World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

# Respiratory infections in the XXI century: Challenges and changes

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World Journal of Advanced Research and Reviews, 2024, 23(03), 1900–1906

Publication history: Received on 27 July 2024; revised on 06 September 2024; accepted on 08 September 2024

Article DOI: https://doi.org/10.30574/wjarr.2024.23.3.2730

## Abstract

Respiratory infections are still a social and therapeutic problem facing the medical community worldwide. A number of factors such as age, comorbidities, immune status, lifestyle, emerging viral infections with pandemic potential (pandemics), and antimicrobial (bacterial) resistance influence the incidence, clinical course, and treatment of respiratory infections. Knowledge of these factors is essential for the correct choice of therapeutic approach.

**Keywords:** Respiratory Infections; Antibiotics; Resistance; Modulators

## 1. Introduction

### 1.1. Epidemiology

The discovery of Penicillin in 1928 by Flemming has marked the beginning of a new era – the era of antibiotics. A new remedy to fight infections, one of the major causes of death during the pre-antibiotic era, has been discovered. Presently different classes of antibiotics are in use, much of the lethal infections until 100 years ago are already curable and do not threaten patients' life as a century ago [1]. Nevertheless, in the XXI century infections and particularly the respiratory ones, are still a problem for the medical community [2].

Pneumonias are pointed out on the first place as cause of death from infectious diseases in a report published in 2020 analyzing the morbidity and mortality from different diseases worldwide, comprising the period between 1990 and 2019 – worldwide 2.49 mln people has died from pneumonia. The recent COVID-19 pandemia has caused the death of 2 mln people, acute gastroenteritis – of 1.52 mln, tuberculosis – of 1.18 mln, the HIV infection – of 860 000, malaria – of 640 000. At the bottom of this peculiar "ranking" are the meningitis (240 000 deaths), the neo-natal sepsis (230 000 deaths), the typhus (130 000 deaths), the pertussis (120 000 deaths), the encephalitis (90 000 deaths) [2].

Pneumonias are leading cause of death in the countries in Sub-Saharan, Equatorial and South Africa, Western South America, Central and South-Eastern Asia (Afghanistan, Thailand, Laos, Cambodia, Malaysia, the Philippines, Papua-New Guinea). The distribution by age shows mortality decrease among children up to 5 years of age and increase among elderly above 70 years of age [2]. A similar tendency is also noticed in developed countries like the USA for example. In a two years research studying the burden of community acquired pneumonias (CAP) on the US healthcare system is established that almost 1.5 mln people are hospitalized because of CAP. The hospitalizations rate increases by age exponentially – in the range between 18 and 64 years of age it is 3.27 cases per 1000 people, and in the range above 65 years of age – it is 20.93 cases per 1000 people [3]. From all hospitalized with CAP 20% are with severe pneumonia and need intensive care [4].

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### 1.2. Modifying factors

A number of modifying factors influence the clinical course of pneumonia like age above 65 years, immunosuppression, life style (alcohol and drugs use), comorbidities like COPD, diabetes mellitus, asthma, heart failure, antibiotic therapy during the last 3 months begore hospitalization, prolonged (more than 5 days) hospitalization. These factors are called modifying because they influence the clinical course of pneumonia and some of them are associated with certain causes of lung parenchymal inflammation requiring therapy with certain antibiotics [5-8]. During the annual European Respiratory Society (ERS) congress in Milan, 2023, Dr Catia Campos has defined the following challenges standing in front of the respiratory infections in XXI century:

- Increase of elderly population.
- Increase in number of people with obesity.
- Increase in number of people with diabetes mellitus.
- Increase of tobacco products consumption.

#### *1.2.1. Increase of elderly population*

It is expected by 2030 the elderly people to account 16% of world's population, and by 2050 people above 65 years of age to become near 1.5 bln [9]. The aging changes that occur in the elderly above 65 years of age in the immune, respiratory, vascular, and nervous systems are the reason for more frequent and longer hospitalizations of these patients in intensive care units (ICU) [10]. An observational study that has lasted for 10 years explores the ICU hospitalizations for acute respiratory infections and acute COPD exacerbations. A rate increase by age is reported – it is significantly higher among people above 80 years of age compared to those between 75-79 years of age and below 74 years of age [11].

