ingestion. The alveolar and distal airway secretions include: 1. the surfactant augmenting opsonization and phagocytosis of pathogens; 2.proteins associated with surfactant A (Sp-A) and D (Sp-D) modulating phagocytosis and production of phagocytes generating reactive oxygen radicals and development of cytokines, 3.inhibitory and direct microbicidal agents such as iron-binding proteins, lysozyme and defensins, 4. respiratory airway commensal bacteria (alpha-hemolytic streptococcus and coagulase-negative staphylococcus) attached to the mucosa and releasing bacteriocins and other substances that prevent adherence, replication and possible opportunistic invasion of different pathogenic strains.

Usually there is a sterile respiratory mucosa at birth. Later, it becomes colonized by microorganisms from mother or environment. Children requiring endotracheal intubation are at high risk for a fast access of pathogens to distal respiratory structures and ciliary clearance overcoming. In addition, delivery of high oxygen concentrations and pressures in the airway as well as large volumes of intrapulmonary gas may interfere with ciliary function and mucosal integrity. As a consequence, an increased physical disturbance of the epithelial and mucosal barriers ensues. The use of less invasive respiratory support means, such as nasal ventilation, nasal positive airway positive pressure (CPAP) and nasal cannula (conventional or humidified high throughput) may produce to a lower degree the lung and parenchymal mucosal disturbances. Still, these impairments are almost always present.

IMMUNE DEFENSE SYSTEMS

Immunological defense mechanisms against specific pathogens are represented by specific lymphocytes sensitised after antigens presentation to macrophages. These mechanisms include cytotoxic, killer, suppressor and memory functions; systemic and secretory antibodies; consecutive cascades of cytokines, complement, vasomotor regulatory molecules, haemostatic factors and other agents. Secretory antibodies are typically multimeric and contain secretory components and J chains that make them more opsonizable and more resistant to microbial proteases. IgGs, for example, have an opsonising role for alveolar macrophages, forming immune complexes with antigens. Many of the biochemical cascades triggered by specific immune responses serve to isolate microbial invasion thru phagocyte recruitment amplification and concentration in the affected sites disrupting microbes structural and metabolic integrity. The role of these cascades in triggering apoptosis both in the host and the invading cells is still under research. Secretory antibodies and mucosal lymphoid tissue are absent or minimal in the first month of postnatal life. Systemic antibodies can enter lung tissue and usually consist of maternally derived passive antibodies. Specific systemic antibodies may be generated, but many components of the immune system are relatively slow.

Complement components are generally reduced to 50% of its concentration in older children although alternative pathway components are present in sufficient amounts to serve as effective opsonins. In neonates, granulocytes number frequently decreases in response to early infection as well as in non-inflammatory processes such as maternal preeclampsia. Moreover, phagocytes move much more slowly to the inflammatory site, whether it is an infectious outbreak or a tissue necrosis event. Once reaching the target, phagocytes ingest the invaders less efficiently even though intracellular microbicide activities seem to be normal. Intercellular communications through cytokines and other mediators are blocked. Overall, in fetus and newborns, there is a slower, less effective and less concentrated inflammatory response than in older children. The infection is less localizable and ineffectively inhibited by host defense.

