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Respiratory infections: A current and future threat

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ABSTRACT

Despite all the medical progress in the last 50 years pulmonary infections continue to exact and extremely high human and economic cost. This review will focus on the human, pathogen and environmental factors that contribute to the continued global burden or respiratory diseases with a particular focus on areas where we might hope to see some progress in the coming decades.

Key words: burden, cost, respiratory infection.

INTRODUCTION

Despite all the advances in medical science in the past four decades, lower respiratory tract infections remain the fourth most common cause of death in middle to high income countries and the leading cause of death in low income countries.[1] Mortality aside, respiratory tract infections have an enormous economic cost. The annual global cost is unknown, but in the USA the direct cost of community and nosocomial lower respiratory tract infections was estimated at US$15 billion in 1985.[2] By 2001 the economic burden of non-influenza viral respiratory tract infection alone had increased to US$40 billion in the USA.[3] Including direct and indirect costs (such as loss of work time), the cost of influenza alone in the USA is currently estimated at US$87 billion per year,[4] although total indirect costs have been estimated by others at over US$100 billion annually.[5] Clearly, the global cost of respiratory infection must be in the trillions (US$) per year.

In this final article in the pulmonary infectious diseases series we will discuss why pulmonary infections remain a major health problem and are likely to continue to be so well into the foreseeable future.

THE ENVIRONMENT IS NOT STERILE

The first and most obvious reason why pulmonary infections remain a problem is that potential pathogens abound in our everyday environment. While some pathogens are dependant on human-to-human spread, there are numerous examples of pathogens that normally invade their host directly from an environment source. Typical examples include *Legionella* spp., non-tuberculous mycobacteria and a plethora of fungi and molds, including *Cryptococcus*, *Histoplasma*, *Aspergillus* and *Coccidiomycosis*, just to name a few. While our immune systems have adapted in response to environmental threats, these pathogens will always remain a threat, particularly in subjects whose immune response becomes compromised by age or disease.

Human disease may also result from pulmonary pathogens crossing directly from animals to humans. Among the well-recognized respiratory zoonoses are *Chlamydia psittaci* (psittacosis), *Coxiella burnetti* (Q-fever), *Fracisella tularensis* (tularaemia) and of course viral infections such as Influenza and Hanta. While many of these infections can be avoided by strict hygiene protocols, wherever there is close

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proximity between humans and animals, such as in large parts of the developing world, some inter species transmission inevitable.

The largest risk in the environment, however, comes from other humans, as the vast majority of pulmonary infections are acquired from other infected individuals. This is particularly true of viral infections. The more crowded the human environment, the faster the spread of respiratory pathogens through the population. During the severe acute respiratory syndrome (SARS) outbreak, extensive public health campaigns aimed at reducing spread of respiratory droplets by good cough hygiene, the avoidance of work, school or day care during acute infections, and a massive uptake in mask wearing in the general populace had a dramatic effect on the rates of all viral respiratory infections in Hong Kong.[6] As relaxing these efforts led to a return to normal rates of viral transmission, much more can clearly be done to reduce community spread of pulmonary pathogens, especially during pan/epidemics.

Nosocomial transmission of pulmonary pathogens is also a major environmental problem. Hospital outpatient clinics are a well-documented source of transmission of multi-resistant bacteria between patients with cystic fibrosis[7] and bronchiectasis.[8] Intensive care units, particularly those with long-term ventilated patients, are also a frequent source of recurrent cross infection with multi-resistant bacteria.[9]

Environmental pools of organisms within hospitals themselves have also been commonly associated with outbreaks of nosocomial pneumonia with pathogens, such as *Legionella*,[10,11] *Aspergillus*[12,13] and *Mucormycosis*.[14] While it is clear that strict infection control can reduce nosocomial infection rates,[15] the practical necessity of pooling vulnerable hosts together combined with the inevitable ageing of health-care facilities will ensure that nosocomial outbreaks continue to be a problem.

WE ARE INCREASING THE POOL OF VULNERABLE HOSTS

Not only is the average age increasing, but the number of very elderly people in whom senescence-related immune compromise is common has dramatically increased over the past few decades in most western countries. A very large number of age-related immune deficits have been described. Key changes increasing the risk of pulmonary infections include the production of lower affinity antibodies, reduced phagocytic ability and reduced responsiveness of naïve CD4-positive T cells.[16] What is also important is that the pro-inflammatory response becomes progressively less regulated in the elderly,[17] often termed 'inflamm-ageing'.[18] The excess pro-inflammatory cytokine response is almost certainly a significant factor in the increased the risk of septic shock, ARDS and multi-organ failure in elderly patients with pulmonary sepsis.[19]

Further complicating the fact that we have more vulnerable aged people in our communities is that we cluster them together. The close contact between elderly individuals in nursing homes and other aged-care residences frequently leads to rapid spread of new pathogens throughout the facility, as many case series have documented.[20–25] While this close clustering is to some extent an economic necessity, much more study is required into how to limit the spread of respiratory pathogens in aged-care facilities, particularly in epidemic circumstances.

