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THE MEDICAL IMPLICATIONS OF AEROSOLS: AN IN-DEPTH REVIEW

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Abstract: **This paper explores the medical implications of aerosols, defined as suspensions of particles or droplets in the air. Aerosols, which include airborne dust, mists, fumes, and smoke, play a crucial role in medical science, particularly in the delivery of drugs to the airways and systemic circulation. Aerosol therapy is a non-invasive method beneficial for patients with conditions like asthma and chronic obstructive pulmonary disease (COPD), offering rapid action and reduced side effects due to lower medication doses. The paper discusses the expanding therapeutic applications of aerosols, including gene therapy, vaccination, and treatment of both respiratory and non-respiratory diseases. Additionally, aerosols present health and safety hazards in various occupational settings, with the potential for inhalation, skin absorption, or ingestion of harmful particles. Advances in aerosol devices and technologies, such as nebulizers, metered dose inhalers (pMDIs), and dry powder inhalers (DPIs), have enhanced the efficiency and effectiveness of aerosol therapy. This comprehensive review underscores the importance of ongoing research and technological innovation in maximizing the medical benefits of aerosols while minimizing their risks.**

Keywords: **Aerosols, Aerosol Therapy, Respiratory Diseases, Inhalers, Occupational Health.**

1. INTRODUCTION

Aerosols, aerocolloids, or aerodispersed systems are collections of tiny particles. An aerosol may be defined as a suspension of particles or droplets in the air and includes airborne dust, mists, fumes, or smoke. Suspended particle sizes may range from a few nanometers to hundreds of micrometers in diameter and particles can be manufactured or naturally occurring (NIOSH, 2023).

Aerosols play a crucial role in medical science, particularly in the treatment of specific and often complex diseases that require the delivery of drugs to the airways and systemic circulation. Aerosol therapy is a non-invasive method of delivering medication, which is beneficial for patients who may have difficulty with invasive procedures. Aerosolized medications can act rapidly, making them effective for treating conditions like asthma and chronic obstructive pulmonary disease (COPD). Aerosol therapy often requires lower doses of medication compared to systemic administration, which reduces the risk of side effects. Aerosols are being explored for a wide range of therapeutic applications, including gene therapy, vaccination, and treatment of various respiratory and non-respiratory diseases. Aerosolized medications can have systemic effects, such as insulin for diabetes, and are being researched for their potential in treating various conditions. Advances in aerosol devices and technologies have made aerosol therapy more efficient and effective, with options like nebulizers, metered dose inhalers (pMDIs), and dry powder inhalers (DPIs) (Rubin, 2010; Boe et al., 2021)

Aerosols in the workplace pose both health and safety hazards and are encountered across multiple industrial sectors. Particles can be inhaled, absorbed by the skin, or ingested. Depending on particle size, composition, shape, and concentration, particles can cause adverse health effects in workers (NIOSH, 2023).

This paper explores the medical implications of aerosols, covering their types, sources, transmission mechanisms, and health effects. It examines both natural and anthropogenic sources of aerosols relevant to healthcare, and the role aerosols play in the transmission of diseases. The health impacts of aerosols, including respiratory infections and chronic conditions like asthma and COPD, are discussed. The paper also reviews the use of aerosols in medical diagnostics and treatments, along with preventive measures and control strategies. Finally, it highlights recent advancements and future research directions in aerosol science within the medical field.

Types of Aerosols

Aerosols are generally defined as colloidal systems of liquid or solid particles suspended in a gas (Hinds, 1999; Baron and Willeke, 2001; Fuzzi et al., 2006). Particle diameters are typically in the range of 1 nm to around 100 mm, where the lower limit is given by the size of small molecular clusters and the upper limit by high settling velocities comparable to the magnitude of atmospheric updraft velocities 1ms1 (Hinds, 1999; Seinfeld and Pandis, 2006). Primary atmospheric aerosol particles are emitted directly into the atmosphere from the source material, whereas secondary particles are formed in the atmosphere by condensation of gaseous precursors (Po¨schl, 2005; Fuzzi et al., 2006).

