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Urbanization in Lahore leads to Respiratory Issues – A Microbiological Perspective

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Abstract

Pakistan is an important country of South Asia. Lahore is its historical city with rich cultural values. The development of cities like construction of new roads, is indication of economic progress of a country. During last decade, Lahore city remains in the state of construction of new roads for providing Metro bus service facilities to the public in general which is considered a blessing. Due to continuous construction, dust clouds were normally observed. These contain dust particles which harbor microorganisms. By inhalation, these dust particles cause upper and lower respiratory tract infections which leads to respiratory health issues. As professionals, school going children, street hawkers cannot avoid the dust, it can be cope up by adopting the precautionary measures.

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Introduction

Lahore – a historical city of Pakistan

Asia is a continent that is famous for its diversity, population, and culture. Currently it covers about 30% of Earth's land and is home for 60% of population. Pakistan is an important South Asian country. It has four provinces namely Punjab, Sindh, Baluchistan and Khyber Pakhtunkhwa (Song *et al.*, 2015). Lahore is a major city of Punjab (Amin, 1988). Drastic changes have modified this city during last decade. The Punjab government has invested a lot of money to make new road and to modernize the city. The mega project of Metro buses in Lahore has helped public to find living for them and also helped the people to make their journey easy (National Logistic Cell, 2017). For construction of routes for Metro bus track, Lahore city is under construction for one decade. Lot of dust during construction was faced by the local public.

Urbanization – an introduction

Urbanization is the modernization of cities. It is rapidly taking place all around the globe. Apart from affecting the biodiversity of animals and plants, it is also affecting the microbial ecology. It directly changes the properties of soil which affects the microbial flora of that land (Yan *et al.*, 2016). It also disturbs the demography of a city, traffic pattern, economic activities, construction of new plaza, construction of new roads, etc. (Hopke *et al.*, 2008; Beirle *et al.*, 2011; Ma *et al.*, 2012; Zhang *et al.*, 2014). It also covers the vast topic of industrial development. It leads to major health risks including throat problems, respiratory problems, skin allergies, cardiac problems, high blood pressure, etc. (Matus *et al.*, 2012; Wong, 2013; Rohde and Muller, 2015). The persistent presence of high levels of fine particles (PM 2.5) is responsible for making the air quality declared as bad (Liu *et al.*, 2012; Yuan *et al.*, 2012; Fang *et al.*, 2015). It is already reported that people are always exposed to bioaerosols and other non-biological materials. The origin of bioaerosols and non-biological material is mostly anthropogenic. These particles pose constant health threats to public in general (Peccia *et al.*, 2011; Veillette *et al.*, 2013). China is an example where the quality of air is damaged by modernization of cities.

Dust

Air is considered an important transport medium for dispersal of microorganisms over long distances. Due to air, microorganisms cross long range geographic distances (Burrows *et al.*, 2009; Creamean *et al.*, 2013). The importance of aerosol microbiology in sustaining the ecosystem cannot be ignored (Maki *et al.*, 1974; Dimmick *et al.*, 1975; Sattler *et al.*, 2001; Amato *et al.*, 2007; Mohler *et al.*, 2007; Womack *et al.*, 2010; Yooseph *et al.*, 2013). Dust is very small and fine particles of soil that contains spores, ash, soot and microorganisms. It can be originated from various sites like construction, demoliation, agricultural lands etc. It is reported that even exposure to very small time period can lead to respiratory problems and health complications like allergy (Methods for dust control, 2016). By word dust, the first thing that comes to mind is deserts.

The larger deserts of this planet include Sahara, Sahel of North Africa, Gobi, Takla Makan, Badain Jaran of Asia. Their top soil travel through larger distances and becomes source of dust in nearby areas (Griffin, 2007). Alone Sahara and Sahel of North Africa contributes about 50 – 75% of dust sources. But in Asia in last two decades, dust is the major source of climatic changes and air pollution (Moulin *et al.*, 1997; Goudie and Middleton, 2001; Prospero and Lamb, 2003; Zhang *et al.*, 2003).

