Chapter 13
Sex Differences in Respiratory Infection

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Abstract  Respiratory infections are an important and frequent cause of morbidity and mortality globally. Sex and gender-based differences in lung infection are recognized and gradually gaining importance due to the potential for gender-tailored therapeutics. While sex and gender differences are widely acknowledged in the evaluation of chronic respiratory disease states such as asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF), acute and chronic respiratory infection complicate all of these and, in themselves, depending on age and organism, demonstrate sex differences. Males are disadvantaged in the occurrence and severity of lower respiratory tract infections such as pneumonia, while females suffer more commonly with upper respiratory tract ailments including tonsillitis and sinusitis. Differences in genetics and immunity have been forwarded as explanations for such differences; however, it is likely that a complex interplay of sex steroid hormones, host immunity, genetics, anatomical variation, and lung physiology, in addition to sociocultural and behavioral factors, influences the observed sex differences in respiratory infection. This chapter aims to assess the current state of the literature in this field and expound the range of its contributory factors.

Keywords  Respiratory infection · Sex · Male · Female · Gender

13.1 Introduction

Respiratory infection remains a leading cause of morbidity and mortality across all age groups internationally. Sex and gender differences in respiratory infection are recognized and rapidly gaining interest from both clinical and academic communities (Table 13.1). Little is known about the underlying mechanisms that drive sex differences observed in respiratory infection as the area has been best studied in

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P. Silveyra, X. T. Tigno (eds.), Sex-Based Differences in Lung Physiology, Physiology in Health and Disease, https://doi.org/10.1007/978-3-030-63549-7_13
| Title of study (author, year) | Study type and population | Study focus | Male (M)/female (F) differences | Other factors and analytical approach |
|-------------------------------|---------------------------|-------------|-------------------------------|-------------------------------------|
| Retropharyngeal (RPA) and Parapharyngeal Abscesses (PPA) Among Children and Adolescents in the United States: Epidemiology and Management Trends, 2003–2012. (Woods et al. 2016) | Retrospective using Kids’ Inpatient Database from 2003, 2006, 2009, and 2012. N = 2685 hospital discharges for PPA and N = 6233 hospital discharges for RPA | Epidemiology of children with PPA and RPA | (M:F) PPA – 1.47:1 (M:F) RPA – 1.63:1 | Study relied on reports given by students and guardians and not on any diagnostic measures |
| Epidemiology of pharyngitis as reported by Zambian school children and their families: implications for demand-side interventions to prevent rheumatic heart disease. (Musuku et al. 2017) | Cross-sectional study; Lusaka, Zambia; Sep 2014–Nov 2015. N = 3462; 5–29 years, median age of 14 year | Epidemiology of pediatric pharyngitis and its treatment | Female students reported more yearly episodes than male students (0.38 vs. 0.25, p < 0.0001). Parents/guardians reported more yearly episodes for their daughters vs. sons (0.35 vs. 0.27, p = 0.0036) | |
| Epidemiological and clinical features of group A Streptococcus (GAS) pharyngitis in children. (Lin et al. 2003) | Prospective study; Taiwan, 2001–2002; N = 252, 1–15 years | Prevalence of GAS pharyngitis | M:F = 1.29:1 | Prevalence of GAS pharyngitis was shown to be related to gender, age, and month of the year |
| Relative frequencies of symptoms and risk factors among patients with chronic rhinosinusitis with nasal polyps using a case-control study. (Bohman et al. 2018) | Prospective study; Sweden, 2008–2013; N = 368, M = 251, F = 117; mean age = 57 years | Frequency of symptoms of chronic rhinosinusitis with nasal polyps and association with smoking | Frequency of nasal polyps with chronic rhinosinusitis greater in males (68.7%). Statistically significant increases in univariate (OR, 2.86; 95% CI, 1.98–4.14) and multivariate (OR, 1.03; 95% CI, 1.02–1.04) models | Male gender, increasing age, and asthma were associated with chronic rhinosinusitis |
Summary health statistics for US adults: National Health Interview Survey, 2010. Vital and health statistics.Series 10, Data from the National Health Survey (252): 1–207. (Schiller et al. 2012)

Prospective study, US, 2010; N = 29,821 for sinusitis (>18 years) National estimates of health measures for noninstitutionalized civilian US adults

Frequency of sinusitis reported

\[ F = 63\% \quad (N = 18,800) \]
\[ M = 37\% \quad (N = 11,021) \]