The science and technology of aerosols matured rapidly in the twentieth century due to the increasing interest in their chemistry and physics. Aerosols vary widely in properties depending on the nature of the suspended particles, their concentration in the gas, their size and shape, and the spatial homogeneity of dispersion (Hidy, 2003). The term is generally restricted to clouds of particles that do not readily settle out by gravity, creating a stable suspension for an extended period. They exist in nature as part of planetary atmospheres. Aerosols have extensive involvement in technology, ranging from agricultural sprays to combustion, the production of composite materials, and microprocessor technology (Hidy, 2003).

Biological and non-biological aerosols

Bioaerosols (short for biological aerosols) are a subcategory of particles released from terrestrial and marine ecosystems into the atmosphere. They consist of both living and non-living components, such as fungi, pollen, bacteria, and viruses (Fröhlich-Nowoisky et al, 2015) Common sources of bioaerosols include soil, water, and sewage.

Bioaerosols are typically introduced into the air via wind turbulence over a surface. Once in the atmosphere, they can be transported locally or globally: common wind patterns/strengths are responsible for local dispersal, while tropical storms and dust plumes can move bioaerosols between continents (Smets et al, 2016) Over ocean surfaces, bioaerosols are generated via sea spray and bubbles Bioaerosols can transmit microbial pathogens, endotoxins, and allergens to which humans are sensitive. A well-known case was the meningococcal meningitis outbreak in sub-Saharan Africa, which was linked to dust storms during dry seasons. Other outbreaks linked to dust events include Mycoplasma pneumonia and tuberculosis(Smets et al, 2016)

Recently, several investigations have suggested that biological particles can have a substantial influence on clouds and precipitation and thus may influence the hydrological cycle and climate at least on regional scales (e.g., Andreae and Rosenfeld, 2008; Prenniet al., 2009; Po¨schl et al., 2010). Biological particles have been linked to many different adverse health effects spanning from infectious diseases to acute toxic effects, allergies, asthma, and even cancer (Peccia et al., 2011). The negative effects that bioaerosols can have on the human respiratory system are particularly well-documented and illustrated in Figure 1 (Verhoeff and Burge, 1997; Burge and Rogers, 2000; Douwes et al., 2003; Lee et al., 2005). Figure 1 shows the circulation and impacts of primary biological aerosol particles in the atmosphere and biosphere.

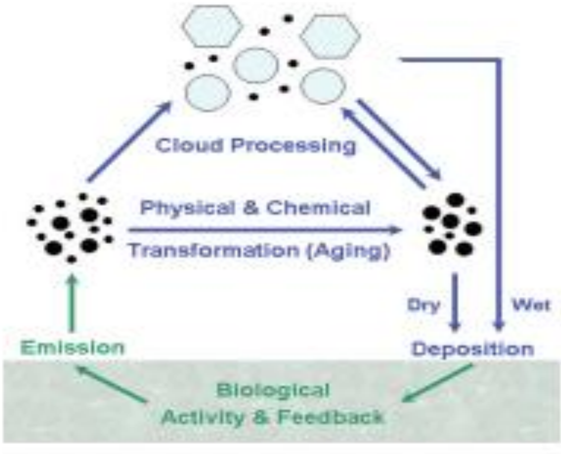

Figure 1: Circulation and impacts of primary biological aerosol particles in the atmosphere and biosphere (Poschl, 2005).

Non-biological aerosols are particles suspended in the air that do not originate from living organisms. They can come from various sources, including Secondary Organic Aerosols (SOA): Formed through chemical reactions involving volatile organic compounds (VOCs) and oxidants in the atmosphere, and Secondary Inorganic Particles: Formed through chemical reactions involving sulfur dioxide, nitrogen oxides, and ammonia in the atmosphere (Siyao et al., 2022). Natural particles from soil, sand, or other inorganic sources can be lifted into the air through wind or human activities. Particles are generated by combustion processes, such as vehicle emissions, industrial processes, or wildfires. Aerosols can also be generated by human activities like construction, mining, or manufacturing, as well as by industrial processes like cement production or coal combustion. Non-biological aerosols can significantly impact the environment and human health, including air pollution, climate change, and respiratory issues (Siyao et al., 2022).

