Infection (2014) 42:459–467
DOI 10.1007/s15010-014-0592-6

REVIEW

Particle exposures and infections

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Received: 19 August 2013 / Accepted: 15 January 2014 / Published online: 2 February 2014

Abstract Particle exposures increase the risk for human infections. Particles can deposit in the nose, pharynx, larynx, trachea, bronchi, and distal lung and, accordingly, the respiratory tract is the system most frequently infected after such exposure; however, meningitis also occurs. Cigarette smoking, burning of biomass, dust storms, mining, agricultural work, environmental tobacco smoke (ETS), wood stoves, traffic-related emissions, gas stoves, and ambient air pollution are all particle-related exposures associated with an increased risk for respiratory infections. In addition, cigarette smoking, burning of biomass, dust storms, mining, and ETS can result in an elevated risk for tuberculosis, atypical mycobacterial infections, and meningitis. One of the mechanisms for particle-related infections includes an accumulation of iron by surface functional groups of particulate matter (PM). Since elevations in metal availability are common to every particle exposure, all PM potentially contributes to these infections. Therefore, exposures to wood stove emissions, diesel exhaust, and air pollution particles are predicted to increase the incidence and prevalence of tuberculosis, atypical mycobacterial infections, and meningitis, albeit these elevations are likely to be small and detectable only in large population studies. Since iron accumulation correlates with the presence of surface functional groups and dependent metal coordination by the PM, the risk for infection continues as long as the particle is retained. Subsequently, it is expected that the cessation of exposure will diminish, but not totally reverse, the elevated risk for infection.

Keywords Particulate matter · Smoking · Quartz · Air pollution · Tuberculosis · Meningitis

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Introduction

Particle exposures have challenged humans for thousands of years [1]. Such exposures have been recognized to be associated with an increased risk for infections. Moreover, in the past, particle exposures and infections have been so interrelated that medicine has been incapable of distinguishing between them. Subsequently, particle-related disease was frequently, but erroneously, considered a variety of infection (e.g., coal workers' pneumoconiosis was previously identified as "miners' consumption" and "miners' phthisis"). Currently, particle-related infections continue to significantly impact human health [2].

It is proposed that all particulate matter (PM) exposures are associated with an increased risk for infections. Recognition of this relationship between PM exposures, however dissimilar they might appear, and an increased risk for infections allows for their compilation. In addition, defining particle-related infections can assist in the recognition of potential pathways of biological effect.

Human exposures to particles

Human exposure to PM varies in magnitude, composition, and particle size (Table 1). In most nations of the world, cigarette smoking presents the greatest particle challenge.

Table 1 Human exposure to particulate matter

Exposure	Particle burden	Composition	Particle size (microns)
Cigarette smoking	Tens of thousands of μg/cigarette	Organic, combustion product	<0.1
Burning of biomass	Tens of thousands of μg/m^3	Organic, combustion product	<2.5
Dust storms	Hundreds to thousands of μg/m^3	Inorganic; largely silica, silicates, and mineral oxides	0.1–10
Mining	Legally allowable levels of 100 and 2,000 μg/m^3 for silica and coal, respectively	Usually inorganic; coal is organic but not a combustion product	0.1–10
Agricultural work	Hundreds to thousands of μg/m^3	Inorganic and organic, but the latter is not a combustion product	0.1–10
Wildfires, wood burning stoves, wildfires	Hundreds of μg/m^3	Organic, combustion product	<2.5
Environmental tobacco smoke	Hundreds of μg/m^3	Organic, combustion product	<2.5
Traffic-related emissions	Tens to hundreds of μg/m^3	Organic, combustion product	<2.5
Gas stoves	Tens of μg/m^3	Organic, combustion product	<2.5
Ambient air pollution	Tens of μg/m^3	Inorganic and organic	<10

Smoking one cigarette exposes the human respiratory tract to between 15,000 and 40,000 μg of PM [3]. The mass median aerodynamic diameter (MMAD) of these particles is frequently less than a micron and they subsequently have a high total deposition rate in the human lung [4] [respirable is considered to be PM with an MMAD of 10 μm or less (PM_{10})].

The burning of biomass (defined as some combination of wood, charcoal, agricultural residues, and animal dung) is likely to be the PM source of the second greatest concern internationally [5, 6]. More than two billion people around the world use biomass as their main source of energy for domestic heating and cooking; almost all of this occurs indoors in developing nations [7]. While such burning is intermittent, it can introduce indoor concentrations of PM which approach tens of thousands of μg/m^3 [8]. These particles can be fine and ultrafine (with diameters of 0.1–2.5 and <0.1 μM, respectively) in size and certainly respirable.

