Chapter 1

Understanding the Intersection of Environmental Pollution, Pneumonia, and Inflammation: Does Gender Play a Role?

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Additional information is available at the end of the chapter

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Abstract

Accumulating evidence indicates that exposure to air pollution is associated with increased mortality from respiratory disease. Exposure to ambient pollutants, such as ozone, particulate matter, sulfur dioxide, nitrogen dioxide, and other agents has been associated with decrease in lung function and immunity, and with increased rates of hospitalization for lung disease, including pneumonia. Furthermore, sex differences in frequency and severity of pulmonary disease and infection have been reported, suggesting a role of sex hormones in mediating these differences. Pneumonia, which is commonly caused by bacterial infection and subsequent lung inflammation leading to hospitalization and death, occurs at different rates in men and women. In this context, male and female hormones can have direct effects on the immunity system by binding to receptors in immune cells, and these responses can be modulated by environmental exposures. This chapter summarizes clinical, animal, and epidemiological studies linking exposure to air pollution and pneumonia in both males and females. Understanding sex-specific mechanisms in pneumonia pathogenesis and environmental responses can help in the development of more effective therapeutics and treatment options to reduce negative health outcomes in men and women.

Keywords: sex differences, ozone, particulate matter, air pollution, sex hormones, community-acquired pneumonia, environmental exposures

1. Introduction

Regulation of the lung inflammatory response is critical to the successful resolution of pneumonia. Exposure to air pollutants has been linked to negative lung health outcomes, and both male

and female sex hormones have been shown to control the lung immune response [1, 2]. This chapter combines evidence of three areas: pneumonia infection, air pollution, and hormonal control of sex-specific immune responses. We will discuss common pathogens responsible for pneumonia and associations with environmental exposures, and lessons learned from animal models of infection and exposure to various air pollutants. Together, this information could help better explain the differences observed in susceptibility to pneumonia between men and women, and help in the development of better treatment options for male and female patients.

2. Pneumonia in the clinic: classification, comorbidities, and pathogenesis

2.1. Classification

Pneumonia is classified according to the patient population affected as: (a) community-acquired pneumonia (CAP), (b) hospital-acquired pneumonia (HAP), (c) ventilator-associated pneumonia (VAP), and (d) nursing home-associated pneumonia (NHAP) [3]. Of these classifications, CAP is the most frequently found, predominantly affecting young children because of the immaturity of their immune system, and older adults due to their immunosenescence and comorbidities of aging [4].

Community-acquired pneumonia is a common infection that affects the lower respiratory tract and it is acquired outside of the hospital or within 48 h of admission, and it is primarily associated with the presence of a new infiltrate on the chest radiograph [2, 3]. Community-acquired pneumonia is often caused by pathogens of the not multidrug-resistant type (MDR), which is an important distinction from the other types of pneumonia. However, some patients with recent antibiotic therapy could also present infection with MDR organisms [3, 5]. Furthermore, most patients are presented with common clinical symptoms, such as fever, cough, pleuritic chest pain, and breathing difficulty, although these symptoms can be absent in elderly patients. Elderly patients, on the other hand, can also have delirium, abdominal pain, or acute cardiac disorders as part of their clinical presentation [4].

2.2. Incidence and risk factors

Despite newer antimicrobial therapy and treatment guidelines, CAP continues to be a significant problem associated with high mortality, morbidity, and cost. In the United States alone, CAP affects approximately 5.6 million patients annually, and it is the sixth cause of death in individuals older than 65 years of age [6, 7]. According to the National Vital Statistics Report of the Centers for Disease Control, pneumonia and influenza were listed as the eighth leading causes of death in the United States in 2011 [8]. As a result, the economic burden of CAP remains significantly high, at more than $17 billion dollars annually in the United States [9].

Several risk factors have been associated with CAP, including age and comorbid diseases [10]. Furthermore, exposure to air pollution and circulating levels of sex hormones also seem to play

an important role in the predisposition of some respiratory infections [11, 12]. Although some studies in animals have shown that females are more resistant than males to some bacterial infections [13, 14], others have shown that these patterns are reversed if animals are pre-exposed to environmental pollutants, such as ozone [15–20]. Incidentally, some clinical studies have reported that men are more susceptible to developing CAP and receive more intensive care than women, and show increased risk to die from pneumonia [21]. Moreover, exposure to air pollution has been associated with an increased risk for respiratory disorders due to its negative effects on lung function and immunity [22]. In this regard, long-term exposures to air pollutants, such as ozone, nitric oxide, and particulate matter in older adults have been linked with increased hospitalization rates for CAP [11, 21, 23, 24]. In addition, exposure to diverse environmental agents has been linked to negative lung health outcomes in children and adults (**Table 1**). The mechanisms associated with these clinical outcomes will be discussed in the following sections.

Children			**Adults**		
Environmental exposure	Health outcome	Sex differences	Environmental exposure	Health outcome	Sex differences
Secondhand smoke	Pneumonia (incidence and severity)	N/A	Particulate matter (PM_{10})	Chronic laryngitis	Higher in males
Air pollution	Pneumonia, Bronchitis	N/A	House biomass fuel use	Various communicable respiratory disease	Higher in women
Household air quality	Pneumonia	Higher in males	Secondhand smoke	Community-acquired pneumonia (elderly)	N/A
Air pollution	Outpatient visits for respiratory disease	Higher in females	Air pollution	Outpatient visits for respiratory disease	Higher in males
Solid fuel	Pneummonia, Mortality	Higher in females	Air pollution ($PM_{2.5}$, SO_2, NO_2)	Pneumonia	Higher in males (smokers) Higher in females (never smokers)
Environmental tobacco smoking	Pneumonia Chronic bronchitis	N/A	UV radiation, sulfur oxides	Invasive pneumococcal disease	N/A
Indoor air pollution (solid fuel cooking, keeping large animals)	Severe pneumonia	N/A	Tobacco smoke	Sinusitis, middle ear infections	Flight attendants
SO_2, total suspended particles	Pneumonia	N/A			

Table 1. Effects of the environment on respiratory tract health in children and adults and observed sex differences.