PATHOLOGY

Pneumonia is characterised by terminal air space and alveolar inflammation in response to the invasion of an infectious agent in the lungs due to inhalation or haematogenic dissemination. The inflammatory cascade triggers plasma extravasation and surfactant loss, resulting in air loss and parenchymal enhancing. The active inflammatory response often determines the target migration of phagocytes, the release of toxic substances from granules and other microbicidal vacuoles, and the initiation of poorly adapted cascades (e.g., complement, coagulation, cytokines). These cascades can directly disrupt host tissues and can alter endothelial and epithelial integrity, vasomotor tone, intravascular haemostasis, and activation status of fixed and migratory phagocytes at the inflammatory site. The apoptosis role in pneumonia is not well understood. Pulmonary lesions are caused directly and/or indirectly by the invasion of microorganisms or foreign materials, and by the poor, imprecise a responses of the host's defense system on the healthy host tissues. The uninterrupted hosts defense system with consequently severe secondary lesions are even worse than the invading agent itself. Pathogen synthesis and secretion of microbial enzymes, proteins, toxic lipids and toxins disrupt host cell membranes, alter cellular metabolism and extracellular matrix with direct invasion. This matrix has an inhibitory effect on microbial migration. Indirect lesions are mediated by structural molecules such as endotoxin, leucocidin and toxin 1 (TSST-1). These molecules can alter local vasomotor tone and integrity, the characteristics of the infused tissue, generally providing oxygen and nutrients to remove waste from local tissues (2, 3). At a macroscopic level, invading agents and host defense tend to increase the tone and resistance of smooth airway muscles, mucus secretion and the presence of inflammatory cells and debris in the secretions. The excessive mucus can further enhance respiratory tract resistance partially or totally obstructing the airways causing local emphysema (air capture), atelectasis, and the increase of alveolar dead space.Endothelial and alveolar epithelial integrity impairments may allow the surfactant to be inactivated by the proteinaceous exudate which can be further exacerbated by the direct effects of pathogenic microorganisms and/or meconium.

The main consequences are the following: 1. the airway conduction is affected by a much greater resistance and can become obstructive; 2. the alveoli may become atelectatic or hyperexpanded; 3. the alveolar perfusion may be significantly disturbed; and 4. the multiple tissues and cell populations of the lungs and other parts of the body maintain lesions that increase the basic (O2) and (CO2)

removal requirements at a time when the lungs are less able to do so.

Alveolar diffusion barriers may increase, possible intrapulmonary shifts may worsen, and altered V/Q ratio may further damage gas exchange despite endogenous homeostatic attempts to improve communication via regional airways and through constriction or vasodilation. Since the myocardium has to work harder to overcome the changes in pulmonary vascular resistance related to pneumonic process (see above), the lungs may be less able to deliver O2 and remove venous blood CO2. Infection spreading or the inflammatory response, either systemically or in other focal areas, exacerbates the situation. Viral infections are characterised by mononuclear cells accumulation in the submucosa and perivascular space, resulting in partial airway obstruction. Patients with these infections have asthma (wheezing) and subcrepitant syndrome. The disease progresses when alveolar type II cells lose structural integrity, and surfactant production is diminished, a hyaline membrane is formed, and pulmonary edema ensues. In bacterial infections, the alveoli are filled with protein, triggering a rapid influx of erythrocytes and polymorphonuclear cells (red hepatosis), followed by fibrin deposition and inflammatory cell degradation (grey hepatisation). During resolution, intra-alveolar debris are ingested and removed from alveolar macrophages.

Four stages of lobar pneumonia have been described. In the first stage, within 24 hours of the infecting moment, the lung is microscopically characterised by vascular congestion and alveolar edema. There are many bacteria and some neutrophils present. The 2nd stage of "red hepatosis" (2-3 days) reveals the presence of many erythrocytes, neutrophils, desquamated epithelial cells and fibrin in the alveoli. In the 3rd stage, "grey hepatic phase" (2-3 days), the lung is brown-grey to yellow due to fibrinopurulent exudation, erythrocytes' degradation and hemosiderin. Fibrinogen inflammation can result in resolution or organisation and pleural adhesions. Resorption and pulmonary architecture restoration occur in the final stage(4th).

Bronchopneumonia is a non-uniform condensation syndrome involving one or more lobes. It usually affects pulmonary areas dependent on the inhaled airflow, a model that can be associated with the aspiration of the oropharyngeal content. The neutrophil exudate is centred on the bronchi and bronchioles, with a centrifugal spread in the adjacent alveoli.