Dust – a source of air pollution

The dust particles are major source of air pollution. There are many sources of dust like paved and unpaved roads, storage piles, rural areas, demoliation sites, garbage burning, sewage disposal, etc. (Methods for dust control, 2016). Dust particles get settled on plantation by roadside and affect them (Joshi, 2008).

Dust and microorganisms

The diversity of microorganisms is known since last two centuries. Their presence in outdoor air and dust is already reported (Darwin, 1846; Pasteur, 1861;

Tyndall, 1882). Their number ranges from 10^4 to 10^6 cells per m^3 (Burrows *et al*., 2009). Every hour spent outdoor, we inhale thousands of microorganisms and their spores, and their health impacts are well known (Barberán *et al*., 2015).

It is reported that non-anthropogenic dust emission occurs at desert surface and agricultural lands (Tegen *et al*., 2004; Ginoux *et al*., 2012; Lee *et al*., 2012). They vary from 3300 Tg/ year (Shao *et al*., 2011). Such dust winds travel a greater distance (Prospero *et al*., 2003; 2014). It is usually carrier of organic materials, xenobiotics, and microorganisms. It is estimated that one gram of agricultural soil contains about 1.03 x 10^5 to 6.19 x 10^7 colony forming units (Taylor *et al*., 2002; Acosta-Martínez *et al*., 2015).

Microorganisms present in dust plays important role in global, regional and local processes like nutrient cycling in biogeochemical cycles (Gardner *et al*., 2012; Li *et al*., 2007), maintaining ecosystem, microbial biogeography (McTainsh and Strong, 2007; Smith *et al*., 2010; 2013), climate formation, formation of clouds (Konstantinidis, 2014). But their role in pathogenicity cannot be ignored (Griffin *et al*., 2001; Hara and Zhang, 2012; Prospero *et al*., 2003). Microbial rich dust was reported by Darwin in 1845. During travel on H. M. S. Beagle, Charles Darwin along with his colleagues collected the samples of airborne dust near the island of Santiago in Cape Verde. Later it was proved that dust contained many forms of Infusoria which were minute organisms (Darwin, 1845). By innovation in science and technology, recently it was proven that dust was originated from Sahara desert (Gorbushina *et al*., 2007). Perhaps the studies of Darwin were the earliest to show that microbial-dust exists and they are result of Aeolian entrainment and transport. Such wind driven dust may results in enrichment of biodiversity of one area but loss of biodiversity of some other area (Acosta-Martínez *et al*., 2015).

Breathing is important for human health. No breathing, no life. By breathing, air is inhaled. Indoor air does not contain much particulate matter as compared to outdoor air. Outdoor air is reported to contain particulate matter. Nature has blessed human nose with nose hairs which serves as first line of defence. Moreover, the mucous secreted by mucus glands lining the respiratory system traps the particulate matter that gets entry via nose hairs. Once inhaled, these glands exhale the particulate matter by cough or mucus secretion by nose (Griffin, 2007).

How microorganisms get attached to dust?

Dust itself is considered an important vehicle for the transport of bacteria or fungus spores (Yoon and Brimblecombe, 2000). According to Tarnowski *et al.* (2004), the first thing is the adhesion of microorganism to the dust particle. Important factors for adhesion include call surface, natural polymer and electrostatic forces. Adhesion can be non-biological or biological. Non-biological adhesion is done by non-biological mechanisms like electrostatic interactions, capillary condensation, molecular dispersive forces, etc. (Phenix and Burnstock, 1990). Electrostatic forces and Van der Waal forces are responsible for bringing bacteria very close to dust surface. As microorganisms feel or sense close interaction with the substratum, microorganisms face a physiological response which leads to modification in cell surface due to which adhesion take place. According to Mozes *et al.* (1991), type of interaction with surface depends on microbial species and surface physicochemical surface properties. Much work is already done which reports about biofilm formation at solid-liquid or liquid-air interfaces, aerophytic biofilms can also occur at solid-air interfaces (Gu *et al*., 2000).