2.3. Pathogenesis of pneumonia

Pneumonia is characterized by a severe inflammation of the peripheral alveolar compartment and abnormal filling with fluid consolidation and exudation caused by infection with viruses, bacteria, and/or pathogen-related molecules. The most common cause of CAP is bacterial infection, but the disease can also be triggered by viral agents (**Table 2**) [6, 25, 26]. Pneumonia-causing microorganisms are classified as typical, atypical (zoonotic and non-zoonotic), Gram-negative, and viruses. *Streptococcus pneumoniae* is the most common cause of pneumonia in adults in the United States. Nevertheless, other typical organisms are also included with some important associations. For example, *Haemophilus influenzae* is found particularly in patients who smoke or have chronic obstructive pulmonary disease (COPD), *Moraxella catarrhalis* and *Staphylococcus aureus* are often found in pneumonia following influenza infection, and in the form of methicillin-resistant *Staphylococcus aureus* (MRSA) [6]. In addition, atypical pneumonia could be produced by zoonotic pathogens, such as *Chlamydia psittaci*, *Francisella tularensis*, *Coxiella burnetii* (also known as Q fever) and by non-zoonotic pathogens like *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila*. Furthermore, patients with these atypical infections have a more frequent presentation of a mild or ambulatory CAP, and also present extrapulmonary manifestations not found in CAP caused by typical pathogens [26]. *S. pneumoniae* colonize the human nasopharynx and can be transmitted from animals in captivity to humans [27]. Differences in strains of *S. pneumoniae* are responsible for differences in virulence and the presence of antigens [27].

Community-acquired pneumonia can also be caused by a variety of viral infections. The most frequent viruses associated with CAP are influenza A and B, and parainfluenza. Less frequently, respiratory syncytial virus (RSV), severe acute respiratory syndrome virus, varicella, hantavirus, and adenovirus, are also responsible for CAP. Furthermore, most of these viral infections present in combination with multiple bacterial pathogens including *S. pneumoniae* and *C. pneumoniae*. However, patients with congestive heart failure (CHF) are at increased risk of acquiring CAP caused by pure viral infections [6, 25]. Gram-negative bacteria (*Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter* spp., and *Serratia* spp.) are common in patients with CAP who have had recent contact with health care environments, such as previous hospitalization, probable aspiration, antimicrobial treatment, and pulmonary comorbidities [28]. **Table 2** summarizes common associations of pathogens with clinical factors, history, and environmental factors in patients with CAP [4–6, 25, 26].

Typical
Streptococcus pneumoniae, Haemophilus influenza, Moraxella catarrhalis, Staphylococcus aureus

Atypical
Zoonotic: *Chlamydia psittaci, Francisella tularensis, Coxiella burnetii*
Non-zoonotic: *Mycoplasma pneumoniae, Chlamydophila pneumoniae,* and *Legionella pneumophila*

Gram-negative
Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli, Enterobacter spp., *Serratia* spp., *Proteus* spp.

Viruses
Parainfluenza virus, Influenza virus A and *B*
Less frequently: Respiratory syncytial virus (RSV), severe acute respiratory syndrome virus, varicella, hantavirus, and adenovirus

Table 2. Common pathogens in community-acquired pneumonia.

The main mechanism of infection in CAP is micro-aspiration from a previously colonized oropharynx, but inhalation of suspended aerosolized microorganism is the route of infection for viruses and bacterial agents, such as *L. pneumophila* and *Mycobacterium tuberculosis*. However, other factors related to the host immune response, the virulence of the infecting organism, and the size of the inoculum also define the development of the disease [29]. Furthermore, the presence of medical comorbidities, such as chronic respiratory and cardiovascular diseases, cerebrovascular diseases, Parkinson's disease, epilepsy, dementia, dysphagia, HIV infection, and chronic renal, or liver disease can also lead to a defective cough, abnormal mucociliary clearance, and impaired humoral and local immunity that can influence the pathogenesis of pneumonia [30–32]. In addition, lifestyle and social factors including smoking and alcohol consumption, contact with pets, households with more than 10 people, interventions of upper airways, and poor dental health have also been associated with an increased predisposition for the development of CAP [10] (**Table 3**). Smoking affects the respiratory epithelium and the clearance of bacteria from the respiratory tract, increasing the susceptibility to respiratory infections, even in passive smokers [33–35]. Alcoholism has also been linked to alterations in innate and adaptive immunity [36]. Moreover, nutritional deficiencies appear to affect mechanisms of innate immunity, and are associated with the increased risk of CAP development and mortality [37–39].

2.4. Gender differences in community-acquired pneumonia

Increasing evidence suggests that sex hormones play a role in the expression of genes involved in the regulation of the immune system, which in turn can impact the individual susceptibility to infectious agents, and incidence of autoimmune diseases [13, 14]. In this regard, patients suffering from systemic autoimmune diseases (including systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, polymyositis/dermatomyositis, Sjögren's syndrome, and others) are at increased risk of developing pulmonary infection, aspiration pneumonia, and bronchiolitis obliterans organizing pneumonia [40]. Furthermore, studies have shown that androgens in males can affect the immune system leading to an increased susceptibility to infection and disease caused by parasites, fungi, bacteria, and viruses. On the contrary, estrogen leads to an increase of cell-mediated and humoral immune responses in females, making them more resistant to some infectious diseases [41]. However, the role of estrogen in modulating the immune response remains controversial [42, 43].