Interstitial pneumonia is a non-uniform or diffuse inflammation involving interstitium. It is characterised by lymphocyte infiltration and macrophages. Alveoli do not contain significant exudates but protein-rich hyaline membranes, similar to those found in adult respiratory distress syndrome (ARDS) which can delineate alveolar spaces. Bacterial superimposed infection on viral pneumonia can also produce a mixed pattern of inflammation of the interstitial and alveolar airspace. Milliary bronchopneumonia is a term attributed to multiple discrete lesions resulting from the spread of the pathogen into the lungs through blood flow. It is the consequence of the various degrees of immunodepression for tuberculosis(TB), histoplasmosis and coccidioidomycosis. Milliary bronchopneumonia can manifest as granulomas with caseous necrosis. Milliary bronchopneumonia in herpes viruses, cytomegalovirus (CMV) or varicella-zoster virus infections in patients with severely depressed immunity results in many acute necrotic hemorrhagic lesions.

ETIOLOGY

Pneumonia can be caused by many microorganisms. The clinical suspicion of a certain etiology is suggested by the anamnestic-clinical data. While virtually any microorganism can lead to pneumonia, specific bacterial, viral, fungal and mycobacterial infections are the most common in previously healthy children. Age of infection, exposure history, risk factors for unusual pathogens, and history of immunization provide clues for the infective agent. In a prospective multicenter study, 154 hospitalized children with acute community-acquired pneumonia (PAC), were completely screened for the etiology. A pathogen was identified in 79% of cases. The pyogenic bacteria were identified in 60% of cases, 73% of which were due to Streptococcus pneumoniae. Atypical germs such as Mycoplasma pneumoniae and Chlamydia pneumoniae were detected in 14% and 9%, respectively. Viruses were documented in 45% of children. From these cases, 23% had concomitant viral and bacterial disease. In the study, pre-school children had as many episodes of lower respiratory tract infections due to atypical bacteria as the older children. Multivariate analyzes showed that the high temperatures (>38.4 °C) recorded 72 hours after admission to hospital and the presence of pleural effusions were significantly associated with bacterial pneumonia (4).Different etiological agents vary according to age groups (ie newborns, infants, toddlers, preschool children, school-age children and young teenagers, older teenagers).

NEONATES

In newborns (0-30 days age old) the bacteria responsible for premature neonatal sepsis are usually involved in the pneumonia etiology. This reveals the role played by maternal genital tract and the gastrointestinal tract flora. Infections with Group B Streptococcus, Listeria Monocytogenes or Gram-negative (e.g., Escherichia coli, Klebsiella pneumoniae) are common causes of bacterial pneumonia. These pathogens can be acquired in the uterus, by aspiration of organisms present in the utero-vaginal canal, or by postnatal contact with other people or with contaminated equipment. The Streptococcus Group B (GBS) group was the most commonly bacterial isolate in most locations from the late 1960s to the late 1990s.

During this period the impact of intrapartum chemoprophylaxis in reducing neonatal and maternal infection with this agent became evident. Since then, E. coli has become the most commonly bacterial isolate among infants from VLBW (1500 g or less)(5).Other potential bacterial organisms include unstable Haemophilus influenzae (NTHi), other Gram-negative bacilli, Enterococci, Staphylococcus aureus.

Some perinatal infective microrganisms cause the disease only after birth: Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma hominis and Pneumocystis Carinii. Chlamydia trachomatis is transmitted at birth during transit through the infected pelvic genitals. Neonates are asymptomatic within the first 24 hours and develop pneumonia 2 weeks after birth. Group B streptococcal infections are most often transmitted to the fetus in the uterus due to the streptococcal colonization of the mother's vagina and cervix. Chronic congenital infections with CMV, Treponema pallidum (causing white pneumonia) or Toxoplasma gondii start with pneumonia during the first 24 hours of life. Clinically, other organs are also affected. Acute viral infections occur in neonates less frequently than in older children. Respiratory syncytial virus (RSV) is the most frequently isolated viral strain. The protection of newborns and infants from such infections is accomplished by maternal antibodies transfer. Premature babies do not benefit from sufficient immunoglobulin transplacental transfer [Ig G] which makes them vulnerable to CRI infections. Premature babies may also have chronic pulmonary disease that associates bronchial hyperreactivity, fewer functional alveoli, and increased basal oxygen demand. Newborns can also be affected by bacteria and viruses that frequently cause infections in infants and older children. Risk factors for infection include family contact, group care and lack of immunization.