#### *1.2.2. Increase in number of people with obesity*

It is expected by 2035 51% of world's population to be overweighted [9]. Systemic inflammation that develops in overweight people has a negative effect on immune system, that's why they get ill severely from respiratory viral infections like flu for example [12]. A big prospective study shows higher rate of lower airways infections (pneumonias, bronchitis) in obese patients. This association is more pronounced among females than males [13].

#### *1.2.3. Increase in number of people with diabetes mellitus*

In 2021 529 mln people has been with diabetes mellitus, 96% of them with type 2 diabetes, 22% are older than 70 years of age [9]. Diabetes mellitus is considered as independent risk factor for lower airways infections development and as determining factor for their severity [14,15]. Among people with diabetes the immune response is generally impaired. Hyperglycaemia damages different components of cell immunity – chemotaxis, adhesion, phagocytosis and intracellular killing in different degrees. The anaerobic conditions in the tissues created by the vascular disorders that develop in diabetes mellitus and the systemic inflammatory response impair the additionally immune response [16]. Metabolic decompensation and certain immunological problems like defective neutrophilic function are determined as worsening respiratory infections factors [14,17]. The fact that the impaired bronchomotor activity also contributes to the worsened pneumonia prognosis in diabetic people by impairment of airways defensive reflexes and by ventilation/perfusion mismatch as well should not be ignored [18]. On the other hand, neuroadrenergic dysfunction may slow down the recovery from respiratory infection by mucociliary clearance impairment which is physiologically stimulated by adrenergic stimuli or by provocation of bronchospasm in predisposed people [19].

Among people with diabetes mellitus the rate of infections is increased and some of them are with complicated course [20]. According to Tiengo *et al*. hyperglycaemia is associated with bad prognosis pneumonias and acute COPD exacerbations [21]. According to Baker *et al*. among COPD patients the absolute risk for unfavorable side effects (death or hospital stay longer than 9 days) is significantly increased at blood sugar level above 7 mmol/l [22].

#### *1.2.4. Increase of tobacco products consumption*

In 2022 22% of world's population has been using tobacco products, 37% of them are men and 8% women [9]. Tobacco smoking increases the risk of airways infections. This is due to the negative influence of tobacco smoke (no matter whether from traditional cigarettes or electronic smoking devices) on different structures of respiratory system – epithelial barrier impairments, mucus hypersecretion, impaired mucus clearance facilitating the colonization with pathogen microorganisms. The long-term tobacco smoking impairs immunity by suppressing immune molecules production thus also facilitating airways colonization by pathogen microorganisms. Tobacco smoke suppresses phagocytosis of bacteria and dead cells by the macrophages and suppresses maturation of dendritic cells and their α-

interferon expression. In addition, long term smoking leads to lymphopenia, suppresses T- and B-cell immune response and causes decreased antibodies production. In an extensive review studying the influence of tobacco smoking on respiratory infections, Jiang *et al*. establish increased rate, more frequent hospitalizations and prolonged hospital stay among smokers because of infections caused by influenza, parainfluenza, *M. tuberculosis*, pneumococci, atypical microorganisms (*M. pneumoniae*, *Chl. pneumoniae*, *L. pneumoniae*). In addition, reactive oxygen species in tobacco smoke impair the integrity of respiratory tract and alveolar epithelial cells, thus increasing the risk of infections development. The reactive oxygen species impair the alveolar epithelial cells mitochondrial function by suppressing the adenosine triphosphate production which on its side leads to cell necrosis and progressive inflammation in the lungs. On the other hand, the nitric oxide which is endogenously produced in the airways reacts with the reactive oxygen species in tobacco smoke, reactive nitrogen species are formed that damage the DNA, lipides, proteins and carbohydrates of the epithelial cells and this leads to their apoptosis and necrosis [23].

### 1.3. Immunosuppression and polymorbidity

Immunocompromised and polymorbidity patients should be added to the four challenges stated above.

Systematic review comprising 70 studies from 55 countries with different economic status shows that for a period of 25 years (1992-2017) increase of polymorbidity (presence of more than two chronic diseases in one organism) together with increase of age is present, with more than 50% of people above 65 years of age being polymorbid. The tendency is almost equally pronounced in the two genders [24]. Polymorbidity is the cause for more frequent short termed or long termed hospitalizations and for increased mortality in the ICUs among patients older than 65 years of age [25,26].

