Respiratory disease - congestion in the respiratory system

Lung diseases are by far the most frequent cause of death worldwide. Every year, three million people die from chronic obstructive pulmonary diseases, 2.3 million die from lung cancer and 1.5 die from tuberculosis (WHO – World Health Organisation). There is no improvement in sight and experts believe that the number of deaths will continue to rise, particularly in the case of chronic obstructive pulmonary diseases (COPD), lung cancer and tuberculosis (TB). It is estimated that of 68 million deaths worldwide in 2020, 11.9 million people will die of lung diseases.

The main cause of two of the most important lung diseases (lung cancer and COPD) is cigarette smoking, making these diseases theoretically preventable. However, there is a large number of other causes, ranging from genetic influences to factors such as nutrition, environment and poverty.

Lung diseases consume on average six per cent of a nation's health budget; in Germany the cost of treating respiratory system diseases accounts for 5.1 per cent of the health budget (around 12 billion euros).

The solution is simple in theory but more difficult in practice: many lung disease sufferers could improve their situation simply by giving up smoking. People with lung diseases often have to undergo long-term therapies; in many cases, the disease is chronic and life-threatening.

A growing understanding of asthma

Asthma is a common, often life-long chronic condition in which the airways become inflamed and narrowed. Asthma affects about 300 million people worldwide and around four million in Germany. The majority of deaths occur in people over 45 years of age. Every year, around 180,000 people worldwide die of asthma. Only a small proportion of patients suffer from the pure form of asthma (allergic or non-allergic).
Asthma can manifest itself at any age; it is the most frequent chronic disease in young children. It is impossible to prevent or treat asthma and its causes are not yet known in detail. It is known that a number of genes are related to an elevated asthma risk. Environmental factors such as contact with allergens and harmful substances can trigger asthma attacks. The airways become more susceptible to a broad range of different stimuli.

The majority of patients respond well to the traditional therapy involving beta2 agonists (bronchodilators) and inhaled inflammation inhibitors (corticosteroids). About five to ten per cent of severe asthmatics do not respond to these kinds of therapies. Monoclonal antibodies are one of the new therapies used to treat severe asthma; one such antibody has been on the market since 2005; a second one, which is directed against pro-inflammatory interleukin 13, is in late clinical development. Aerovance, a biopharmaceutical spin-out of Bayer based in the USA, has three substances in Phase II trials, including one for asthma.

A better understanding of the disease mechanisms has in the meantime led to the development of different phenotypes. Nevertheless, knowledge about the inflammatory mechanisms in the airways is still limited. Experts believe that effective treatment is still a long way off. Nevertheless, we now have a better understanding of asthma pathogenesis. Researchers are hoping to come up with a therapy involving several drugs targeted to specific subtypes.

COPD – an acronym for the devastating effects of smoking

The wider public is largely unaware what the English acronym COPD stands for. COPD stands for chronic obstructive pulmonary diseases, comprising chronic obstructive bronchitis (inflammation and narrowing of the airways) and lung emphysemas (destruction of the lung structures). COPD is life-threatening and irreversible. It is mainly caused by the inhalation of tobacco smoke and it affects both men and women in the same way.

Among the major causes of death, COPD is the only one that is on the increase worldwide. One in ten people over 40 years of age suffer from COPD. The European EMEA believes that this number is probably lower than the real figure, as COPD is only detected, i.e. becomes clinically relevant, once it has progressed considerably. 210 million people worldwide suffer from COPD. WHO figures show that the majority of deaths occur in underdeveloped countries. The WHO estimates that in 2020 six million people will die of COPD.

There is no cure for COPD, although there are some forms of treatment that can delay the progression of the disease. Medicinal therapies focus on improving quality of life and reducing mortality. Smoking has been identified as the cause of COPD in nine out of ten cases. As not all smokers develop COPD, it is assumed that genetic factors modify the individual risk of developing COPD. The only known genetic risk factor is the innate defect of alpha-1 antitrypsin. It is still unclear to what extent air pollution contributes to the development of COPD, but it is known that air pollution in cities is harmful for people with COPD. Passive smoking also gives rise to respiratory symptoms and diminishes the lung function in schoolchildren. In adults, these alterations can lead to COPD.