The biological method of adhesion includes biofilm formation by exopolymers. Bacterial attachment structure like fimbriae, sticky polymers (exopolysaccharides) and electrostatic forces are responsible for this binding. Exopolysaccharide also known as exopolymers or biofilms, are secreted by microorganisms and composed of polysaccharides, proteins, nucleic acids, humic acids, lipids, and other carbohydrates (Roldan *et al*., 2003). Biofilms are composed of microorganisms including bacteria, fungi, etc. (Varnam, 2000; Flemming, 2002).

Medical complications due to dust

The particulate matter less than 10 µm can get penetrate into lungs whereas those less than 2.5 µm can get penetrate into deep lung tissue and subepithelial environment. These particulate matter results in health complications starting from oxidative stress (Delfino *et al*., 2005; Donaldson *et al*., 2001; Zanobetti and Schwartz, 2005) to allergy or asthma. The dust storms can be related to allergy, asthma, silicosis or pulmonary fibrosis risk (Norboo *et al*., 1991; Saiyed *et al*., 1991; Xu *et al*., 1993; Kwon *et al*., 2002; Park *et al*., 2005; Chang *et al*., 2006; Griffin, 2007).

Respiratory tract infections due to dust

As air contains dust, it gets inhaled by us. It leads to many respiratory diseases. Respiratory tract infections are an important health issue in developing countries (Zaman *et al*., 1993; Muhe, 1994; Erling *et al*., 1999). Ahmed *et al*. (2015) reported respiratory issue in male children under five years of age. Uchiyama, (2013) enlisted the respiratory disorders due to dust as follows:

1. Pulmonary fibrosis (asbestos, silica)
2. Pneumoconiosis
3. Pneumonitis or farmer's lung
4. Occupational asthma
5. Occupational lung cancer (asbestos, hexavalent chromium)

Asthma and dust

Dust is one of the major reasons of asthma (Bener *et al*., 1996; Howitt, 2000; Al Frayh *et al*., 2001). The human population in Middle East and Carribean has been found to suffer by asthma. African desert dust had increased the incidence of asthma by 17-fold during 1973-1996 on the Carribean island of Barbados (Howitt *et al*., 1998; Prospero, 1999). African desert dust was also correlated with respiratory stress in children (Gyan *et al*., 2005). The authors of published literatures (Ezeamuzie *et al*., 2000; Kwaasi, 2003; Ichinose *et al*., 2006) reported the allergens (fungal spores, plants and grass pollens, organic detritus, anthropogenic emissions) with dust particles (Griffin, 2007) which are an important reason for asthma.

Microbiology of dust

Microorganisms are present in dust and they affect health of human beings by pathogenicity and allergic reactions like asthma. Sensitive people are more prone to get sickness due to dust borne allergies. Dust-borne dispersion of pathogenic and non-pathogenic microbial species plays an important role in biogeographical distribution of species. They are capable of long-range transport to far way areas and affect much population in general (Moreno *et al*., 2001; Martiny *et al*., 2006). The following microbial flora was found predominant in dust; *Proteobacteria*, *Acidobacteria* and *Actinobacteria* (Janssen, 2006). The 20% genera found in four dust and one non-dust events composed of *Micrococcus* sp. (6.4%), *Saccharococcus* sp. (7.4%), *Planococcus* sp. (8.5%), *Kocuria* sp. (12.8%) and *Bacillus* sp. (38%) (Kellogg *et al*., 2004; Griffin *et al*., 2007).

Medical complication due to dust – Cough

Cough is a reflex of air from throat with noise. This reflex usually occurs to expel out mucous irritants, particles, etc. that might be cause problem in pulmonary system. This is natural response of body to get rid of foreign particles that causes disturbance in tracheobronchial tree of respiratory system (Kvale, 2006; Wee *et al*., 2012).

Causes

There can be many causes of cough including infection in respiratory tract, post-nasal drip, lung tumors, ACE inhibitors, gastroesophageal reflux disease, asthma, smoking, air pollution, bronchitis (Myers, 2005). According to previous literatures, the triggering factors for cough includes external stimuli like singing, talking, perfume, outdoor air, etc. (Matsumoto *et al*., 2012; Morice *et al*., 2014a; Song *et al*., 2014a). These factors alone are not responsible for chronic cough but several other factors like gender, allergy, age, chronic health issues may trigger it (Morice *et al*., 2014b; Song *et al*., 2014b; Song *et al*., 2015).