Internationally, desert dust is a major inhalational exposure, with dust storms transporting huge quantities of mineral oxide displaced from land surfaces by wind [9]. The Sahara-Sahel region is responsible for half of the worldwide total of atmospheric desert dust; drylands around the Arabian Peninsula, Iran, Mongolia and China, Pakistan and India, Australia, southern Africa, and western United States are other major sources for dust storms. Respirable particle (<PM_{10}) in severe dust storms can exceed a few thousand μg/m^3 [10] and consequently impact human health. These storms can also transport particles thousands of kilometers and contribute to ambient air pollution PM elsewhere in the world [11]. Exposures to crustal particles also include mining and agricultural work. Particle exposures during mining can range up to a legally allowable level of 2,000 and 100 μg/m^3 for coal and silica, respectively; these exposures were much higher historically in the United States and are currently even greater in other nations. Agricultural work can also result in exposure to respirable particle levels ranging up to thousands of μg/m^3 [12].

Firefighters and those residing in an area of a forest fire are exposed to wood smoke particles which can approach PM_{10} concentrations measured in thousands of μg/m^3 [13]. Domestic wood burning is a major source of particle exposure in many developed countries and can elevate indoor PM exposures to hundreds of μg/m^3 [14, 15]. These are fine and ultrafine in size. Wood smoke can also be a significant contributor to PM in ambient air [16]; in the United States, between 8 and 85 % of fine ambient air pollution PM is attributed to residential wood burning [15, 17].

Exposures to environmental tobacco smoke (ETS) are intermittent, with levels of respirable suspended particles that approach 600 μg/m^3 in restaurants and 1,140 μg/m^3 in bars [18, 19]. Ambient air PM levels are usually lower (PM_{10} levels of 10–100 μg/m^3), although they can approach hundreds of μg/m^3 at several urban sites of the world. Air pollution particles represent a constant exposure to what can be predominantly fine and ultrafine particles [20]. Diesel exhaust particles occur most frequently at concentrations of less than 10 μg/m^3 in the ambient air [21], but can be much higher in specific environments (e.g., 1,000 μg/m^3 in coal mines) [22]. Particles from gas cooking have been found to be as high as 380 μg/m^3 [6],

but are usually lower. ETS, diesel exhaust particles, and particles from gas cooking similarly include PM in the fine and ultrafine range.

Regarding composition, particles associated with cigarette smoking, the burning of biomass, forest fires, wood-burning stoves, diesel exhaust, gas stoves, and ETS expose individuals to carbonaceous combustion products, and while dust exposures associated with coal and agricultural work are also predominantly carbonaceous, they are not produced by combustion processes. Mineral oxide exposures, including desert dust, which is predominantly silica and silicate, are strictly inorganic. Ambient air pollution PM can range from crustal silicates and plant debris to carbonaceous products of combustion.

Particle-related infections

PM deposits in the nose, pharynx, larynx, trachea, bronchi, and distal lung and, accordingly, the respiratory tract is the system most frequently infected after such exposure; however, meningitis also occurs (Fig. 1). There appears to be a dose–response relationship between PM and risk for infections. Exposures with the greatest particle burden are associated with the largest increases in the incidence and/or prevalence of infectious disease. Cigarette smoking is the particle-related exposure which presents the greatest burden of PM, and smokers have more respiratory tract infections than their non-smoking peers [23–25]. Smoking elevates the risk for pneumonia and can be the strongest independent risk factor for this infection [26–29]. People who smoke have twice the risk for community-acquired pneumonia relative to non-smokers and approximately one-third of all community-acquired pneumonia cases are attributable to cigarette smoking. A dose–response relationship between the amount of smoking and the risk of community-acquired pneumonia is evident [26]. The severity of pneumonia due to bacteria such as *Streptococcus*, *Legionella*, *Mycoplasma*, and *Haemophilus*, is increased among smokers [27, 30–32]. Similar to bacterial infections, viral respiratory infections are increased among smokers. Women who smoke cigarettes have a higher risk of developing prolonged colds [33]. Among adults with varicella, smokers have a risk of pneumonitis 15 times that of non-smokers [34]. Smokers suffer an elevation in the number and severity of otitis media [35], which are predominantly viral. There are also data supporting a relationship between cigarette smoking and mycoses, with smoking at least doubling the rate of *Cryptococcus neoformans* infection [36]. The smoker's risk for these respiratory infections declines after the cessation of smoking, but ex-smokers remain at some increased risk relative to the life-time non-smoker [26]. This continued elevation of risk among ex-smokers likely reflects an effect of the retained particle.