Properties of Aerosols

Aerosols can be composed of a complex mixture of organic and inorganic compounds, including soot, heavy metals, salts, and thousands of organic compounds from combustion sources. The chemical composition of aerosols influences their physical properties and behavior. Aerosols span a wide range of sizes, from nanometers to tens of micrometers. Particle size and morphology (shape) affect properties like light scattering and absorption, as well as the ability to act as cloud condensation or ice nuclei. Techniques like mobility particle sizers are used to measure aerosol size distributions (Bzdek et al., 2020; Hays, 2014). Aerosols can exist in liquid, semi-solid, or glassy solid phases depending on their composition and environmental conditions like humidity. The phase and viscosity of aerosols impact their chemical reactivity and can transform into other substances (Bzdek et al., 2020).

Sources of Aerosols

Aerosols can be natural or anthropogenic. Examples of natural aerosols are fog or mist, dust, forest exudates, and geyser steam. Examples of anthropogenic aerosols include particulate air pollutants, mist from the discharge at hydroelectric dams, irrigation mist, perfume from atomizers, smoke, steam from a kettle, sprayed pesticides, and medical treatments for respiratory illnesses(Hidy 1984) When a person inhales the contents of a vape pen or e-cigarette, they are inhaling an anthropogenic aerosol (WHO, 2022) The chemicals in tobacco smoke include some carcinogens, including nicotine and some of its derivatives, as well as poisonous gases including carbon monoxide and nitrogen dioxide.

Microbial aerosols (i.e. airborne particles of microbiological origin) are usually naturally present in the environment. They are ubiquitous both indoors and outdoors (Burrows et al., 2009). They can derive from industrial and non-industrial settings and differ significantly in terms of their emission efficiency. In the first case, the most effective occupational aerosolization processes (being responsible for microbial aerosol concentrations up to 10^{12} cfu m^{-3}) are silo loading/unloading, animal feeding in broiler houses, piggeries as well as different dust-releasing tasks in composting plants, granaries, animal food stores, malt-houses, and reloading of stored moldy raw materials (Dutkiewicz and Jabłoński, 1989). Against this background, non-industrial indoor sources are less productive and usually closely connected with the presence and physical activity of humans (including numerous physiological processes such as breathing, talking, sneezing, coughing, or scratching as well as movement and dust, including microbial dust residues, resuspension). Such types of emissions are usually able to create microbial concentrations of about 10^3 cfu m^{-3}; however, some chamber bioaerosol studies revealed that even one person under seated conditions can release up to 106 biological aerosol particulates per hour into the air and the origin of such a microbial cloud can be assigned to the individual that emits it (Bhangar et al., 2016; Meadow et al., 2015). Also, indoor water reservoirs such as aquariums, toilets, sinks or even washing machines may load the air with high numbers of both saprophytic and pathogenic microorganisms. Such emissions (reaching usually 10^3-10^4 cfu m^{-3}) may result not only in contamination of surrounding surfaces but pose a real threat to exposed individuals through inhalation of different pathogens (Stapleton et al., 2013; Best et al., 2012; Getto et al., 2011).

Mechanisms of Aerosol Transmission

The mechanism by which diseases are transmitted via aerosol is that viral particles and/or some attached to the environmental particulate matters (PMs) remain active and suspended in the air for long periods until being contacted by humans and deposited on mucous membranes, where they reproduce to form infections (Ma et al., 2021; Chen et al., 2016). According to studies, the exhalatory actions of virus carriers, such as breathing, talking, singing, shouting, coughing, and sneezing, result in the production of a certain number of viral aerosols (Scheuch, 2020; Lindsley et al., 2010). Furthermore, people can shed lots of viruses into their exhaled breath and do not need to be coughing to do so. There is great variation in exhaled breath viral shedding and temporal dynamics throughout infection (Klompas et al., 2021; Milton, 2012). Work by Kristen Coleman and others shows that coughing and singing can increase the viral load emitted into aerosols from the respiratory tract (Coleman et al., 2022).