Age aside, advances in medical care have also meant a vastly expanded pool of people with chronic organ failure living in the community. Cardiac failure, chronic renal failure and diabetes in particular are all associated with a significantly greater risk of death from pneumonia.[26] Unfortunately, it also appears that immunization, at least against influenza, has substantially reduced efficacy in these vulnerable groups.[27–29]

Adding to increasing age and increasing numbers of people with chronic organ failure in our communities is the additional factor of deliberate immunosuppression. In recent years the marked increase in tumour necrosis factor antagonists and monoclonal antibodies targeting specific lymphoid populations in patients with inflammatory arthritis (and especially rheumatoid disease) has significantly over taken patients on immunosuppressant therapy after solid organ transplantation as the major cause of iatrogenic immunosuppression. An increased risk of tuberculosis in particular has been a major problem with TNF antagonist therapy.[30]

At the milder end of iatrogenic immunosuppression is recent evidence that inhaled corticosteroids, commonly used in asthma and COPD, probably increase the incidence of pneumonia.[31] However, whether this statistical increase in pneumonia is clinically important remains unclear as total mortality is not increased and total hospitalizations are lower, suggesting that the small increase in risk of pneumonia is more than compensated for by other beneficial effects.

SOME PATIENTS PRESENT TOO LATE TO MODIFY THE COURSE OF THEIR DISEASE

Austrian and Gold demonstrated that it takes time, possibly days, for antibiotics to alter the natural course of pneumonia.[32] More recent papers demonstrating potential benefits of combination antibiotic therapy in pneumococcal pneumonia show a similar delay between the onset of antibiotic therapy and an identifiable benefit,[33,34] and a review of all deaths from community-acquired pneumonia in young adults in the UK also found that many presented too late to benefit from any available therapy.[35]

Patients delay presentation to medical care when they have pneumonia for many different reasons. In some cases it is possible that the onset of disease is so swift that they are unable to seek help, especially if they live alone. However, many complex psychological and practical factors, including financial ability to access health-care, factor into the decision to delay medical treatment.[36]

The lack of potential for new antibiotics to alter early mortality requires new approaches to be developed. Drotecogen alpha does appear to reduce some of the organ damage in patients with pneumonia and sepsis but the survival benefit is modest.[37] As discussed in the review on *Streptococcus pneumoniae*,[38] reducing the virulence of invading pathogens is one promising line of research.

In nosocomial pneumonia, and especially ventilator-associated pneumonia, delayed recognition and hence delayed initiation of therapy is also associated with increased mortality.[39,40] Due to the frequent lack of significant inflammatory response and often the very non-specific nature of patient symptoms (if any), diagnosis of nosocomial pneumonia remains a clinical challenge. All recent guidelines have called for significant research in new diagnostic methods;[41–43] however, this remains a significant unmet need.

PATHOGENS ADAPT TO CHALLENGES FASTER THAN WE DO

Human pulmonary pathogens are so well adapted to their human hosts that many cause little or no disease in animals. Some pathogens have also developed substantial adaptations to evade our immune responses to them. Structural change to the cell wall of *Mycobacterium tuberculosis* enabling it to resist digestion after phagocytosis is one well-characterized adaptation. An example of the extent to which human pathogens can adapt is the production by some viruses of an IL-10 like protein that can directly downregulate immune response.[44]

As well as adapting to our innate immune response, pathogens also modify their genome in direct response to our attempts to reduce their virulence. The multitude of mechanisms by which bacteria have become antibiotic resistant is well documented, and due to these adaptations we now have problems with a wide range of pulmonary pathogens such as pan-resistant *Pseudomonas aeruginosa*[45] and extensively drug-resistant *M. tuberculosis*.[46] Even in the community setting drug-resistant pathogens, such as methicillin-resistant *Staphylococcus aureus*, are beginning to become a significant concern as a cause of pneumonia in some regions.[47] Viruses can also adapt to anti-viral agents, for example neuraminidase inhibitor-resistant influenza.[48]

While not responding to any external pressure, the constant modification of viral genomes also ensures a steady supply of pathogens. Antigenic drift and antigenic shift continue to keep influenza near the top of the list of pulmonary pathogens. New pathogens, like the coronavirus responsible for SARS,[49] are also certain to continue to emerge, much as HIV did in the 1980s. Finally, if new threats do not arise naturally, there is always the unfortunate possibility that humans will deliberately introduce them.[50]

Given the capacity for pathogens to adapt, it seems likely that regardless of what antimicrobials we develop, the development of resistance is inevitable. However, even if antibiotic resistance does not develop, clearing out one pathogen simply creates space for another to move in. Bronchiectasis and cystic fibrosis are classic examples of a procession of bacteria occupying vacated niches. Non-tuberculous mycobacteria, which have increased significantly in the past few decades as problematic pulmonary pathogens,[51] are another example of bacteria finding new niches. The emerging data on serogroup replacement in pneumococci in response to pneumococcal vaccination[52] are further evidence that the efficacy of any strategy we develop to reduce bacterial infections is likely to reduce over time as bacteria adapt to the niche available.

CONCLUSION

Human pathogens have evolved with us and are well adapted to overcome our innate immune responses. When pressure has been applied, either through antibiotics, antivirals or vaccination, pathogens have either shown the capacity to adapt to them or new pathogens have occupied the vacated niche. As we continue to increase the population of vulnerable hosts, pulmonary infections will remain a major health problem for the foreseeable future. New antibiotics and antivirals may help with specific threats, but will not address most of the fundamental problems. New therapeutic and diagnostic approaches coupled with clinical vigilance, strict infection control and solid public health measures are the hopes for reducing the burden of pulmonary infectious disease over the coming decades.

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