Classification of cough

According to literature (Myers, 2005), cough can be divided into dry and wet forms. Dry cough is mostly occurs with common cold exhibiting early signs of laryngitis or bronchitis (inflamed bronchi). It can also be called as acute cough. Whooping cough is also a dry cough. Wet cough is a chronic bronchitis which is responsible for phlegm, also called as productive cough. The most probable causes of wet cough include use of breathing machines, pulmonary edema, bacterial infections, cystic fibrosis, and gastroesophageal reflux.

This type of cough can be associated with tuberculosis. Smith *et al.* (2006) made an attempt to classify the cough on the basis of sound it produced which includes dry, brassy, rattling, loose, productive, moist, bovine, hoarse, wheezing, or barking. Any kind of cough is annoying for the patient, family member especially sleeping partner. It is mostly observed that cough results in sleeplessness and shortness of breath. Lungs got hurt and patient is unable to attend social gatherings. It should be treated as soon as possible to avoid incontinence (Kvale, 2006; Wee *et al.*, 2012).

Chronic cough

Chronic cough is a disease condition resulting from host-environmental interactions, and is associated with a high global epidemiological burden (Duki *et al.*, 2003; Singh *et al.*, 2015). According to Song *et al.* (2015), cough that persists for more than 3 months in a year is categorized as chronic cough. The reason for it can include residence near heavy traffic road or active smoking areas. Duki *et al.* (2003) reported about 16,663 pairs of junior high school students and their mothers affected by persistent cough. In short, chronic cough is a gift of host-environment interactions and due to urbanization it is creating a huge burden for developing as well as developed countries (Song *et al.*, 2015).

Diagnosis of chronic cough

The detection of chronic cough involves detail study of laboratory diagnosis involving molecular diagnosis as mentioned in sections below (Daxboeck *et al.*, 2003; Tully *et al.*, 1979; Gavranich and Chang, 2005).

Pathophysiology

The portal of entry of bacteria in upper respiratory tract is by inhalation. Once inhaled, they reach alveoli, immune system of human body gets triggered. Neutrophils reaches alveoli where they engulf attacking microorganism and kill it but at the same time releases cytokines which is the normal response of immune system. The release of cytokines results in chills, fever and fatigue common symptoms of bacterial and fungal pneumonia.

Laboratory diagnosis

Laboratory diagnosis is crucial because of many reasons like nature of microorganism, lack of sensitive and rapid detection method, sampling, improper information from patients, etc. The sampling of lower respiratory tract is a difficult task. Moreover, self-medication is a big hinderance because many time patient take medicines by listening to other people, herbal remedies often results in false positive results of lab diagnosis.

Serology

Serological tests are usually non-specific and very helpful in determining the cause of outbreak. They are still considered a "gold standard" from detection of microorganisms like *M. pneumoniae* infections. Following are famous serological methods that are widely employed (Atkinson *et al.*, 2008). They are used to differentiate between acute and chronic nature of cough (Jayantha, 2007).

Complement Fixation (CF) method

This method usually detects IgM response which is acute and early in nature. It helps in the detection of acute and chronic disease. For example, in *M. pneumoniae* infections, 1: 64 titre exhibits a recent infection (Lind *et al.*, 1984).

Enzyme Immunoassay (EIAs)

In serology, they are considered very useful because widely used, simple to perform and their sensitivity can be compared with PCR. They help in IgG and IgM detection. They are of two types (Kashyap and Sarkar, 2010):

Ramel EIA

It helps in simultaneous detection of IgG and IgM. It is helpful for early detection of infection.

***I**mmunocard*

It detects IgM only.

Antigen detection technique

Antigenic detection of microorganisms can be done by the following methods. These methods have disadvantages like cross reactivity with other antigens and least sensitive.