According to the current state of knowledge, COPD is much more than just a lung disease. It is a complex disease that is associated with a broad range of pathological changes: elevated mucus secretion, narrowed airways, the loss of alveolores, reduced body mass as well as cardiovascular effects on the systemic level. There are different clinical symptoms, severity and progression rate between one COPD patient and another.

According to the EMEA, different drugs are used to treat different COPD symptoms - either to improve the obstruction of the airways, alleviate the symptoms, change or prevent acute exacerbations, interfere with the progression of the disease or change the lung structure. The choice of strategy - without or with the use of drugs - that suits the requirements of individual patients and the stage of disease, remains a challenge. Nine COPD drugs are expected to receive marketing authorisation by 2013, including a substance produced by Boehringer Ingelheim that appears to have a positive effect on the progression of the disease.

Lung cancer: the prognosis remains bad
The lungs’ great enemy: smoking is regarded as a high-risk factor for COPD and lung cancer.

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Lung cancer affects the air tube (trachea), the airways (bronchia) or the lung tissue (alveoles). Cancer affecting the bronchia is the most frequent type of lung cancer. Lung cancer is the most frequent cause of death in Europe and worldwide. One out of every five cancer patients dies of lung cancer. There are two major types of lung cancer: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). The chances of surviving NSCLC, the most common type of lung cancer, are better than the chances of surviving SCLC, which tends to metastasise earlier than NSCLC.

The survival rates of lung cancer patients are worse than those of patients suffering from other common cancers. The five-year survival rate for men is 12 per cent and for women, 14 per cent. In Germany, the number of new lung cancer cases in men has been decreasing since 1990, while in women under 50 the number is on the increase. In Germany, lung cancer is the third most frequent type of cancer in both men and women.

As in COPD, the consumption of tobacco is also the reason why nine out of ten people develop lung cancer. 30% of all heavy smokers run the risk of developing lung cancer. Non-smokers only have a one percent risk of developing lung cancer. Certain genetic factors make smokers more susceptible to the effects of smoking, and hence increase the risk of developing lung cancer. “Passive smoking” increases the risk of developing lung cancer in non-smokers. Other substances (carcinogens) can increase the risk of developing lung cancer in both smokers and non-smokers.

The early diagnosis of lung cancer can probably improve individual survival rates, however, final evidence that this really is the case is still missing. Lung cancer therapy involves surgery, radiation and chemotherapy either individually or in combination. The treatment needs to be adapted to the individual type of lung cancer and the disease progression. Surgery to remove all of the lung cancer tissue is only possible in a limited number of cases.

The Association of Research-Based Drug Manufacturers lists 21 lung cancer drugs that are currently under development, the majority of these for the treatment of NSCLC. Bayer Schering (one drug candidate) and Boehringer Ingelheim (four drug candidates for both types of cancer) hope to launch their respective drugs by 2013.

Pneumonia – an underestimated danger

Pneumonia is an infection caused by bacteria, viruses, fungi and other microbes. The alveoles accumulate liquid produced by the inflamed tissue. The severity of the disease depends on the pathogen that causes the pneumonia. Pneumonia occurs in non-industrialised or less developed countries, but epidemiological data are rare. Since 1998 in Germany, pneumonias have become one of the major causes of death in men and women.

Patients with severe pneumonia require intensive medical care and occasionally also need to be respirated. It takes a long time to recover from pneumonia. In adults, mortality due to pneumonia increases with age. The incidence of pneumonia is highest in small children and older adults. Viral pneumonias are often very mild, but can have life-threatening consequences in very old and very young patients as well as in patients with weakened immune systems.

Bacteria, in particular pneumococci, are the major cause of pneumonia. Studies on the most frequent causes of community-acquired pneumonias (CAP) are unavailable for the majority of countries. More than ten CAP pathogens are known. In many European countries, CAP bacteria have developed resistances to common antibiotics. Little information is available about the causes of nosocomial pneumonia (hospital-acquired pneumonia). The multiresistance of bacteria to antibiotics increases in the case of nosocomial pneumonia.
Smoking is the most important risk factor in the development of CAP, and it is a risk factor that can be prevented. Increasing age, COPD and previous respiratory tract infections are additional risk factors. In older patients, alcoholism, asthma, immunosuppressive therapy, chronic lung diseases, chronic heart diseases, living in nursing homes and increasing age are important risk factors in the development of pneumonia.