Pneumonia causes significant clinical burden on immunocompromised patients. On one hand, millions of people live with compromised immunity due to cytotoxic treatment for carcinoma, biological treatment, solid organ transplantations, inherited or acquired immune deficiencies and other impairments [27]. At the same time, the number of immunocompromised adults is increasing due to the greater life expectancy because of the improved medical cares and the increasing indications for immunosuppressive treatment [28-31]. The immunosuppression increases the risks for and the severity of the primary or reactivated infections. Its distribution has consequences for the safety of foods and water, tuberculosis control, vaccination programs, control of infections strategies, epidemic control, travel medicine and other aspects of public health [28]. Harpaz *et al*. present interesting data. According to them almost 3% of the US population is with immunosuppression, with its rate decreasing together with the age – it is 4.4% among people between 50 and 59 years of age, 3% among those between 60 and 69 years of age, 3.1% among those between 70 and 79 years of age, and 2.5% among those older than 80 years of age. The group of immunocompromised patients is heterogenous – carcinoma patients, transplanted patients, patients receiving immunosuppressive medications for other conditions, e.g. HIV, autoimmune diseases [32].

Extensive study comprising 3702 patients from 222 hospitals from 54 countries shows that almost 18% of patients have at least one immunocompromised condition. Distributed by rate, the steroid overuse, the haematological malignant diseases, patients on chemotherapy, those with HIV-infection, with neutropenia, on biological treatment for different tumours or other conditions are at leading positions. Patients receiving immunosuppressive therapy for solid organ transplantation are on the last place. Bacteriemia is established in 6% of immunocompromised, the most isolated causative agent among those receiving standard therapy for CAP (i.e. therapy according to the consensuses) is *P. aeruginosa* (5.9%, $p<0.02$), among patients not receiving standard therapy *Nocardia spp* is isolated (0.7, $p<0.007$) followed by nontuberculous mycobacteria (0,8%, $p<0.002$), *A. fumigatus* (1.3%, $p<0.01$), *P. jirovecii* (2.0%, $p<0.02$) and viruses like coronavirus (0.5%, $p<0.047$) and respiratory syncytial virus (1.0%, $p<0.03$). It is an interesting fact that patients not receiving standard therapy for CAP (i.e. who are not treated according to the consensuses) are more frequently associated with COPD, tracheostomy, and severe pneumonias. Among patients with AIDS and haematological neoplasms mycotic infections are more frequent, among patients with haematological neoplasms and severe pneumonias – viral infections different from influenza, and among patients with AIDS and malnutrition – mycobacterial infections. Additional analysis has shown that infection with *M. tuberculosis* is more frequently established among patients with malnutrition, and among patients with AIDS – infection with nontuberculous mycobateria [33]. Pneumococcal infection (pneumonia) is noticed more often among carcinoma patients receiving chemotherapy followed by those with advanced carcinoma, advanced HIV-infection receiving steroid therapy. The rate of pneumococcal pneumonia is comparatively low among patients on biological treatment, with primary immune deficiency, rheumatological patients treated with antimetabolites like cyclosporine, cyclophosphamide, hydroxychloroquine and methotrexate, and transplanted patients [34].

### 1.4. Influence of COVID-19

The recently past pandemia caused by SARS-CoV-2 virus is another factor influencing the respiratory infections. Tashiro *et al*. present interesting data. They have established decrease of hospitalizations for pneumonias and decrease of the 30-day mortality from pneumonia in Japan during the pandemia. According to them this is due to the nonpharmacological measures taken by the government to cope with the pandemia – working from home, wearing of masks, enhanced disinfection, keeping the distance, etc. [35]. Similar data are reported in a Canadian study held during the pandemia – sharp decrease of the seasonal morbidity from influenza A and B and respiratory syncytial virus for the 2020/2021 season. Thanks to the anti-epidemic measures prematurely interruption of the seasonal influenza epidemy is noticed in the United Kingdom, Japan, Taiwan, Korea, Thailand, Australia and New Zealand [36]. The goal of these measures is to limit the distribution of SARS-CoV-2 virus but at the same time thanks to them a limitation of the distribution of the rest respiratory viruses is reached.