1. Immunoblotting
2. Counter immunoelectrophoresis
3. Direct Immunofluorescence
4. Antigen capture enzyme immunoassay

Culture

It is a routine microbiological detection method. It is time consuming, expensive and laborious. The expenses on purchasing specific growth medium and API strips makes it an expensive method. Species identification needs expertise in microbiology. For culture processing, many things should be kept in mind like specimen collection, storage and transport (Kashyap and Sarkar, 2010).

Molecular biology techniques

The molecular biology techniques for diagnosis of chronic cough are given below (Loens *et al*., 2003):

DNA probe: Previously, 16S rRNA genes were targeted and used to detect the suspected microorganism. But it is no longer in use due to its high cost (Andreu *et al*., 2006).

Polymerase Chain Reaction (PCR): It is a famous diagnostic technique owing to its high sensitivity. It requires only one specimen and 3-4 hours to complete the test procedure.

It can also work on dead microorganisms; viable microorganism is not required. The target for PCR other than 16S rRNA gene includes *ATPase* gene, *P1* adhesin, *tuf* gene, etc. (Loens *et al*., 2003).

Positive PCR but negative serology: It is observed by Gnarpe *et al*. (1992) that 5% - 13% healthy individuals have microorganisms in their throat. Such presence is not related with clinical symptoms. This might be due to early successful antibiotics therapy. Sometimes PCR is positive but microorganism cannot be cultured. In such case, serology tests for detection of both IgM and IgA are preferred. Both these helps in differentiating chronic with acute cough (Atkinson *et al*., 2008). The advancements in PCR including real time PCR, real time multiplex nucleic acid sequence-based amplification (NASBA assay) has made detection easy and more reliable. These advancements offer advantages with respect to handling, speed and less number of samples (Hardegger *et al*., 2000; Loens *et al*., 2008).

Microbiology of chronic cough

Previous literature reported both Gram positive and Gram negative bacteria as responsible factors for chronic cough.

Gram positive bacteria

Streptococcus pneumoniae, *Staphylococcus aureus*, *Bacillus* species are major Gram positive bacteria responsible for pneumonia.

Gram negative bacteria

Gram negative bacteria are less reported. The most probable Gram negative microorganisms responsible for cough may include *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, *Bordetella pertussis* and *Klebsiella pneumoniae*.

Microorganisms and chronic cough

Some of the important bacteria that cause persistent cough include *Chlamydia pneumoniae, Mycoplasma pneumoniae, Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, Bordetella pertussis, Pseudomonas aeruginosa* and *Mycobacterium tuberculosis*.

Chlamydia pneumoniae

Chlamydia pneumoniae is an important bacterium associated with chronic cough. It is a Gram negative aerobic and obligate intracellular bacterium that uses host energy to survive and proliferate inside it. It forms cytoplasmic inclusions within host. It has a biphasic developmental cycle that consists of two forms, a smaller extracellular form named elementary bodies (EBs) and relatively larger intracellular form named reticulate bodies (RBs) (Miyashita *et al.*, 2003).

Pathogenesis

The first step in pathogenesis involves attachment of elementary bodies to cell which afterwards are internalized within phagosome. Internalization of EBs inhibits fusion of phagosome with lysosomes to avoid its degradation. EBs differentiate into reticulate bodies that divide rapidly inside the cell forming cytoplasmic inclusions. Before releasing from cell, these RBs revert to EBs and following cell lysis are released from cell to infect other cells (Miyashita *et al.*, 2003).

Mycoplasma pneumoniae

Mycoplasma pneumoniae belong to family Mycoplasmataceae, order *Mycoplasmatales*, and class *Mollicutes* including *M. pneumoniae*. The unique characteristic of *M. pneumoniae* is that it lacks cell wall due to which it is resistant to those antibiotics which affect cell wall of organism including penicillin, cephalosporin etc. It is capable of cell free mode of living. It is an important cause of upper and lower respiratory system. Several Mycoplasma species inhabit human's respiratory and urinogenital tract and cause diseases. It consists of a specialized attachment organelle P1 that allows it to adhere to mucosal epithelial cells and also protects it from ciliary action (Kashyap and Sarkar, 2010).