During coughing and sneezing, liquid droplets with a wide diameter range from sub-μm to >100 μm are atomized from saliva and fluids further down the respiratory tract (Han et al., 2013; Johnson and Morawska, 2009). It is now recognized that normal breathing and speech atomize droplets also (Borak, 2020; Scheuch, 2020; Stadnytskyi et al., 2020; Gralton et al., 2011). Half a minute of speech releases a liquid volume comparable to a cough (Wei and Li, 2016). The volume of droplets emitted during speech depends on loudness (Asadi et al., 2020; Asadi et al., 2019) and may be greater during singing (Anderson et al., 2020; Asadi et al., 2019). The breath emission rate is considerably increased during physical exercise (Chao et al., 2009).

Large (>50 μm) droplets are directly infective only if they reach another person before settling below face height (Dbouk and Drikakis, 2020; Liu et al., 2017). That is the idea underlying social distancing guidelines of 1 or 2 m, although violent coughing or sneezing can carry the virus >2 m (Qureshi et al., 2020). Aerosol particles move with the air. Remaining infective for an hour or more, they can potentially travel much greater distances in that time (Wei and Li, 2016), although social distancing is still effective because the virus concentration is reduced by dispersion (Halloran et al., 20112). Figure 2 describes the pathway through which airborne respiratory viruses progress.

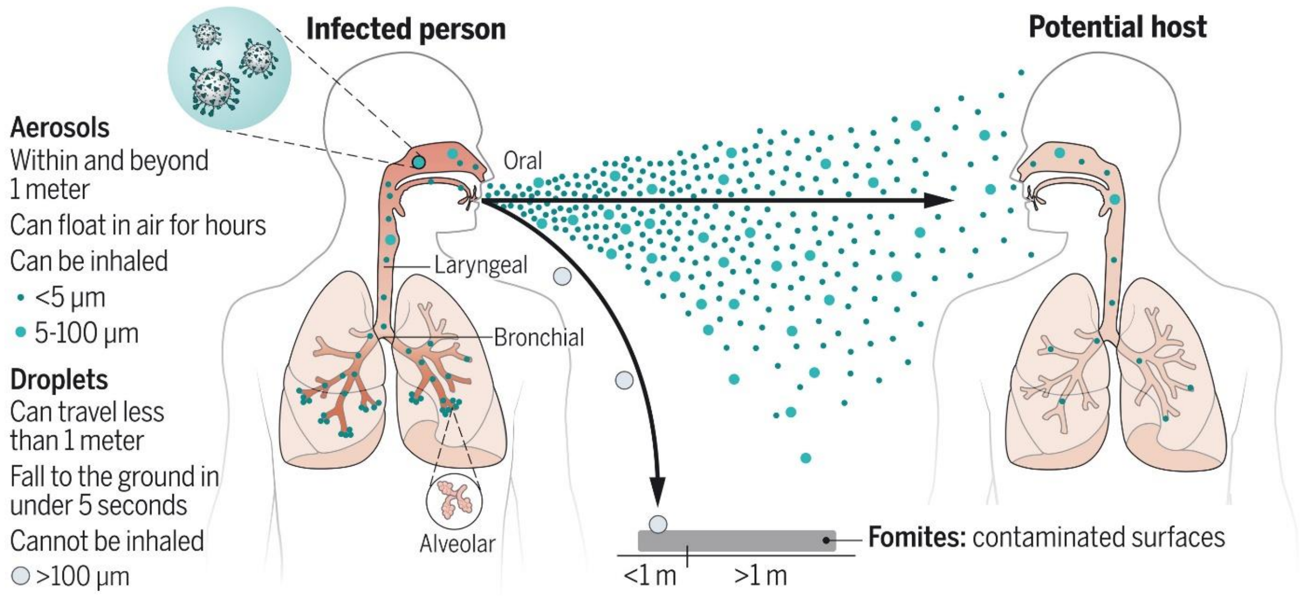

Figure 2: Phases involved in airborne transmission of respiratory viruses (Wang et al., 2021).