SMALL INFANTS

In the young infant (1-3 months age), the previously mentioned perinatal pathogens remain incriminated. Nevertheless, S. pneumoniae, S. aureus and Nontypeable Haemophilus influenzae are common bacterial strains involved in the pneumonic process in this age group, but S.pneumoniae is the most common. Lung abscess, parapneumonic pleura and empyema might complicate any of these bacterial infections. S. Aureus is a well-known pathogen for such complications (6). At this age, infants are incompletely , and the risk of H. influenzae type B and pneumococcal disease is higher. Still, the immunity from the large-scale population immunization largely protects them. It is noteworthy that the conjugated pneumococcal vaccine provides protection against 13 common types of pneumococcus, but non-vaccinal strain types remain problematic.

Most CRI infections in young infants occur during the respiratory virus season and are therefore of viral origin, especially bronchiolitis. The most common viral agents include RSV, paragripal viruses, influenza virus, human adenovirus and metapneumovirus (hMPV). Atypical organisms can infrequently infect infants. Of these, C. Trachomatis, U. Urealyticum, and P. Carinii are described.

Infection with Bordetella Pertussis leads to pneumonia in 20% of infected infants (pneumonia, seen as a complication of cough infection).

Among other potential atypical pathogens, U. Urealiticum and U. Parvum were isolated from endotracheal aspirations shortly in very low birth weight (VLBW) and were variably associated with various adverse pulmonary effects, including pulmonary bronchospasm (BPD), (7, 8, 9, 10). These organisms could be causal or simply markers of high risk, it is not clear yet.

INFANTS, TODDLERS AND PRESCHOOL CHILDREN

In this age group, viruses are most common cause of pneumonia , accounting for approximately 90% of all infections of the lower respiratory tract. Tsolia et al. identified a viral infection in 65% of hospitalised children with community-acquired pneumonia (11). RSV is the most frequent viral strain, followed by paragripal type 1, 2 and 3 and influenza A or B. RSV infection occurs during winter and early spring. Type 3 paragripal infection occurs in spring while types 1 and 2 in the autumn, most commonly in winter. Other pneumonia-causing viruses, less common in infants and young children include adenovirus, enterovirus, rhinovirus and coronavirus. Recently, hMPV was mentioned on this list, causing a disease similar to RSV, and may be responsible for one-third to half of the non-RSV bronchiolitis. Herpesviruses (HSV, VZV and CMV) rarely cause pneumonia, especially in children with immune system disorders. In this age group, bacterial infections are more common. Pneumonia with S. pneumoniae is the most common. Among hospitalised children with bacterial pneumonia, S. pneumoniae is responsible for 21-44% of cases (4, 12, 13). Other pathogens: H. Influenzae type B (HiB) (very uncommon in immunised children), (14), S. pyogenes, and S. aureus. Children aged less than five years, children admitted to daycare centres or those with frequent otic infections present an increased risk of invasive pneumococcal disease and infection with resistant pneumococcal strains. Evidence suggests that breastfeeding has a protective effect against invasive pneumococcal infection.

SCHOOL-AGE CHILDREN AND YOUNG TEENAGERS

Mycoplasma pneumoniae is the most common pathogen in younger children and adolescents pneumonia. Mycoplasma represents 14-35% of hospitalizations with pneumonia in this age group (4,11,15). Homeless children, children's homes and family contacts pose a special risk. Similarly, a positive diagnosis in this respect should be

considered in immunocompromised children. In this age group, piogenic bacterial pneumonia remains a concern, usually caused by S. pneumoniae. Other pyogenic pathogens to be considered include S. Aureus and S. Pyogenes. Chlamydia Pneumoniae can also cause pneumonia. Chlamydia psittaci, is an unusual cause of pneumonia that occurs in families manipulating birds. Immunosuppressed individuals may experience opportunistic infections with Aspergillus, Pneumocystis Jirovecii and CMV. Viral pneumonia is common in this age group and is a particular concern because it is predisposed to bacterial superinfection, usually with S. pneumoniae or S. aureus.