Pathogenesis

Initial step involves the proper attachment of the organism to the epithelial cells. Adhesin molecules like P1 and P30 complexed with B and C proteins are involved in adherence process through a series of events. P24 and P41 play a crucial role in timing and location of attachment organelle assembly complex during cell growth and proliferation. Following adhesion *M. pneumoniae* affects the epithelium by the production of free radicals. Superoxide ions inhibit the breakdown of peroxide particularly hydrogen peroxide that accumulates inside the cell leading to oxidative stress causing epithelial damage. Its surfactant protein A is an important factor for colonizing the respiratory tract. It was reported earlier that CARDS (Community acquired respiratory distress syndrome toxin) was responsible for the induction of inflammatory response by triggering inflammasome (component of innate immune response) activity. Major pathway of *M. pneumoniae* pathogenesis is induction of inflammation via the TLR-mediated cytokine release and generation of free radicals (Kashyap and Sarkar, 2010).

Haemophilus influenzae

Haemophilus influenzae is a Gram negative coccobacillus with a variable shape. It is able to grow in both aerobic and anaerobic conditions. In order for the organism to grow aerobically it requires hemin and nicotinamaide adenine dinucleotide factors. Based on the presence or absence of a polysaccharide capsule, *Haemophillus influenzae* is classified as typeable and non-typeable strains. Typeable strains are further divided into 6 serotypes. NTHi strains are classified into two biotypes based on indole, urease and ornithine decarboxylase tests. Nasophrynx is the reservoir of NTHi and could reach to lower respiratory tract (King, 2012).

Pathogenesis

Outer membrane proteins P2 and P5 bind the bacteria to the mucus. Lipopolysaccharide present in cell wall of organism inhibits the ciliary function. After the mucociliary interaction next is the adherence to respiratory mucosa which is mediated by adhesins. NTHi have pili that aid in attachment. 25% of the NTHi strain lack adhesins/ pili but some other factors like Hia and Hap proteins help in attachment of these strains. Following the attachment, evasion of immune response via proteases takes place that cleave IgA to prevent the bacterial colonization. Bacteria forms microcolonies on mucosal surfaces that inhibit the function of lysozymes, lactoferrin and antibodies. Finally, it invades the local tissue surviving intracellularly. *H. influenzae* triggers both innate and adaptive immunity (King, 2012).

Streptococcus pneumoniae

Streptococcus pneumoniae are lancet shaped, Gram positive bacteria that grow either in pairs or short chains. It consists of cell wall, plasma membrane and capsule. Pathogenic ability of *Streptococcus pneumoniae* is due to virulence factors like capsule, cell, cell wall polysaccharide and pneumococcal proteins. These proteins include pneumolysin, autolysin and pneumococcal surface protein A (Savini *et al.*, 2008; Worrall, 2008).

Pathogenesis

Attachment of the bacteria is mediated by disaccharide receptor on fibronectin present on human pharyngeal epithelial cells. Immune status at the time of colonization decides whether the organism will remain confined to the respirator epithelia or translocate to blood. Pneumolysin affects the ciliary mechanism and IgA1 protease inhibits the mucosal immunity. Production of hydrogen peroxide cause epithelial damage. Both epithelial damage and pneumolysin increase the chance of organism's translocation to blood from where it could reach to meninges. Uncontrolled growth of *Streptococcus pneumoniae* inside meninges or middle ear results in lysis of cell accompanied with the release of cell wall products and pneumolysin that triggers inflammation response (Savini *et al.*, 2008; Worrall, 2008).

Moraxella catarrhalis

It belongs to Family Moraxellaceae. It is Gram negative, aerobic and diplococcus organism. It is found as a commensal of upper respiratory tract (Ariza-Prota *et al.*, 2016).