An early antibiotics therapy can effectively treat bacterial pneumonia. No general treatment is available for viral pneumonia, although some newer antivirals have been shown to be effective in individual cases. The major pneumonia pathogen, Pneumococci, fascinates immunologists and frustrates physicians.

Although the respiratory tract has numerous defence mechanisms, the pathogen has a broad range of virulence factors that enables it to circumvent immunological defence. The potential ability of Pneumococci to become resistant to antibiotics has led researchers to focus on different strategies for treating Pneumococci infections: new vaccines, new antibiotics and improved medicinal therapies. Large pharmaceutical companies are working on the development of new antibiotics and vaccines against bacterial infections. Bayer Schering is developing a substance against pneumonia that is caused by Gram-negative bacteria and that will be used to treat intubated and artificially ventilated patients.

**Powder keg: resistant TB bacteria**

Since the 1990s, tuberculosis (TB) has once again become a priority issue for public health systems. The number of TB cases has dramatically increased in Eastern Europe. Tuberculosis is caused by mycobacteria (Mycobacterium tuberculosis) where the slow progression of inflammation leads to the destruction of tissue, particularly lung tissue. Minimal mycobacterial infections can spontaneously cease, but, if left untreated, they can break out again and progress.

The major risk factors for TB are poverty, malnutrition, bad living conditions, inadequate health systems, drug misuse and advanced age. It is also assumed that genetically determined susceptibility plays a role in whether an infected person develops an active disease. HIV patients have a far higher risk of becoming infected (up to 70-fold higher) and an up to 100-fold higher risk of developing active TB.

Antibiotics have been shown to effectively treat TB in nine out of ten cases. A range of different antibiotics are combined and administered over a period of at least six months and sometimes running to 12 months or even longer. The treatment of multiresistant TB requires the use of special drugs over a period of more than two years.

In Germany, TB has been decreasing in the last fifty years. However, on the global level, the frequency of TB cases is on the increase. According to WHO estimates in 2002, the number of tuberculosis sufferers is as high as 8.7 million and the number of deaths is around two million per year. More than two billion people are infected with Mycobacterium tuberculosis. Although only one in ten people develops TB, the number of resistant pathogens is nevertheless increasing. Almost fifty per cent of all multiresistant pathogens are resistant to certain antibiotics right from the start. Resistances usually develop following the abandonment of drugs or due to the administration of low doses of antibiotics. The WHO estimated that in 2007 there were 9.27 million new TB cases and 1.78 million deaths; at least 14.8% of those that had newly developed TB were also infected with HIV. The head of the WHO, Ms. Chang, compared the growing resistance of the mycobacteria with a powder keg (2009).

Recent publications leave some room for hope: benzothiazinone showed excellent results in vitro, the substance was able to block a mycobacterial enzyme and kill the mycobacteria, including strains that are resistant to one or more available antibiotics (doi: 10.1126/science.1171583). Another study (Science 323, 1215-128 (2009)) reported about laboratory experiments that led to the successful sterilisation of bacteria. Bayer Schering and the TB Alliance are developing a new antibiotics combination that will be used as part of a combinatorial therapy. According to information from the VFA, a second substance is currently being developed in Japan.

**Cystic fibrosis: still no causal therapy available**

Mucoviscidosis or cystic fibrosis is a common hereditary disease that mainly affects the respiratory organs and the digestive tract of children and young adults. The gene that results in cystic fibrosis was identified in 1989. More than 1,500 mutations are known, but the effect is only known in a few of these. The disease is not found in Asia and Africa, but is quite common in Northern Europe.

Mucoviscidosis leads to the production of thick mucus that obstructs the bronchia, thereby leading to permanent infection and irreversible lung damage caused by scarring. The thick mucus in the lungs has a counterpart in thickened secretions from the pancreas which block the movement of the digestive enzymes into the duodenum. 94% of all mucoviscidosis fatalities are the result of the failure of the respiratory organs.

Better medical therapies have increasingly improved the prognosis of mucoviscidosis sufferers who now have a life expectancy of around 30 years. However, children born with mucoviscidosis in the 1990s now have a life expectancy of around 40 years. Specific treatments that would make it possible to correct the genetic defect are still not available. Different medicinal treatment strategies have been tested, gene therapy is still in the experimental stage. 34% of all European mucoviscidosis patients have reached adulthood, and it is estimated that this proportion will increase. According to VFA, five substances are currently in late development phases.

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