Prevalence of acute and chronic tonsillitis in children and associated healthcare costs

\[ M = 49.1\% \]
\[ F = 50.9\% \]

Evaluation of risk factors for hospitalization in children in the first year of life

Multivariate analysis identified male gender along with prenatal exposure to maternal smoking, newborn respiratory disease, surfactant therapy, breastfeeding, siblings < 10 year, crowded living.
| Title of study (author, year) | Study type and population | Study focus | Male (M)/female (F) differences | Other factors and analytical approach |
|-------------------------------|---------------------------|-------------|-------------------------------|-------------------------------------|
| Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. (Chen et al. 2020) | Retrospective single center study; China; 2019; N = 99 | Epidemiology and clinical characteristics of 2019-nCoV | Males more susceptible than females Males: 67 (68%) Females: 32 (32%) | Multilobular infiltration, bacterial coinfection, lymphopenia, smoking history, hypertension, and age appear early predictors of mortality |
| Prevalence, Risk Factors, and Outcomes of Bacteremic Pneumonia in Children. (Fritz et al. 2019) | Prospective surveillance study; USA; January 1, 2010 to June 30, 2012; N = 2143 (<18 years) | Prevalence, risk factors, and clinical outcomes of bacteremic CAP in children | Male children with bacteremia were significantly more (74%) than females | Data was collected from the Etiology of Pneumonia in the Community (EPIC) study. Low prevalence of positive bacterial cultures may be due to predominance of viral etiologies in the pediatric population |
relation to chronic respiratory disease states including asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, and pulmonary hypertension. Despite such lack of mechanistic data, strong evidence does exist from both human and animal studies indicating that males remain disadvantaged in terms of their susceptibility, course, clearance, and resolution of respiratory infection with the exception of some upper respiratory tract infections (URTIs) including sinusitis, tonsillitis, and otitis externa, all of which are more frequent in females (Ben-Shmuel et al. 2018; Binet et al. 2012; Chamekh et al. 2017; Falagas et al. 2007; Ingersoll 2017; Kadioglu et al. 2011). What drives such variation in the occurrence and response to respiratory infection between the sexes? There is no single factor that explains such differences but rather a complex interaction of diverse and varying factors that have been summarized in Fig. 13.1 and are detailed in the current chapter.

Differences in lung structure and function may also at least in part explain such sex-related disparities in lung infection. Sex hormones, for instance, play a critical role in lung development and direct the growth and maturity of the central and peripheral airways in addition to roles in surfactant production. While the lungs of males are generally larger than those of females throughout life, female lungs importantly attain an earlier maturity and long-term airway patency, which in turn leads to greater expiratory flow and mucociliary clearance potentially explaining why young males may be prone to a higher frequency of lower respiratory tract infections.

Furthermore, sex hormones have central roles in directing different responses across a range of respiratory pathogens (Caracta 2003). Apart from effects on lung growth, development, and maturity (Sathish et al. 2015; Seaborn et al. 2010), sex hormones also exert substantial influences on the immune response to infection.
Such hormonal-endocrine-lung interplay could well be critical for observed sex and gender disparities in the response to lung infection. Overall, estrogens, the predominant female hormones, exert a substantially vigorous humoral and cellular immune response leading to overall more favorable outcomes through pathogen clearance, while androgens, the key male hormones, reduces immune competence rendering this latter group more susceptible to infection (Bouman et al. 2005; Klein 2000). The best-studied example of a respiratory tract infection in human and murine models is pneumonia, where sex steroid immune modulation causes a significantly enhanced inflammatory response in male mice leading to higher overall mortality (Chamekh et al. 2017; Gannon et al. 2004; Kadioglu et al. 2011; Neupane et al. 2010). In contrast, females with cystic fibrosis illustrate poorer outcomes, particularly in the setting of Pseudomonas aeruginosa infection, largely attributed to the increased risks of its mucoid conversion (Abid et al. 2017; Chotirmall et al. 2012). During states of increased inflammation, pro-inflammatory cytokines also reach significantly higher concentrations in males (Casimir et al. 2013) leading to further tissue injury, inflammation, and damage. Male sex is identified as an independent risk factor for respiratory syncytial virus (RSV) infection (Simoes 2003), whereas avian and pandemic influenza viruses demonstrate more severe disease in females (Ghosh and Klein 2017; Larcombe et al. 2011). Even within the current COVID-19 pandemic, males appear to demonstrate poorer clinical outcomes (Jin et al. 2020; Sharma et al. 2020; Wenham et al. 2020). Therefore, when taken together, sex hormones appear critical in promoting sexual dimorphism in response to pulmonary infection; however, it must be considered that the measured responses are likely pathogen- and tissue-specific (Enarson and Chretien 1999; McClelland and Smith 2011).