Pathogenesis

Adherence is primary step in pathogenesis of *Moraxella catarrhalis* which is mediated by multiple adhesins like a family of ubiquitous surface protein A (UspA), the human erythrocyte agglutinin/ *Moraxella* Immunoglobulin D-binding protein (hag/MID), Outer membrane protein CD(OMP-CD), *M. catarrhalis* adherence protein (McaP) and Lipoligosaccharide (LOS). After it adheres to the respiratory epithelia, it invades it by the help of LOS, UspA1 and other outer membrane proteins. Invasion allows the organism to divide and survive within host. The UspA family and Hag/MID are associated with biofilm formation. Following biofilm formation, *M. catarrhalis* evades host's immune response leading to infection (Ariza-Prota *et al.*, 2016).

Bordetella pertussis

It is a Gram negative, coccobacillus, non-spore forming and encapsulated bacteria. It is arranged singly or in small groups. It is strictly aerobic in nature (Birkebaek, 2001).

Pathogenesis

Multiple adhesins like fimbriae, PRN and FHA aid in attaching the bacteria to the ciliated epithelial cells and other type of cells in respiratory tract. Following adhesion *Bordetella pertussis* produce a variety of virulence factors like pertussis toxin (PT), Adenylate cyclase toxin (ACT), Tracheal cytotoxin (TCT) and lipooligosaccharide (LOS). ACT and PT as mentioned modulate the immune system by affecting ciliary action and mucosal immunity. Both ACT and PT disturb the signaling pathway by increasing cAMP level and modifying the molecules involved in signaling leading to infection. In case of pertussis systemic spread is rare. These toxins play a crucial role in the pathogenesis of *Bordetella pertussis* but role of some of the toxins is not clearly known (Birkebaek, 2001).

Pseudomonas aeruginosa

Pseudomonas aeruginosa is a ubiquitous, Gram negative aerobic rod. It possesses polar monotrichous flagella for motility and also pili that help in adhering to respiratory epithelium. It produces many pigments like flourescent yellow green and blue green pigment called pyocyanin which gives it a characteristic appearance (Wainwright *et al*., 2009).

Pathogenesis

Pseudomonas aeruginosa consists of a polar flagellum and type 4 pili that allows it to adhere to the respiratory epithelial cells. It also produces exopolysaccharide called alginate that enhances adhesion to solid surfaces. Type 4 pili is involved in twitching motility and biofilm formation as well. Microcolonies are formed on target tissues thereby concentrating bacteria at one place and protects it from host immune system and antibiotics. After successful accumulation of bacteria, it produces number of toxins that are injected inside the host cell. Quorum sensing (QS) is a specific mechanism that controls bacterial survival, biofilm formation and virulence. Following QS mechanism biofilm formation takes place that provide protection from certain antibiotics and host defense mechanism thereby making its survival possible within host. Many different proteases are secreted by *Pseudomonas aeruginosa* that degrade immunoglobulins and fibrin. In case of respiratory infections, it is responsible for tissue damage (Wainwright *et al*., 2009).

Mycobacterium tuberculosis

Mycobacterium tuberculosis is a rod shaped, non-motile and intracellular obligate aerobe. Its unique characteristic is the presence of mycolic acids present in cell wall. It is not distinguished on the basis of Gram staining but acid-fast staining. Mycolic acids present in its cell wall take up the acid and so they are termed as acid-fast bacteria (Jones-Lopez *et al*., 2016).

Pathogenesis

Mycobacterium tuberculosis enters the body through droplets dispersed in air and reaches the alveoli. Alveolar macrophages phagocytes kill it but if they fail to do so it replicates in alveolar macrophages diffusing to the neighboring epithelial and endothelial cells. In early steps of infection, it might disseminate to other organs and spread the infection. Neutrophils, lymphocytes and other immune cells form cellular infiltrate that acquire the form of granuloma that encapsulates the bacteria. This primary lesion enables the bacteria to remain dormant for years but if it starts replicating inside it would result in active infection (Jones-Lopez *et al*., 2016).

Viruses associated with chronic cough

Following is given the examples of viruses that are associated with chronic cough.

Human Respiratory Syncytial Virus

It is enveloped, negative sense and single stranded RNA virus that belongs to Paramyxoviridae family and Pneumovirus genus. Viral genome is 15.2 kb long that consists of 10 genes that encode 11 proteins (Falsey and Walsch, 2000).