Diagnostic and Therapeutic Uses of Aerosols

A diagnostic test is only as useful as the options in treatment that follows (including discontinuation of unnecessary therapy!). An important advantage of using inhaled aerosols for diagnosis, which is shared with therapeutic aerosols, is that the active agent is delivered selectively to the desired area of the body (Gonda, 1990). The alternative to this type of "physical" targeting would be to use chemicals or biologicals that can distribute themselves selectively because of differential affinity toward different cells or tissues. Another advantage of diagnostic aerosols for certain applications (e.g., bronchial provocation tests) is that the entry of the diagnostic aerosol simulates the "real" situation. A short pulse of an aerosol bolus delivered at a particular point during the inspiration can undergo spreading due to convective mixing, shifting to a different volumetric depth due to asymmetric filling and emptying of the lung, and reduction in the particle content due to deposition. All these parameters are likely to be affected by the presence of obstructive pulmonary disease as observed in cystic fibrosis (Igor, 1993). One of the disadvantages of the bolus technique is that it is rather time-consuming. A new method -the single breath concentration technique-has been recently developed which combines the advantages of the aerosol bolus and recovery methods (Igor, 1993).

Radioactive gases have been used to obtain the outlines of the respiratory tract. However, aerosols containing TcDTPA have gained popularity as a substitute for gases in these ventilation images because they are readily available and relatively cheap and their escape is easier to prevent (Strong and Agnew, 1989).

Inhaled aerosol therapies are the mainstay of treatment of obstructive lung diseases. Aerosol devices deliver drugs rapidly and directly into the airways, allowing high local drug concentrations while limiting systemic toxicity (GICO, 2010; Pasteur et al., 2010)

Aerosol Devices

There are three major aerosol device categories:

1. Metered Dose Inhaler (MDI)
2. Nebulizer, and
3. Dry Powder Inhaler (DPI).

MDIs deliver a fixed medication dose from a pressurized canister containing a medication/propellant mixture. For most MDIs, depressing the canister into a holder/mouthpiece usually actuates aerosol release. Nebulizers create an aerosol by agitating a medication solution held in a small reservoir (Sims. 2011). The patient must load the reservoir for each treatment. Vibrating mesh nebulizers force medication solution through a fine mesh or aperture plate to generate an aerosol. DPIs create an aerosol by directing the patient’s inspiratory flow through a powdered medication within the device. Some are preloaded with multiple doses that are aerosolized one at a time, and some are single-use devices that the patient must load with a powdered medication capsule for each dose (Sims, 2011).

Health Effects of Aerosols

In most situations, exposure occurs to complex mixtures of toxins and allergens (and chemicals) and a wide range of potential health effects must be considered. Three major groups of diseases associated with bioaerosol exposure can be distinguished: infectious diseases, respiratory diseases, and cancerous diseases.

Infectious diseases: Infectious diseases arise from viruses, bacteria, fungi, protozoa, and helminths and involve the transmission of an infectious agent from a reservoir to a susceptible host through direct contact, a common vehicle, airborne transmission, or vector-borne transmission. These may be attributable to:

1. Occupation-specific exposures may occur, for example, health workers (tuberculosis, winter stomach flu, measles), farmers, abattoir workers, veterinarians (Q-fever, swine influenza, anthrax), and forestry workers (tularemia)

2. Clustering of people in the workplace such as in the case of office, military, or aviation workers (influenza, winter stomach flu, TB, etc.) (Driver et al., 1994; Van den Ende et al., 1998). Exposure to aerosols during pregnancy has been linked to low birth weight and preterm births (Stefanie, 2016).

Respiratory diseases: Respiratory symptoms and lung function impairment are probably the most widely studied among organic dust-associated health effects. They can range from acute mild conditions that (at least initially) hardly affect daily life, to severe chronic respiratory diseases that require specialist care. Generally, occupationally-related respiratory symptoms result from airway inflammation caused by specific exposures to toxins, pro-inflammatory agents, or allergens.

Based on the underlying inflammatory mechanisms, and the subsequent symptoms, a clear distinction between allergic and non-allergic respiratory diseases can be substantiated. Non-allergic respiratory symptoms reflect a non-immune-specific airway inflammation, whereas allergic respiratory symptoms reflect an immune-specific inflammation in which various antibodies (IgE, IgG) can play a major role in the inflammatory response. In occupational medicine, it has long since been recognized that a substantial proportion of work-related asthma symptoms are non-allergic. This type of asthma is often referred to as 'asthma-like disorder or syndrome' or 'irritant-induced asthma' (Bernstein et al., 1999) and is highly prevalent in farmers and farm-related occupations and is in these occupations assumed to be caused by bioaerosol exposures (particularly endotoxin) (Anonymous, 1998).