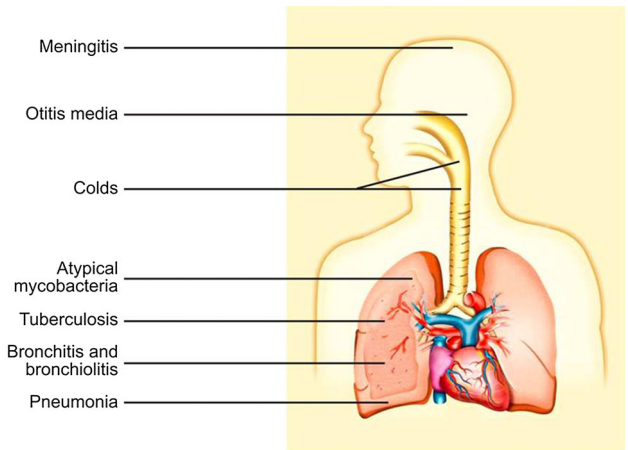

Fig. 1 Particle-related infections. Those infections which increase following particle exposures include colds, otitis media, bronchitis, bronchiolitis, tuberculosis, atypical mycobacterial infections, pneumonia, and meningitis

Regarding the elevation of risk for respiratory infections after particle-related exposures other than cigarette smoking, the burning of biomass for purposes of heating and cooking results in an elevation of such infections and these are a major cause of premature mortality in the world, especially among those in less developed countries [5, 8, 37]. Exposure to desert dust can similarly elevate the incidence of respiratory infections [38, 39]. During mining, the inhalation of coal and mineral oxides increases the rate of respiratory infections [40, 41]. Other occupational exposures to particles increase the risk for pneumonia [42]. Lung infections are reported to be increased in agricultural workers [43]. Forest firefighters [44] and persons using domestic wood burning have an increased number of upper respiratory infections and pneumonias [45, 46]. The relationship between ETS and the occurrence of otitis media, colds, bronchiolitis, and pneumonia in exposed populations has been described [47, 48]; this is true not only for children in the household but also for adults [49]. The risk for respiratory infections after secondhand smoke, especially bronchiolitis, increases when any household member smokes but is most strongly correlated with maternal smoking. Among hospital admissions for infants aged under 2 years in England alone, 10 % of respiratory tract infections were estimated to be due to passive smoke exposure [50]. Ambient air PM levels can be associated with increases in infections, including pneumonia [51, 52] and viral respiratory illness [53]. The use of gas stoves and exposure to diesel exhaust are also associated with an excessive incidence of colds in children [54, 55]. Finally, desert dust increases the risk for respiratory tract infections.

In the United States, dust pneumonia was a term coined during the "dust bowl" (during the mid-1930s) and referred to lower respiratory tract infections which followed a dust storm; these were quite common [56].

Those particle-associated exposures which are greatest in magnitude also increase the risk for several infections which are less frequently observed in the general population. Cigarette smoking, burning of biomass, occupational exposures to particles (e.g., coal, silica, and asbestos), and ETS increase the risk for tuberculosis and atypical mycobacterial infections. Cigarette smoking increases the risk for tuberculosis, including all infections, active disease, and mortality [57, 58]. Greater than 10 % of the tuberculosis cases in the world can be attributed to smoking [59]. Smokers have higher rates of tuberculin skin test reactivity and conversion, and also of active tuberculosis [60, 61]. A dose–response relationship between the number of cigarettes smoked per day and the rate of tuberculosis was observed among volunteers having radiography [62]. The death rate from tuberculosis was about four times higher in those who ever smoked relative to those who never smoked. Comparable to smoking, the burning of biomass is associated with an increased risk for tuberculosis [58]. Particle exposure during mining, tunneling, and foundry work previously increased the risk for tuberculosis [63]; this was especially true for silica exposure. Agricultural work increases mortality from tuberculosis [64]. ETS increases the incidence for tuberculosis [65, 66]. The increase in mycobacterial infections following particle exposures is not restricted to *Mycobacterium tuberculosis* but also appears to include others [67].

Until relatively recently, particle-related infections had been exclusively described to be respiratory. Investigation now demonstrates that PM exposure increases the risk for infectious meningitis. The carriage of *Neisseria* meningococcus in the nasopharynx is more common among smokers than non-smokers [68]. Relative to non-smokers, cigarette smokers have a several fold higher risk of meningitis [69, 70]. Similarly, the burning of biomass is associated with meningococcal meningitis [71]. Bacterial meningitis also follows exposure to ETS [72, 73] and the strongest risk factor for invasive meningococcal disease in children can be having a mother who smoked [74]. Most recently, it has been demonstrated that desert dusts increase the incidence of this disease, with epidemics of meningococcal meningitis following dust storms [75, 76].