Pathogenesis

Viral infection starts when virion attaches to the cell surface with the help of G protein. F protein binds to its receptor nucleolin. Virus enters in cholesterol rich microdomains in cell surface. Fusion between viral membrane and host cell membrane depends upon the interaction of G and F protein with their receptor and internal arrangement of actin filaments close to cholesterol rich microdomains.

This fusion allows the entry of viral nucleocapsid content inside cytoplasm. The nucleocapsid is dissociated from RNP complex and M protein repetitions. L protein carry out the viral transcription along with N and L proteins. M-21 protein also plays an important role in this process due to interaction with RNP proteins, other host proteins and host heat shock proteins for proper transcription. After viral replication, the newly formed RNA strand is encapsulated by N protein. M protein is involved in viral assembly. The interaction of M protein with F protein is responsible for assembly process. Budding process is controlled by the RAB11 interacting protein 2 family (Falsey and Walsch, 2000).

Parainfluenza virus

HPIVs belong to genera Rubulavirus and Respirovirus within family Paramyxoviridae. Viruses are spherical approximately 150-400nm in diameter. Genome consists of negative sense single stranded RNA (Rubin *et al.*, 1993; Atkinson *et al.*, 2016).

Pathogenesis

The first step involves the binding of virus with sialic acid containing receptors for virus with the help of HN glycoprotein. Following this, interaction of virus with its receptor F protein is activated that helps to fuse the viral envelope with host plasma membrane. Nucleocapsid is released inside cytoplasm that contains RNA/protein complex that serves a template for transcription and replication process. Viral genome encodes proteins like HN, F, M, L, P and NP proteins that are involved in viral transcription and replication. NP, L and P proteins are involved in transcription (Rubin *et al.*, 1993; Atkinson *et al.*, 2016).

Management of chronic cough

The management for chronic cough depends on the proper diagnosis of its underlying cause.

It is reported that depending on causative agent of cough, beta-lactams, glycopeptides, sulfonamides, trimethorpim, polymyxins, nalidixc acid, rifampin, macrolide, tetracyclines can be administered.

Vaccination

In order to avoid re-infection, vaccine development is desirable. The vaccine against *M. pneumoniae* was reported to be about 30% effective (Linchevski *et al.*, 2009).

Natural remedy for dust allergy

Precious literatures reported the use of herbs to ease the cough in general. The medicinal plants used for this purpose includes *Embilca officinalis* (Nosál'ová *et al.*, 2003), *Trichodesma indicum* (Srinath *et al.*, 2002), *Asparagus racemosus* (Mandal *et al.*, 2000), *Ocimum sanctum* (Nadig and Laxmi, 2005), *Passiflora incarnate* (Dhawan and Sharma, 2002), *Adhatoda vasica* (Dhule, 1999), *Glycyrrhiza glabra* (Chang and Butt, 1986), *Zingiber officinale* (Suekawa *et al.*, 1984; Nawaz *et al.*, 2014).

Precautionary measures (Revised as per advised)

Respiratory issues can be avoided by avoiding the exposure to dust by adopting an alternative route, wearing a mask or covering nose and mouth with cloth, sprinkle water in front of homes, shops etc., to inhale steam with or without addition of Vicks® in order to soothen the throat and nasal cavity and gargle with hot water if irritation in throat is felt.

Conclusions

Urbanization is an important element for a developing country. The construction of new roads, etc. cannot be avoided because they are considered a blessing for a public in general. This results in persistence of dust in the local surroundings. Dust harbors microorganisms making it bioaerosols. Inhaling dust can introduce microorganisms in our upper and lower respiratory tract which can leads to infections of ear, nose and throat. Chronic cough in public including professionals, school kids and street hawkers has become common during last decade especially in the areas of Lahore where Metro bus station construction remained in progress for months.

In order to avoid exposure to dust, precautionary measures should be taken like covering the mouth and nose with mask or cloth piece, gargles with salt and luke warm water, intake of lozenges, making habit of drinking lemon, ginger and honey tea. Intake of anti-allergy medicines should be avoided as it can lead to drug resistance in the body.

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