The nonpharmacological measures taken to limit the distribution of SARS-Cov-2 are the reason for sharp decrease of the morbidity from infections caused by pneumococci and *M. pneumoniae*. Observational studies held in the United Kingdom, Germany and Canada show that after the release of the non-pharmacological measures an increase of the morbidity from these infections is noticed at a carrier level of the pathogens and vaccination with antipneumococcal vaccines similar to those before the pandemia [37-40]. The association of the SARS-CoV-2 infection with those caused by *S. pneumoniae*, *S. aureus*, *H. influenzae* is a new one and has been described in studies held after the pandemia [41-45]. It shows the epidemiological influence of the SARS-CoV-2 pandemia on the respiratory infections expressed by the change of the distribution of certain respiratory pathogens.

### 1.5. Bacterial resistance

Bacterial antimicrobial resistance (BAR) is another challenge standing in front of the respiratory infections in XXI century. The main reason for its development is the mass antibiotics prescription not tailored to the guidelines for the treatment of infections and in particular the airways infections.

An extensive report from 2019 on BAR comprising 23 pathogens and 88 combinations pathogen-medication from 204 countries and territories shows that 4.95 mln deaths are due to BAR. The most of them are from Western Sub-Saharan Africa and the least are from Australlia. 1.5 mln deaths are due to BAR, the broadest resistance is established among the next 6 pathogens: *E. coli, S. aureus, K. pneumoniae, S. pneumoniae, A. baumannii* and *Ps. aeruginosa*. 929 000 deaths directly associated with BAR are due to those pathogens and 3.57 mln deaths are associated with BAR [46]. The SARS-CoV-2 pandemia has contributed to the enlargement of BAR in a very large degree. As known, during the pandemia and especially at its beginning at least two antibiotics are used to treat patients, most often fluoroquinolone (moxifloxacine, levofloxacine), β-lactame (ceftriaxone) and macrolide (azithromycine) [47]. This is due to two reasons [48]:

- The symptoms of SARS-CoV-2 infection resemble very much to those of pneumonia and often the tests proving the SARS-CoV-2 become positive on the 3rd or 4th day since the beginning of the infection, a period during which every viral infection is complicated by a bacterial one.
- The SARS-CoV-2 infection is accompanied by bacterial co-infection like every other infection and this requires an antibiotic to be added to the therapeutical scheme.

The association between BAR and SARS-CoV-2 infection is a two-way one:

- emergence of resistance (use of antibiotics, antibiotics supply, noneffective treatment, antibiotics prescription “for assurance”);
- resistance transmission (over use and long use of antibiotics, prolonged hospital stay, healthcare system overload, bad hands hygiene, low vaccination level);
- overload with infections caused by resistant pathogens (over use and over prescription of antibiotics, suboptimal treatment, prolonged hospital stay, low vaccination level, increased antibiotics intake “for assurance”) [48].

On the other hand, BAR influences the SARS-CoV-2 pandemia by causing co-infections with extensive resistant strains of bacteria and fungi – broad spectrum β-lactamase producing (ESBL) *K. pneumoniae*, carbapenem resistant New Delhi metalo-β-lactamase producing (NDM) *S. aureus* (MRSA), pan-echinocandin resistant *C. glabrata* and multi-triazole resistant *A. fumigatus* [47].

Materials presented at the session "Community acquired infections - what is changing?" at ERS International Congress, Milan, Italy, 9-13 Sep 2023 are used in this article.

## 2. Conclusion

The highly technological XXI century sets a number of challenges in front of the medical community to cope with the respiratory infections. In this review some of them are pointed out – increase of elderly population, obesity, diabetes mellitus, overuse of tobacco products. To these factors modifying the course and management of respiratory infections immunosuppression and polymorbidity should be added together with the occurrence of infections caused by new pathogens like SARS-CoV-2 and the overuse of antibiotics. The exploration of these modulating factors is essential for the medical community in its fight with the respiratory infections. It will increase our knowledge on how they influence the epidemiology, clinical course and management of respiratory infections, and will improve the cares for the patients and decrease the distribution and mortality of respiratory infections.

## Compliance with ethical standards

*Disclosure of conflict of interest*

No conflict of interest is disclosed by the authors.

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