Remarkably, physiological changes in male and female sex hormone levels (estradiol, testosterone) play important roles in human lung development, and differences in susceptibility to pulmonary infection are also present at an early age [44–47]. Gender disparities are also displayed in expression of surfactant production that appears earlier in female than male during lung development, and in the incidence of neonatal conditions of prematurity, such as respiratory distress syndrome and bronchopulmonary dysplasia [48, 49]. The earlier presence of surfactant in female neonatal lungs helps open the small airways and may contribute to their higher airflow rate observed [50]. Evidence from human studies suggests that male infants are more susceptible to lung infection, with greater associated morbidity and mortality than female infants, but the reverse is applied in children and adolescents [47, 51, 52]. Regarding respiratory tract infections (RTIs), women are more

CAP pathogens	Environmental associations/comorbidities
Streptococcus pneumoniae, *Gram-negative bacilli*, *Anaerobes*, *Haemophilus influenzae*, *Staphylococcus aureus* (including *methicillin-resistant* forms), *Chlamydophila pneumoniae*, *Mycobacterium tuberculosis*	Nursing home resident
Streptococcus pneumoniae (including drug-resistant *S. pneumoniae*), *Anaerobes*, *Gram-negative bacilli*	Alcoholism
Streptococcus pneumoniae, *Haemophilus influenzae*, *Salmonella*, *Cytomegalovirus*, *Cryptococcus*, *Pneumocystis jirovecii*, *Anaerobes*, *Mycobacterium tuberculosis*	HIV infection
Streptococcus pneumoniae, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Legionella*	Chronic obstructive lung disease
Anaerobes, *Gram-negative bacilli*	Aspiration, enteric chemical pneumonitis
Anaerobes	Poor dental hygiene
Pseudomonas aeruginosa, *Pseudomonas cepacia*, *Staphylococcus aureus*	Structural disease of the lung: (bronchiectasis, cystic fibrosis)
Streptococcus pneumoniae, *Staphylococcus aureus*, *Haemophilus influenzae*	Recent influenza infection
Drug-resistant *pneumococcus*, *Pseudomonas aeruginosa*, *Gram-negative bacilli*	Recent antibiotic therapy
Chlamydophila psittaci, *Cryptococcus neoformans*, *Histoplasma capsulatum*	Exposure to birds
Coxiella burnetii (Q fever)	Contact with farm animals or parturient cats Exposure to rabbits
Coccidioides immitis	Travel to southwest USA
Histoplasma capsulatum	Exposure to bats
Parainfluenza virus, *Influenza virus A* and *B*, *Respiratory syncytial virus* (RSV)	Congestive heart failure, mixed infections

Table 3. Common pathogens in community-acquired pneumonia and environmental associations.

commonly affected by upper RTIs, such as sinusitis, tonsillitis, and otitis externa. On the other hand, men are at higher risk of developing otitis media, croup, and lower RTIs, including CAP [11]. Furthermore, these infections are more severe and show poorer outcomes and more complications in male than female individuals, leading to increased mortality, especially in CAP [21]. To date, the specific contributions of sex hormones or other factors, such as exposure to air pollution, socioeconomic, racial, and/or behavioral factors, obesity, and other comorbidities have only been explored in small studies [24, 53–56]. Several other factors including anatomic differences of the respiratory tract, behavioral, socioeconomic, and lifestyle factors have also been related with differences in incidence and severity of respiratory infections between genders [11, 41]. **Table 1** summarizes epidemiological data on associations of sex and environmental exposures on various lung health outcomes including pneumonia in children and adults [10, 27, 57–72].

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3. Pneumonia in the laboratory: animal models and mechanisms of infection

3.1. Animal models of pneumonia

Wide-ranging research is required to understand the mechanisms underlying pulmonary diseases, such as pneumonia. Studies of human populations, *in vitro* experiments, and exploratory infections of species are needed to advance in the development of new treatments for this condition. Animal models have been widely used in the field and have often provided insight into the physiological processes associated with the disease.

A variety of species have been used as animal models of pneumonia. Even though some species, such as *Danio rerio* (zebrafish) and *Caenorhabditis elegans* (roundworm) do not use lungs to acquire oxygen, and do not have similar sexual characteristics when compared to humans, they can be useful models to provide valuable information about host-pathogen interactions in lung disease [73]. Researchers utilize zebrafish as an alternative vertebrate model to study the pathogen's ability to infect the host [74]. Because zebrafish embryos and 3-week old larvae look transparent, it is feasible to follow the evolution of lung infection in real time [74–76]. In addition, zebrafish have a developed adaptive immune system and a high rate of conserved gene orthologs in humans [77, 78]. On the other hand, *C. elegans* is used as a non-vertebrate model for studying lung bacterial agents. Interestingly, the immune system of *C. elegans* and humans has similar signaling cascades in response to infection [79]. Despite anatomical differences, it is possible to recognize pathogen-specific virulence factors in epithelial surfaces of *C. elegans*, making this model ideal for the study of host defense mechanisms. Likewise, insects, such as *Drosophila melanogaster* (fruit fly) are valuable models of infection for the analysis of bacterial pathogenesis and genetic contributions. Insects have an advanced antimicrobial defense mechanism and a complex and conserved immune system [80]. In addition, a large number of genes that encode for proteins in the immune system are found on the X chromosome, which promote a higher activation of toll and immune deficiency signaling in *D. melanogaster* females than males [81]. Together, all these species possess advantages, such as low cost of maintenance, short life span, small size, fast development, and rapid reproduction making them feasible models for the study of infectious diseases. However, most pneumonia studies performed in animals are conducted in mammals because of their anatomical, genetic, and morphological similarities with humans.