Mechanism(s) of particle-related infections

PM exposure can increase the risk for infection by altering various defense mechanisms present in the respiratory tract. Pathways of microbial clearance from the lung are decreased by particles [77, 78]; some portion of this effect is attributable to (1) impaired mucociliary function [79, 80] and (2) diminished phagocytosis by macrophages [81, 82]. Regarding cell functions, studies have shown that PM exposure can alter the capacity of macrophages to inactivate viruses, kill bacteria, disrupt antigen presentation, and produce chemokines that attract inflammatory cells necessary to inhibit the spread of infection [83]. PM can alter native immune cell function to promote either a predominantly TH1 or a TH2 response; this also affects the ability of the lung to inhibit microbial proliferation.

In addition to altering the clearance mechanisms and immune response, increased risk for infection can result from a disruption in iron homeostasis and an accumulation of this metal, which occurs with particle exposure (Fig. 2). Following PM inhalation and endocytosis, oxygen-containing functional groups at the particle surface provide a capacity to bind cell cations. These surface functional groups include silanol (in silica and silicates) and alcohol, diol, epoxide, ether, aldehyde, ketone, carboxylate, and ester groups (in ambient air pollution particles, diesel exhaust particles, wood stove particles, and PM associated with cigarette smoking and burning of biomass). Among the cellular cations available for complexation by the particle surface, iron is abundant and preferred as a result of its electropositivity and high affinity for oxygen-containing functional groups. Cell iron reacts with surface functional groups of a particle to produce a coordination complex [84]. In response to this loss of metal to the particle, iron import (e.g., transport by divalent metal transporter 1) is elevated to meet cell requirements. Following particle exposure, a new iron homeostasis is achieved with elevated iron concentrations allowing continued metal availability to the cell, despite sequestration of the host metal by the particle. Retained PM consistently demonstrates such a capacity to accumulate host iron (e.g., the ferruginous body), providing in vivo evidence of an interaction between the particle and the endogenous host metal [85, 86].

There is an absolute dependency of life (both the pathogen's and the host's) on iron availability. With very few exceptions (e.g., lactobacilli, which substitute manganese for iron), microbes require host iron to proliferate [87]. The pathogen's survival and virulence are directly related to its success in competing for available iron in the host. While the pathogen requires approximately 10^{-6} M Fe for critical processes, metal normally available in the host is 10^{12}-fold lower. Thus, microbes will utilize specialized systems to acquire requisite iron. Siderophores, which acquire iron from either host proteins or low molecular mass compounds, and receptors that bind host transport and storage are most frequently employed. The host will rapidly develop measures limiting iron availability and the