The immune response to respiratory infection further varies with cyclical changes in female sex hormone concentrations, particularly during the variable reproductive phases of the menstrual cycle and physiological states such as pregnancy. As sex hormones remain in relatively low concentrations in the prepubertal and latter stages of life, gender-related differences to infection cannot be solely attributed to sex hormones alone. Genetic-chromosomal-related effects may be useful in explaining observed gaps. Females are natural mosaics in terms of genetic content, deriving genes from both parents. Several immune cell-related genes are also located on the X chromosome, with approximately 10–15% escaping X inactivation (Bianchi et al. 2012; Ingersoll 2017). Such polymorphism associated with these X-linked genes grants females considerable immune advantages over the male sex, particularly in relation to combating and even surviving infection (Bianchi et al. 2012; Fish 2008; Libert et al. 2010; Spolarics 2007). In addition, X chromosome-linked microRNAs are now recognized to further modulate immunity and the associated infection response, with roles in sex-associated susceptibility to infection a particular focus for recent investigations (Chamekh et al. 2017; Pinheiro et al. 2011; Sharma and Eghbali 2014).

Key factors independent of genetics and hormones also have roles. These include sociocultural and behavioral influences, which to some extent explain gender
variation and susceptibility to respiratory infection (Pinkerton et al. 2015; Vazquez-Martinez et al. 2018). Women are generally more likely to be caregivers and hence may be more susceptible to URTIs, while smoke exposure in kitchens or exposures to other household pollutants can further increase susceptibility to developing airway disease and therefore subsequent infection (Falagas et al. 2007). Social status, physical inactivity, poor nutrition, coexistence of chronic respiratory disease, and in some cases, lifestyle choices including smoking can further predispose to acute respiratory infection in relevant patient groups (Cohen 1999; Graham 1990; Haenle et al. 2006).

13.2 Airway Anatomy, Physiology, and Host Genetics

Male sex is described as an independent risk factor for perinatal and postnatal respiratory comorbidity including the occurrence of URTIs (Ben-Shmuel et al. 2018; Greenough et al. 2005; Liptzin et al. 2015; Townsel et al. 2017). Although low birth weight, prematurity, and maternal smoking are all additional contributory factors, anatomical and physiological differences to the development of the lung are equally important to fully appreciate the gender-related differences observed in lung health and in diseased states (Binet et al. 2012; Kotecha et al. 2018; Liptzin et al. 2015). Such differences are observed as early as 16–24 weeks of gestation and continue into adulthood and even as one ages.

Lung development, lung maturity, and the development of lung pathology all appear to be at least in part related to and regulated by sex hormones (Carey et al. 2007a, b; Seaborn et al. 2010; Townsend et al. 2012). Even with smaller-sized lungs and fewer bronchioles at birth, fetal female lungs exhibit overall faster maturation as demonstrated by earlier mouth movement and surfactant production. Estrogens have a key role and elucidate stimulatory effects by promoting surfactant production and proportional airway and lung parenchymal growth leading to higher expiratory flow rates. Conversely, androgens demonstrate inhibitory effects on surfactant production, and growth of the central and peripheral airways is delayed in comparison to that seen in the lung parenchyma. Such airway “dysanapsis” leads to lower expiratory flow rates and likely explains the higher rates of respiratory distress syndrome, bronchiolitis, and lower respiratory tract illness observed in male infants (Boezen et al. 2004; Liptzin et al. 2015; LoMauro and Aliverti 2018; Raghavan and Jain 2016; Sathish et al. 2016). Airway thickening, attributed to increased smooth muscle, further contributes to the higher rate of respiratory infection in young males (Boezen et al. 2004).