Larger mammalian species, such as rabbits, piglets, and primates are ideal for specialized experiments when physiological monitoring and therapies are evaluated [82]. Currently, primates are the only species able to assess primate-specific infectious agents, but due to ethical concerns, piglets are the most frequently used model to study ventilator-associated pneumonia (VAP). Even though large mammalian animals are phylogenetically close to the human species, the disadvantages associated with their use as models is that they are only useful for a limited number of studies, and they are expensive to house and feed, slow to breed, and genetically diverse. For this reason, infections in the lung have primarily been studied in small mammalian species, predominantly rodents. Rodents are small, inexpensive, and highly reproductive.

Inbred strains are preferred to investigate genetically identical groups by facilitating the use of molecular approaches to understand the mechanisms of diseases. Since studies in mice have become popular in scientific research, the creation of new studies benefit from the extensive literature available regarding genetic engineering, immunological responses to pathogens and host defenses.

3.2. Strain differences and associated mechanisms

Knowledge of differences among strains of animals in disease models can provide ideal tools for the discovery of mechanisms of disease development [83]. A strain is defined as a group of genetically identical animals. Laboratory mice are often very diverse in behavior and physiology due to a large variety of inbred, outbred, and transgenic strains produced. In laboratory mice, this is developed through inbreeding. Different mouse strains show different responses to lung infection and environmental exposures, and these can also be affected by sex and age [84]. The most common mice strains used for the study of human pneumonia are BALB/c, C57BL/6, DBA/2, 129/Sy, CBA/Ca, C3H, SJL, and A/J. In addition, a recently developed strain, collaborative cross (CC) is derived from an eight-way cross using several founder strains [85].

A study comparing susceptibility to lung infection in mice reported that, after inducing pneumococcus infection in the respiratory track of various strains, BALB/c mice, which have the ability to produce monoclonal antibodies, show no bacteremia and no lethality. Contrarily, C57BL/6 and DBA/2 mice, which are widely used inbred strains with opposite genetic susceptibility, showed 50% lethality and an intermediate response to bacteremia. Moreover, strains, such as CBA/Ca, C3H, and SJL which are highly susceptible to infection, developed acute bacteremia with 100% lethality [86]. In a similar experiment, following pulmonary *Klebsiella* sp. infection, C57BL/6 strain exhibited more susceptibility to bacterial dissemination and lethality than 129/Sy mice, a strain widely used in the production of targeted mutations [87]. When exposed to *Yersinia pestis*, BALB/c and C57BL/6 mice succumbed to disease, whereas C3H mice were significantly more resistant with 80% survival [88]. Other studies of *Pneumocystis carinii*-induced pneumonia revealed severe effects in C3H mice; moderate effects in BALB/c, C57BL/6, B1O.A(2R), AKR/J, and Swiss Webster mice; and mild effects in DBA/2 and DBA/IJ mice [89]. Furthermore, most strains were unable to get infected by *L. pneumophila.* Finally, it was discovered that A/J mice are susceptible to *L. pneumophila*-induced lung infection because of the lack of cells specific to the adaptive immune system in these mice [90, 91].

In all these species, innate immune mechanisms defend the airways from a wide array of infections that enter the lungs and cause pneumonia. Inbred laboratory mouse strains highly differ in their immune response patterns as a result of mutations and polymorphisms. As an overall rule, toll-like receptor 4 (TLR4) mutant mice, such as C3H/HeJ are more susceptible to Gram-negative infections (e.g. *K. pneumoniae*) than other strains [92]. Moreover, some strains including A/J, DBA/2, DBA/1, FVB/NJ, and SWR are more prevalent to develop pneumonia after infection with microorganisms, such as *Bacillus anthracis*, *Aspergillus fumigatus*, and *Candida albicans.* The latter is due to a mutation in the complement component 5 (C5), which plays a role in the pathogenesis of autoimmune diseases [93, 94]. However, AKR/J mice, which also carry a C5 mutation, are less susceptible to *C. albicans* infection due

to the *C. albicans* resistance loci that modifies host responses in these mice. In addition, studies of the *Klra* natural killer (NK) receptors have demonstrated that *Klra15 is* expressed in 129/J mice, and *Klra12* is expressed in CBA/J and C3H/He mice. None of these, however, are expressed in C57BL/6 mice [95].

Following infection, both human and mouse lungs produce immune mediators, such as cytokines, chemokines, and other components of the immune system. A regulator of IL-1β that is also highly expressed in mouse and human lungs after infection is prostaglandin E (PGE_2), and its precursor enzyme cyclooxygenase-2 (COX2) [52]. Studies using depletion of alveolar macrophages have demonstrated that these contribute largely to the stimulation of pro-inflammatory cytokines, such as IL-6 and TNFα [48]. Moreover, interleukin-1β (IL-1β) is induced only by strains containing the cholesterol-dependent cytolysin, pneumolysin (PLY), a major virulence factor of pneumococci infection [51]. In addition, the levels of toll-like receptor 2 (TLR2) and toll-like receptor 4 (TLR4) increase after *S. pneumoniae* infection in the Crl:CD1 mouse strain [96]. Both BALB/c mice and human lungs liberate hydrogen peroxide leading to DNA damage and apoptosis in lung cells [50, 97].