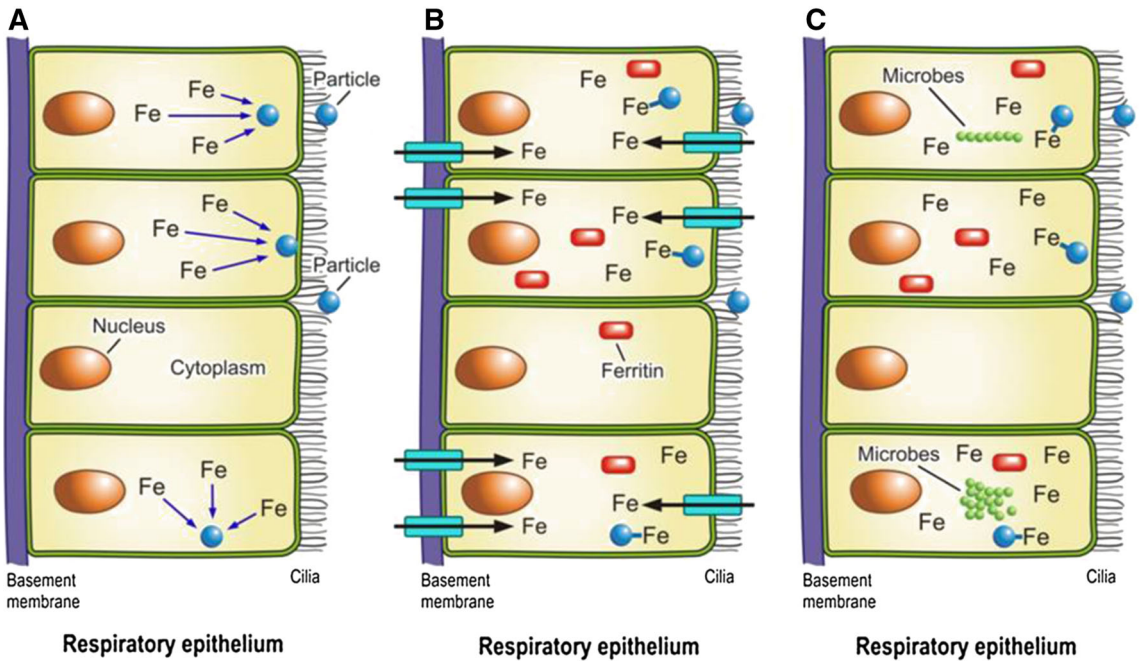

Fig. 2 Schematic illustrating the mechanism of iron accumulation by respiratory epithelial cells exposed to particles [108–110]. As a result of oxygen-containing surface functional groups, particles can sequester host cell iron (**a**; *arrows* refer to complexation of available iron by surface functional groups on the PM). The host responds to a relative deficiency of the metal by increasing the expression of importers (e.g., divalent metal transporter 1; *blue boxes*) (**b**; *arrows* refer to the import of iron by the cell). After cell import of iron to meet increased requirements of the cell following PM exposure, there is a greater concentration of available metal, reflected by higher ferritin levels (*red boxes*). Elevated concentrations of available iron in the cell (**c**) result in increased risk for microbial proliferation and infection

pathogen's impact on its subsistence. An intense competition between the pathogen and the host for metal ensues. Changes in host iron will impact the outcome of infection. Increased levels of available metal will exacerbate many infectious diseases [88]. *Mycobacterium tuberculosis* is adept at the acquisition of host iron, and human disease has been shown to be enhanced by excess availability of this metal [89–93]. Human susceptibility to tuberculosis can be associated with polymorphisms in NRAMP, an importer for iron, reflecting the need for metal [94]. Similarly, the growth of *Neisseria meningitidis* is dependent on iron and the severity of infection can correspond to the availability of this metal [95–97]. Proliferation of the pathogen, whether it be in lung tissue itself or in the nasopharynx as with *Neisseria meningitidis*, is augmented following particle exposure with its consequent accumulation of available iron. While not directly required by viruses, the metal is essential during viral replication in host cells [98].

It is likely that particle exposures elevate the risk for infection by increasing iron levels in cells, tissues, and living systems. In support of a role for increased iron observed in particle-related infections, increased iron availability will similarly elevate the risk for infection, with the injection of neonates with iron resulting in several-fold elevation in episodes of otitis media, pneumonia, and meningitis [99]. Additional support for the relationship is observed with increased dietary iron associated with an increased risk of both developing active tuberculosis and dying with the infection [88]. Finally, siderosis is associated with both tuberculosis infection and its mortality [100, 101].

Conclusions

Exposure to numerous different particles is associated with an elevated risk for infection (bacterial, fungal, viral, and protozoal). The mechanism for the particle-related infection likely includes an accumulation of iron by surface functional groups. Since elevations in metal availability are common to every particle exposure, all PM exposures can predispose to this group of infections; exposures to wood stove emissions, diesel exhaust, and air pollution particles are predicted to increase the incidence and prevalence of tuberculosis, atypical mycobacterial infections, and meningitis, albeit these elevations are likely to be small and detectable only in large population studies. As long as the particle is retained, the risk continues since the iron accumulation correlates with the presence of surface functional groups and the dependent metal coordination. Accordingly, it is expected that the cessation of exposure will diminish but not totally reverse elevated risk for infection, since the

particle is not totally eliminated after clinically significant exposures. This pathway to pathogenicity is shared with other determinants of infection, including aging and alcohol abuse, which are similarly associated with increased iron availability [102, 103]. The same mechanism of disruption of iron homeostasis with metal accumulation may also participate in (1) infections of foreign bodies and equipment [104, 105] and (2) infectious complications associated with numerous diseases [106, 107].

The total elimination of particles from the atmospheric environment is not feasible. However, reduction of exposures to prevent particle-related disease, including infection, can be realized. Recognition of the health risks of particles by both those in health care and the lay public is an important initial step. Smoking cessation will decrease infections associated with both smoking and ETS. The implementation of cleaner energy technologies will reduce indoor air pollution levels. In the nations of the world which burn biomass, an improved design of stoves and ventilation systems will preclude the enormous particle exposures experienced while cooking and heating. Exposures to desert dust can be minimized by those responsible for public health through better communications warning individuals to stay inside during dust storms. Further understanding of particle-related infections will necessitate delineation and compilation of the many pathways by which microbes acquire requisite iron from the host and utilize this metal.

Conflict of interest None.

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