Sex differences in airway hyperresponsiveness to environmental agents are demonstrated in several human and murine studies reaffirming an important role for sex hormones in respiratory tract physiology. Male mice, for instance, following lipopolysaccharide (LPS) exposure, demonstrate excessive airway hyperresponsiveness and greater inflammatory responses compared to female mice. These effects are significantly reduced on castrated male mice, while the
administration of exogenous testosterone in female mice increases inflammation to levels comparable to male mice (Card et al. 2006; Card and Zeldin 2009). Conversely, human studies illustrate that females are more sensitive overall to LPS exposure in comparison to males (Kline et al. 1999). Sex hormones and intersect with lung physiology continue into adult life; however, where disease develops, such axes may be disrupted. Gender differences, for instance, in older adults demonstrate different patterns particularly in the setting of chronic inflammatory respiratory diseases such as asthma and cystic fibrosis, where females tend to have higher disease burdens and greater severity. Therefore, the pulmonary interplay with sex hormones can vary and may depend on an individual’s age and experimental model used for assessment and underlying respiratory disease. However, the significance of the interaction between sex hormones, lung maturity, physiology, and the development of pathology should not be underestimated and remains an important area of ongoing research. The precise relationship between sex hormones and specific roles in individual respiratory tract infections are discussed in more detail in subsequent sections of this chapter.

Anatomical differences between the sexes are not restricted to the lower but remain relevant to the upper respiratory tract. Studies demonstrate that females remain more susceptible to rhinosinusitis, attributed to their relatively smaller ostia compared to age-matched males (Chen et al. 2003; Falagas et al. 2007). Similarly, acute and chronic sinusitis are both more prevalent and demonstrate longer disease duration in females (Shashy et al. 2004; Stalman et al. 2001).

Genetic diversity is an important contributing factor to the observed differences in immune response between the sexes. Human sex is determined by the XY sex-determination system where females demonstrate two X chromosomes, one maternally and the other paternally derived, while males have a maternal X and paternal Y chromosome. X chromosome inactivation is a further and essential physiological process to silence one of the X chromosomes in females to allow regulation and prevent overexpression of X-linked genes (Brockdorff 2011). This confers a highly polymorphic gene expression program that directs various cell types for each to respond differently to immune challenge (Spolarics 2007). While X-linked genes associate tightly with the regulation of the innate and adaptive immune systems (Brooks 2010), disruption can lead to severe developmental and/or health-related consequences (Lyon 1961; Migeon 2017). Pattern recognition receptors (PRRs) including the toll-like receptors (TLRs), innate immune-associated genes, and many transcriptional and translational effectors, all associated with the X chromosome, control important functions downstream of the activated pro-inflammatory cytokine receptors. Other important X-linked control mechanisms include noncoding microRNAs (miRNAs) which influence sex-related differences in immunity including the inflammatory response: the X chromosome contains up to 10% of total genomic miRNA with relatively little locating to the Y chromosome (Dai et al. 2013; Pinheiro et al. 2011).
13.3 The Influence of Sex Hormones on Lung Infection

Lung infection, such as pneumonia, occurs when microbes (bacteria, viruses, fungi, and/or parasites) colonize, infect, and multiply within the lung, eliciting an immune response (Daltro et al. 2011). For microbes to achieve an optimal environment for survival, they utilize signaling molecules including sex hormones to aid communication, facilitate replication, and promote survival (Chadeganipour and Mohammadi 2015; Elizabeth García-Gómez and Camacho-Arroyo 2012).

The major female endocrine hormones, estradiol and progesterone, and key male equivalent testosterone are produced in the ovaries and testes, respectively, but, however, may also be locally produced in adipose tissue and the liver, acting in the latter in largely paracrine fashion (Wierman 2007). Sex steroids, in particular androgens, estrogens, and progestogens, have cholesterol as a base precursor with actions facilitated by their respective receptors: the estrogen receptor (ERα or ERβ), the progesterone receptor (PR-A or PR-B), and/or the androgen receptor (AR). Such receptors are expressed within the lung and homologs described in some microbial pathogens (Elizabeth García-Gómez and Camacho-Arroyo 2012; Tam et al. 2011). Estrogen receptors, expressed in the upper and lower respiratory tract of mice, have been shown to influence the formation of pulmonary alveoli (Massaro and Massaro 2004).

Sex steroid concentrations fluctuate over time and with age, altering across life span due to age, menstruation, pregnancy, menopause, stress, medication, and/or environment. In females, estrogen and progesterone levels alter with menstrual cycling and at even higher levels during pregnancy (Brown 2011). Conversely, the concentrations of steroid hormones decline in women during reproductive senescence, while testosterone in males peaks in the second decade of life and thereafter gradually declines with age (Boyce et al. 2004).