Viruses can also lead to pneumonia. Influenza A and B viruses are the most common causes of pneumonia in adults, but other viruses can contribute to the disease development. The susceptibility of mice models to influenza viruses depends on the strain of virus used. The most commonly used strains in research are A/Puerto Rico/8/1934 (H1N1, PR8) or A/WSN/1933 (H1N1, HSN). Researchers also use several pandemic viruses, such as the 1918 H1N1 pandemic strain, highly pathogenic avian influenza (HPAI) viruses of the H5N1 subtype, certain H7 subtype viruses, a subset of low pathogenic avian influenza viruses, and the 2009 H1N1 pandemic strains. After viral infection in mice, several immunomodulatory mediators are released including IL-1β, IL-6, IL-8, MCP-1, MIP-1α/β, interferon-gamma inducible protein (IP-10) and interferon-beta (IFN-β) in a somewhat strain-specific manner [98–100].

Animal research in viral pneumonia employs either BALB/c or C57BL/6 mice [68]. The majority of laboratory mice are vulnerable to disease and death after infection, whereas, wild mice are resistant to exposure. This is due to the lack of the antiviral factor Mx1 protein in inbred strains [72]. On the other hand, it is possible for researchers to adapt strains to mouse models. DBA/2J and A/J mice are more susceptible to diseases, even with viral isolates that were not adapted to mice, than the more frequently used BALB/C and C57BL/6 strains. Even though mouse-adapted strains are important to model seasonal H1N1 and H3N2 virus infections, certain influenza viruses cause disease in mice without prior adaptation [101]. Therefore, the interpretation of research outcomes in a particular strain may not be applicable in other strains and molecular pathways in pneumonic mouse lungs may differ.

Typically, Th1 cells are important in the clearance of intracellular pathogens, whereas Th2 cells are associated with responses to parasites. C57BL/6 mice display a typical Th1-type bias to pathogens, whereas other strains, such as BALB/c, A/J, and DBA/2 mice, tend toward a Th2 response [102]. These variations may also be reflected in the M1 and M2 macrophage responses to antigen stimulation. In addition, the region *D7Mit341* to *D7Mit247* on mouse chromosome 7 has been reported to be a survival trait against illness associated with *S. pneumoniae*. Susceptibility to experimental pneumococcal infection is strain dependent. In this

regard, strains from least to most sensitive include BALB/c, DBA/2, C57BL/6, NIH, AKR, FVB/N, CSH/He, SJL, and CBA/Ca [103]. The majority of inbred mouse strains are resistant to infection with *L. pneumophila*, however, A/J mice carry the Lgn1-s allele, making them susceptible to infection [104].

Currently, researchers are taking advantage of the phenotypic and genetic variations available in CC mice. The CC combines the genomes of eight genetically diverse founder strains, such as A/J, C57BL/6 J, 129S1/SvImJ, NOD/LtJ, NZO/HlLtJ, CAST/EiJ, PWK/PhJ, and WSB/EiJ [85]. This genetic combination is a significant element for the study on human-host susceptibility to major diseases, including infections, such as pneumonia [105]. In a recent study, scientists used the CC mouse model to determine whether the host genetic background could impact the risk of morbidity and mortality to pneumonia caused by infection with *P. aeruginosa*. In this study, the CC strain reproduced the responses of disease severity commonly observed in humans during infection, suggesting that variations in morbidity and mortality are highly affected by host genetic factors [105]. Whereas no significant gender differences on disease phenotypes were observed, it is important to note the sample size was small. Similar variations in morbidity and mortality were found in another study where scientists used CC animals to perform a quantitative trait locus mapping of host susceptibility to *Klebsiella* sp. infection in a study where females were found to be less susceptible to infection than males [106]. In summary, animal models with high genetic diversity, and large size and number of independent recombination are emerging as a powerful tool for genomic studies, helping scientists better understand and develop more effective therapies for pneumonia [107].

3.3. Sex differences in pneumonia models

It has been known for several years that sex is a contributing factor in the prevalence and development of a number of pulmonary diseases, such as pneumonia [11, 108]. Animal studies also suggest that there is a sexual dimorphism after puberty in innate and adaptive immune response genes in C57BL/6 mice, with innate immune response genes being highly upregulated in postpubertal male mice but not in female mice. In contrast, postpubertal female mice express high levels of adaptive immune response genes, and expression of these genes occurs at lower levels in postpubertal male mice [60].

Several studies in animals have reported that increase in circulating levels of estrogens may lead to reduced innate immunity, as measured by natural killer cell and macrophage activity, and a decrease of cytokine release [109–111]. Animal models of infection are the simplest tool available to study sex differences due to high availability of castrated animals and hormonal replacement therapies. Multiple studies have demonstrated that susceptibility to invasive viral, bacterial, fungal, and parasitic diseases is higher in males than in females in all age groups [57, 61, 112, 113]. The concept that males are more susceptible to lung infection is further sustained by data from mouse models of bacterial infection, such as *Pneumococcal pneumonia* and *Mycobacterium marinum*, where female mice display longer survival than male mice when exposed to severe sepsis [62, 114]. Infection of C57BL/6 mice with *K. pneumoniae* demonstrated a severe effect in male mice, but not in female mice [19]. In contrast, after infection with *P. aeruginosa*, C57BL/6 female mice showed greater weight loss, bacterial load, and

higher levels of inflammatory molecules than male mice. In this context, IL-10-deficient male mice exhibited elevated levels of bacteria when compared to C57BL/6 male mice. These results confirm that both C57BL/6 and IL-10-deficient male mice are more resistant to *P. aeruginosa* infection than female mice [115]. Moreover, external administration of estrogen to adult male mice infected with *P. aeruginosa* resulted in an extreme progression of inflammation and fluid infiltration in lung tissue [116].