TEENAGERS

M. pneumoniae is the most common cause of community-acquired pneumonia in teenagers and young adults. Atypical pneumonia caused by C. pneumoniae may exhibit identical signs and symptoms. S. pneumoniae bacterial pneumonia is also frequent.

Pulmonary infections caused by dimorphic fungi are also observed in this age group. Histoplasma Capsulatum found in nitrate-rich soils, cause the disease as a consequence of inhaling the spores. Cottages and other bird shelters and rotten woods are the most refered sources. Cryptococcus neoformans generates common infection among pigeon breeders but is unusual in other immunocompetent individuals.

Blastomyces Dermatitides, another dimorphic fungus, is found in some geographical locations, especially in the large rivers valleys. As with histoplasmosis, blastomycosis is obtained by inhalation of spores. Although there are three distinct forms of infection, the most common is acute pneumonia, which, in previously healthy individuals is most often resolved without treatment.

Viral pneumonia is common in this age group, usually mild and self-limiting, but influenza pneumonia can be severe or prolonged, especially when a bacterial infection is associated.

TB pneumonia in children deserves a special mention. BK pathogen may cause the infection at any age and it is important to note that children with TB usually have no symptoms for 1-6 months after the infection. Any infant with pneumonia who has a history of TB contact or who has travelled to an endemic area of tuberculosis should be fully assessed for the possibility of tuberculosis.

Legionella pneumophila, the agent of Legionnaires disease, can cause pneumonia, although it is uncommon in the pediatric age group. Not all types of pneumonia are caused by infectious agents. Children with severe gastroesophageal reflux (GERD) may develop chemical pneumonia secondary to recurrent aspiration. Inhalation of certain chemicals or smoke may cause pulmonary inflammation. In addition, aspiration pneumonia is more common in children with neurological pain, abnormalities of swallowing, gastrointestinal motility or the presence of a gastrostomy tube. Oral anaerobic flora, with or without aerobic strains is the most widespread etiological agent.

A study by Thomson et al. has evaluated hospital management by comparing the results of children with neurological pain diagnosed with aspiration pneumonia versus the cases with non-aspiration pneumonia. The study found that hospitalised patients with neurological pain diagnosed with aspiration pneumonia had a significantly longer duration of stay, more transfers to ICU, higher hospitalisation costs, and more than 30 days re-hospitalisation than children with neurological pain diagnosed with non-aspiration pneumonia (16).

ETIOLOGY IN IMMUNOCOMPROMISED CHILDREN

Some immunocompromised children are at risk of opportunistic pneumonia, whether they are secondary to HIV/AIDS or chemotherapy for malignancy or congenital disease. Virtually any bacteria, virus, fungus or even parasite can invade and infect the lungs if the immune system is sufficiently affected. Samples obtained with care for appropriate microbiological testing are of paramount importance in these patients, to optimise their therapy.

Children with cystic fibrosis are particularly prone to develop infections with S. aureus, Pseudomonas aeruginosa, Burkholderia cepacia and other multi-resistance organisms.

Pneumocistys Jirovecii Pneumonia (PCP) is common in severe immunological compromised children leading to respiratory failure and death. Adenovirus infections may be severe in these children, leading to obliterant bronchiolitis or hyperfluent pulmonary syndrome (Swyer-James Syndrome). In addition, CMV presents a high risk for immunocompromised patients. Fungal pneumonia caused by Aspergillus, Zygomycetes or other fungi, occurred in immunocompromised patients who have undergone prolonged hospitalisation, have prolonged neutropenia and/or have received broad-spectrum antibiotics. Patients with underlying haematological malignancies are at the highest risk.

Patients with schizophrenia have problems with the complement system as well as functional asplenia, predisposing them to infections with encapsulated organisms such as S. pneumoniae and H influenzae type B. M. pneumoniae is also a common agent of pneumonia in this group of patients.

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