Exposure to aerosols can cause respiratory issues such as coughing and wheezing. Long-term exposure to aerosols can lead to reduced lung function. Exposure to aerosols has been linked to increased cardiovascular mortality. Aerosols can cause systemic inflammation, which can contribute to cardiovascular issues. Long-term exposure to aerosols can lead to atherosclerosis, a condition that increases the risk of heart attacks and strokes (Stefanie, 2016). Exposure to aerosols has been linked to cerebrovascular impairment, which can increase the risk of strokes.

Cancerous diseases: Cancer can be caused by several factors including oncogenic viruses and other biological agents. To date, the only clearly established non-viral biological occupational carcinogens are the mycotoxins. These occur in industries in which mould-contaminated materials are handled (Anonymous, 1998). Perhaps the best-known carcinogenic mycotoxin is aflatoxin from Aspergillus flavus, which is an established human carcinogen, particularly liver cancer (Hayes et al., 1984; Sorenson et al., 1984; Bray and Ryan, 1991). Ochratoxin A is also considered a possible human carcinogen (National Toxicology Program, 1991). The most relevant route of exposure to aflatoxin and ochratoxin is by ingestion, but exposure can also occur by inhalation in industries such as peanut processing or livestock feed processing and in industries in which grain dust exposure occurs (Sorenson et al., 1984; Autrup et al., 1993). Workers in livestock feed processing have an increased risk of liver cancer as well as cancers of the biliary tract, salivary gland, and multiple myeloma Olsen et al., 1988). Farmers are at increased risk for certain specific cancers, including hematological cancers, lip, stomach, prostate, connective tissue, and brain cancer (Blair et al., 1992; Khuder et al., 1998).

Aerosols can cause autonomic system disorders, including changes in heart rate variability and increased heart rate. Long-term exposure to aerosols has been linked to an increased risk of lung cancer.

Preventive Measures and Control Aerosols

The correlation between ventilation and the transmission and spread of several infectious diseases has previously been extensively demonstrated (Li et al., 2007). A study in the Netherlands analyzed the droplet size distribution, travel distance, and velocity from coughing and speaking, and the airborne time in relation to the level of air ventilation found that ventilation is an important factor in preventing airborne transmission (Somsen et al., 2020). The use of PPE such as face coverings acts as a source control measure to prevent aerosolic transmission by infected patients who sneeze, cough, and speak. The use of a face covering in public indoor areas is advised to prevent large droplet transmission (Lindsley et al., 2020).

Recent Advances and Research Directions

Recent advances in the chemical characterization of aerosols at bulk and molecular levels, and their physical properties, have improved our understanding of aerosol behavior and interactions (Aggarwal, 2010). Aerosolized drug delivery has improved the mechanistic features of current marketed aerosol delivery devices, enhancing the efficacy and safety of aerosol-based treatments (Chandel et al., 2019).

Investigating the characterization of aerosol systems and identifying research directions that can advance their capabilities is crucial for improving aerosol measurement techniques and applications. Recent advances in occupational exposure assessment of aerosols have improved the tools available for characterizing exposure to aerosols in the workplace, enhancing the safety and health of workers (Harper, 2019). Exploring the applications of aerosols in various fields, such as medicine, environmental science, and materials science, can lead to innovative solutions and new technologies.

2. CONCLUSION

Aerosols hold a significant importance in the medical field, impacting human health and therapeutic practices. The health implications of aerosols are profound, ranging from respiratory infections to chronic diseases such as asthma and COPD. Additionally, aerosols play a crucial role in medical diagnostics and treatments, particularly in the targeted delivery of medications. With the advent of aerosol technology, more efficient and effective medical devices, enhancing the delivery and efficacy of aerosolized medications have been achieved. The integration of new technologies and ongoing research in aerosol science promise to improve patient outcomes and expand the therapeutic applications of aerosols. In conclusion, the study of aerosols from a medical perspective offers valuable insights into their beneficial uses and potential hazards. Continued research and technological advancements will be crucial in harnessing the full potential of aerosols in medicine while ensuring safety and health are maintained.

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