3.4. Sex-specific mechanisms of infection and immunity

Currently, there is limited understanding of the molecular processes that lead to either immune-suppression or stimulation during pneumonia pathogenesis in males and females. In general, females display strong humoral immune responses after infection or vaccination when compared to males [114]. This is partially due to high levels of CD4+ T cells and variations in regulatory T cells (Treg) that regulate immune responses during the menstrual cycle in women [117]. It is known that estrogen influences transcription of specific genes that alter host immunity and promotes the proliferation of Treg during the follicular phase of the ovarian cycle [89, 118]. Because estrogen regulates CD4+ T cell subsets, there is a direct effect on Th1/Th2 equilibrium known to be crucial against bacterial and viral infections. On the other hand, studies indicate that negative outcomes from infectious pulmonary diseases in males is associated with testosterone-induced immunosuppression causing a decrease in T and B cell proliferation, and immunoglobulin and cytokine production after puberty [14]. These alterations in the adaptive immune system could help explain why men are more susceptible than women to some pulmonary diseases caused by infectious agents. However, treatments for pneumonia are standardized for both men and women indicating a general lack of understanding of sex-based differences.

4. Sex hormones and lung immunity

4.1. Sex hormones and mechanisms of action

Sex and gender differences in clinical disorders are mostly driven by genetics and sex hormones. In order to understand hormonal effects not only in lung diseases, but also in other health conditions, it is essential to recognize their mechanisms of action, signaling pathways, and active metabolites. The major sex steroid hormones, such as estrogen, progesterone, and testosterone are derived from a common lipid precursor, cholesterol, by a complex series of reactions catalyzed by multiple enzymes [119]. In brief, cholesterol is converted to pregnenolone by the cytochrome P450 enzyme. Pregnenolone, which is a precursor and metabolic intermediate in the biosynthesis of the steroid hormones, can be transformed either to progesterone by the action of 3β-hydroxysteroid dehydrogenase (3β-HSD), or alternatively be converted to dehydroepiandrosterone (DHEA) via cytochrome P450c17 action. DHEA can turn into androstenedione via 3β-HSD and consequently testosterone or estrone via 17β-HSD and aromatase, respectively. Estrone may be further converted to estradiol via 17β-HSD. Testosterone can be also transformed into estradiol via aromatase.

Sex steroids are primarily produced by the gonads (ovaries and testes). Significant evidence suggest that production of sex steroids is also found in peripheral tissues of non-reproductive organs, such as the adrenal gland, heart, breast, and lung implying a dependency on the enzymes present in the organs [120, 121]. It is thought that the source of hormone production can affect the metabolism, circulation, regulation, and concentration of local steroid versus that of circulation, which can play a role in the paradoxical effects observed for some sex hormones [43, 122, 123]. One example is the "estrogen paradox", observed in women with pulmonary hypertension. A large number of animal studies have found estrogen to be protective in the coronary circulation with better outcomes in female mice, and exasperation after ovariectomy. Contrarily, there is a higher prevalence of pulmonary hypertension in women. While some studies in humans have suggested that estrogen may increase the risk of portopulmonary hypertension, others have shown that estrogen enhances pulmonary vascular remodeling [124].

Circulating levels of testosterone range from 2 to 15 ng/ml or 6 to 50 nM in males, and less than 1.5 ng/ml or 5 nM in females throughout life. Even though men produce both estrogen and progesterone, the levels of these hormones are significantly higher in women, fluctuating from 20 pg/ml estrogen and 0.3 ng/ml progesterone in the follicular phase in non-pregnant and postmenopausal women, to 40 ng/ml estradiol and 300 ng/ml progesterone in pregnant women [43]. The significance of the oscillations of hormonal levels consists in their contribution to the local level of any sex steroids. For example, the estrogen produced in tissues may become more prominent in postmenopausal women, while the effect of progesterone may decline. At present, there is not much information available on this issue relevant to the lung.

4.2. Effect of sex hormones in immune responses and lung development

Currently, there is an increasing evidence for sex differences in incidence, morbidity, and mortality of lung diseases. Whether sex steroids play a role in modulating these differences is currently under investigation.

Estradiol levels in the fetus emerge in week 20 during the canalicular phase of lung development, and rise throughout birth [125]. Differences in estrogen levels have been observed in lung maturation, preservation, and regeneration, alveoli development and surfactant synthesis suggesting an active role of estrogen in sexual dimorphism [126–131]. Moreover, it is known that estrogen plays a complicated immunomodulatory role in humans and in animal models, suppressing inflammation in some states while enhancing it in others [116]. In animal models, estrogen blocks both B and T cell development, increases thymic atrophy, and decreases all developing T cell populations, while it enhances B cell survival in response to antigen [132–134]. In humans, hormone replacement therapy reduced the amount of T cells, while B cells were unaltered or upregulated in postmenopausal women, increasing the risk of developing B cell-dependent autoimmune diseases [123, 135]. Other studies propose that estrogen enriches the accumulation of Th1 CD4+ T cells in response to antigen in female mice [136]. It was also stated that estrogen inhibits the induction of Th1 pro-inflammatory cytokines (IL-12, IFNγ, and TNFα), while it enhances Th2 anti-inflammatory cytokines (IL-4, IL-10, and TGFβ) in female mice [137]. However, little is known about how puberty affects

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lung diseases later in life and how the changes in estrogen levels contribute to the pathophysiology of pulmonary diseases. This is important because estrogen can cause effects on the immune system by binding to estrogen receptors (ER) expressed by immune cells, such as B cells, T cells, and macrophages [138]. Variations in the expression of ER in the bronchial and alveolar epithelium suggest a role in estrogen signaling, which can contribute to the gender dimorphism seen in males and females [130, 131, 139, 140]. In addition, estrogen has the ability to indirectly stimulate airway and parenchymal responses by acting on airway and alveolar epithelial cells, which are structural cells [141]. In the case of infection with *P. aeruginosa*, researchers found that female mice were more susceptible than males [115]. Furthermore, in a study where chronic infection of cystic fibrosis (CF) airway by *P. aeruginosa* was studied, researchers found that estrogen increased the severity of pneumonia in adult CF male mice, and proposed two potential mechanisms: enrichment of Th17-regulated inflammation and suppression of innate antibacterial defenses [116]. On the contrary, fetal levels of testosterone are found on week 9 of gestation during the pseudoglandular phase [125]. In this context, elevated levels of androgens, which are any hormones that primarily influence the growth and development of the male reproductive system, are found associated with slow fetal lung development [142–144]. In this context, studies have shown that anti-androgen flutamide can produce high levels of surfactant phospholipid in the male fetal lung, however, androgen dihydrotestosterone (DHT) blocks the synthesis of surfactant phospholipid in the female fetal lung [1, 145]. The development of male fetal lungs depends on the expression of the androgen receptors (AR) [46]. Whether testosterone, and/or its receptors, play a role in modulating sex differences in lung diseases, such as pneumonia remains unknown.

5. Pneumonia and air pollution: epidemiological and experimental data

5.1. Outdoor air pollution and lung health

In the last several decades, an accumulative body of epidemiological, toxicological, and experimental evidence, including various exposure agents, times, doses, and combinations of pollutants, have linked exposure of air pollution to negative cardiovascular and pulmonary health effects [146], and infection rates (**Table 1**). These include increased inflammation, exacerbation of pre-existing inflammatory lung disease (e.g. asthma, wheezing, and COPD) and allergies, altered lung function and immunity, and increased susceptibility to infection and pneumonia. Extensive epidemiological evidence demonstrated inter-individual differences in the susceptibility to environmental exposures, with age, gender, and genetic polymorphisms significantly contributing to its negative health effects [12]. A summary of the most frequently found pollutants and their health effects is summarized in **Table 4**.

Air pollutants are generally present in the environment as a mixture of several gases and particles that are products of combustion of fossil fuels, diesel traffic, wood smoke, and other industrial processes. Some sources of domestic energy used around the world, especially in developing countries, are the result of combustion of fuels, such as wood, dung, and charcoal but also result in the generation of large amounts of indoor pollutants including small

particulates (PM_{10}), nitrogen dioxide (NO_2), carbon monoxide (CO), sulfur dioxide (SO_2), and various hydrocarbons [147]. In this context, individuals who spent time at home, such as mothers and their children are at higher risk of developing respiratory infections [148–150]. In addition, particulate air pollution released by burning plantations has also been associated with pneumonia. For example, in Brazil (one of the main sugar cane producers), the incidence of pneumonia-related emergency department visits has found significant increase during sugar cane burning periods [151]. Air pollution in countries with high industry factory activity, such as Taiwan has also been associated with respiratory diseases, with some differences in age and gender of the patients affected. In these studies, NO and NO_2 were two of the main air pollutants related to respiratory diseases, followed by PM_{10}, $PM_{2.5,}$ $O_{3,}$ CO, and SO_2. Young patients (0–15 years of age) were the most affected by air pollution and meteorology factors, followed by elder patients (age ≥66 years), and aged 16–65. A closer look at gender differences revealed that women were more affected than men in the young age group and in the eldest group, but men were more sensitive between ages 16 and 65 groups [152–155]. Other studies have also reported both women and elderly people to be more susceptible to die from air pollution than other population groups [153, 156, 157].

One of the reasons that could explain the increased mortality in women is their high vulnerability to autoimmune disorders, some of which are associated with air pollution [158]. Moreover, anatomic and physiologic differences between men and women also seem to play a role in this disparity. In general, men have higher lean body mass and water content than women, which results in an increased distribution volume of soluble substances. On the contrary, women have more relative fat mass than men, which gives them a larger distribution volume for fat-soluble substances, and most of the chemical particles in the environment are highly lipophilic. Furthermore, important sex differences in the metabolism of such substances also exist. For example, most of the CYP enzymes are regulated by sex

Pollutant	Health effects
Ozone	Decreased lung function Increased airway reactivity Increased lung inflammation Increased hospital visits for lung disease Increased mortality
Particulate matter	Decreased lung function Increased respiratory symptoms Increased mortality
Nitrogen dioxide	Increased airway reactivity Reduced lung function Bronchitis (children)
Carbon monoxide	
Sulfur dioxide	Increased respiratory mortality Increased hospital visits for lung disease Aggravation of lung disease Increased lung inflammation

Table 4. Common air pollutants and health effects.

steroids. As a result, some substances are metabolized faster in women liver cells than men, and sometimes the end products are more toxic than the original substance, causing a higher toxicity for women due to increased internal exposure [158].

Accumulating epidemiological, clinical, and experimental evidence suggests that exposure to air pollutants can have serious effects in metabolic and endocrine function, particularly in glucose metabolism [159, 160]. Air pollution, especially traffic-related exposures, NO_2, tobacco smoke, and particulate matter, have been associated with obesity, type 2 diabetes, and metabolic syndrome with women showing higher susceptibility than men, and children being especially susceptible [161–164]. Studies conducted in several countries, such as Europe, America, and Asia reported strong associations among exposure to air pollutants, insulin resistance, obesity, and diabetes with women overrepresented in the affected groups [165–170]. These findings have also been recapitulated in animal models, where exposure to particulate matter resulted in increased insulin resistance followed by a high-fat diet [171–173], and these effects were associated with inflammation triggered by mechanisms involving pulmonary oxidative stress [174].

5.2. Metabolic effects of air pollution and their relationship with pneumonia

The relationship between diabetes, obesity, and susceptibility to lung infection and pneumonia has also been evaluated in several studies [175]. In these, an increased incidence and mortality from pneumococcal pneumonia, influenza, and tuberculosis was strongly associated with diabetes and obesity [176]. In this context, it is important to mention that obesity affects more women than men globally, and that a high body mass index has been directly associated with CAP risk in women [177, 178]. Animal models of bacterial infection using the leptin-deficient obese mouse have also shown higher susceptibility to pneumonia [179, 180]. Finally, an "obesity paradox" in CAP has also been reported extensively, in which obesity is associated with a higher incidence of bacterial pneumonia, but increased body mass index was associated with increased survival in patients hospitalized with CAP [181].

5.3. Genetic contributions to pneumonia risk and severity

We mentioned earlier studies reporting gender, racial, and population variability in both pneumonia incidence and outcome. Therefore, it is highly likely that these differences are the result of a complex interplay between both host and pathogen genetic backgrounds together with nongenetic factors, such as those discussed above [182]. With the recent development of fast and affordable high-throughput sequencing techniques, more studies have begun to explore the contributions of host genetics in the context of pneumonia [183–186]. The majority of these have focused on innate immune molecules, such as toll-like receptors and proinflammatory cytokines. Several associations of pneumonia susceptibility and severity with single nucleotide polymorphisms in the interleukin-6, interleukin-10, toll-like receptors TLR2, TLR4, and TLR9, C-reactive protein (CRP), and nitric oxide synthase 3 (NOS3) genes were reported [187–191]. We have summarized these in **Table 5**. Interestingly, most polymorphisms found in the cytokine genes are located in regulatory and promoter regions, where they may be affecting binding of transcription factors, such as GATA1-3, SOX, and heat shock proteins [183].

5.4. Pollution models of infection and pneumonia

Air pollution has been shown to exacerbate respiratory diseases, such as pneumonia. Air pollutants that reach the respiratory tract are currently responsible for its genesis, especially particulate matter having an aerodynamic diameter equal to or less than 10 μm, sulfur dioxide (SO_2), ground level ozone (O_3), nitrogen dioxide (NO_2), and carbon monoxide (CO) [192, 193]. However, these pollutants may also increase the risk for pneumonia by altering the function of alveolar macrophages, epithelial cells, mucociliary clearance mechanisms, particle transport, and local immunity in the lungs [194]. Because of methodological difficulties and ethical issues, there are a limited number of studies on the effects of controlled pollutant exposure and infection in humans. It has now been almost 50 years since the "infectivity model" has been created. This model is based on the study of the effects of pollutants on pulmonary activity after pollutant exposure with disease and mortality as end-points in animals, particularly rodents [147].

The infectivity model is used by researchers to determine the amount and concentration of pollutants at which the immune system is compromised and disease is developed. This is accomplished by challenging animals with virulent agents either before or after exposure to different concentrations of the pollutant. Exposure to NO_2 before and after infectious challenge in mice show significantly higher death rates [195]. Moreover, mice infected with *S. aureus* and then challenged with NO_2 displayed a reduction in lung bactericidal capacity [196]. Exposure to varying concentrations of NO_2 affects respiratory tract susceptibility, macrophage viability, systemic cell-mediated and humoral responses to viral infection in CD-1 mice inoculated intratracheally with murine cytomegalovirus [197]. Moreover, the number of viral particles capable of generating infection is lower in animals challenged with NO_2 than in animals exposed to filtered air. In addition, the risk of reinfection is higher in mice after NO_2 exposure indicating damage in the development of virus-specific immunity following a primary infection [198].

Gene	SNPs
C-reactive protein	rs1205
Interleukin-1 beta	rs16944
Interleukin-6	rs1800797, rs1800795
Interleukin-8	rs4073
Interleukin-10	rs1800896, rs1800871, rs1800872, rs5743629
Nitric oxide synthase 3	rs1799983
Toll-like receptor 2	rs5743708
Toll-like receptor 4	rs4986790, rs4986791
Toll-like receptor 9	rs5743836

Table 5. Single nucleotide polymorphisms associated with pneumonia.

There are several pollution models of pneumonia infection combined with particulate matter [199], SO_2 [200], CO [201], and other common air pollutants. These models generally involve a higher concentration of pollutants than would be normally found in the atmosphere. This is often necessary because a higher dose of most pollutants is required for rodents versus humans to reach comparable concentrations in the distal lung and generating comparable effects on lung function and immunity.

Ozone exposure can impair breathing, induce coughing, reduce lung function, and trigger lung diseases, such as pneumonia. The effect of ozone exposure has been associated with damage of the entire respiratory epithelia and lung immunity [202]. A study showed that mice infected with *K. pneumoniae* following exposure to 2 ppm of O_3 decreased the ability of mice to clear bacteria from the lungs, and that ozone-exposed females were more affected and showed higher mortality rates than males [17, 18]. Contrarily, in the absence of ozone-induced oxidative stress, males were more prompted to have a higher level of propagation of infection compared to females. These mechanisms appear to be mediated by surfactant biology and surfactant protein expression [19].

6. Conclusion

Regulation of the lung inflammatory response is critical to the successful outcome of pneumonia. Exposure to air pollutants has been linked to negative lung health outcomes, and sex hormones have been shown to mediate the lung immune response, especially during lung infection. The negative impact of air pollution on lung health, both in the short and long term, is now well accepted, and air quality indexes or scales are available to alert individuals when the air quality is at harmful levels. In this chapter, we have discussed experimental and epidemiological evidence on pneumonia infection incidence in different populations, influences of air pollution and environmental exposures, and sex-specific mechanisms involving male and female hormones in the context of lung immunity. This information could help researchers better explain the differences observed in pneumonia susceptibility and lung health outcomes in men versus women. Understanding the biological basis of these differences is critical for the development of more effective prevention and management strategies for pneumonia in men and women, and could help in the development of better treatment options for these patients.

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