The classical mechanism associated with sex steroids occurs through binding specific intracellular nuclear receptors to induce a series of conformational changes that regulate gene expression. Through alternate and nonclassical mechanisms, sex steroids can also bind membrane-based receptors, which are commonly coupled to G-proteins, with subsequent downstream stimulation of a range of signaling pathways. In this latter non-genomic mechanism, the involvement of ion channels, enzyme-linked receptors, cyclic AMP and cyclic GMP production, mitogen-activated protein kinases (MAPKs), tyrosine kinases, and lipid kinases has all been described (Elizabeth García-Gómez and Camacho-Arroyo 2012). To induce such action at the cellular level, these hormones are transported systemically through binding to plasma-based carrier proteins including sex hormone-binding globulin (SHBG), although small proportions freely circulate and enter target tissues by diffusion (Klinge 2018).

A comparable steroid hormone to receptor binding interaction in microbial systems has been examined but is currently poorly described. Estrogen (Rowland et al. 1992) and progesterone binding proteins (Mosier et al. 1991) have been described in gram-negative bacteria such as Pseudomonas aeruginosa, while
estradiol has a high affinity for an estrogen-binding protein demonstratable in fungi such as *Candida albicans* (Madani et al. 1994).

In addition to utilizing host signaling molecules, bacteria in particular can produce their own sex steroid-like compounds including compounds such as acyl-homoserine lactones (AHLs) that adopt comparable modes of action to human sex steroids using lipidic-based signaling. These compounds freely diffuse across bacterial cell membranes, bind their respective receptor, and lead to a coordinated cell density-based gene regulation termed “quorum sensing.” This sensing mechanism is well-characterized in *P. aeruginosa* and regulates its airway colonization, persistence, and infection including its behavior within biofilms (Hughes and Sperandio 2008).

In parallel to the host’s hormonal influence on microbes and microbial-driven signaling to promote pathogenesis, sex steroids also importantly influence other aspects of host physiology which in turn affects susceptibility to infection (vom Steeg and Klein 2016). This includes anatomic influences (covered previously) and effects on host immunity, which are covered in a separate section of this chapter. Taken together, it is therefore most likely that a complex interplay that varies between individuals and over time occurs between host, hormone, and microbial factors collectively contributes to and explains the observed sex differences in respiratory infections.

Increasing evidence further illustrates that sex steroids directly influence microbial pathogenesis, which in turn translate into more severe outcomes from respiratory tract infection (Table 13.2). This emerging field of microbial biology, addressing interkingdom signaling, is termed “microbial endocrinology” where interactions between microbes and hormones are studied including their interaction and in particular how microbes utilize sex steroids for survival advantage (Elizabeth García-Gómez and Camacho-Arroyo 2012; Yong et al. 2018). The use of sex steroids to further microbial survival, facilitate replication, and promote persistence includes direct effects on growth, metabolism, and the production of virulence factors through either direct or indirect hormone-associated signaling mechanisms (Fig. 13.2). Sex variation in regard to infectivity is further altered according to the specific pathogen and individual sex steroid fluctuations (Table 13.2).

### 13.4 Microbial Growth and Sex Hormones

#### 13.4.1 Bacteria: *Coxiella burnetii* and *Neisseria spp.*

*Coxiella burnetii* is an intracellular bacterium causing Q fever, and concerns have been raised about its potential for use in biological warfare as its clinical picture resembles that of an acute respiratory tract infection akin to pneumonia (Kazar 2005). Males are generally more symptomatic, and higher bacterial loads are observed in infected male mice, while the administration of estradiol interestingly reduces the bacterial load in ovariectomized female mice (Leone et al. 2004).
### Table 13.2  A summary of the respective sex steroids and their described effects on specific respiratory infection-related microbes

| Sex steroid | Physiological concentrations and associated reference | Microbial-host interaction | Related respiratory infection |
|-------------|------------------------------------------------------|-----------------------------|------------------------------|
| **Estrogens** | | | |
| E1: estrone | *Postmenopausal (pg/ml)* (de Padua Mansur et al. 2012) 14.1–102.6 *Pregnancy (ng/ml)* (De Hertogh et al. 1976) 1st trimester: 0.54–1.83 2nd trimester: 3.34–5.61 3rd trimester: 5.57–8.09 | Unknown | Unknown |
| Commonly found in postmenopausal women | | | |
| E2: estradiol | *Menstrual cycle (pmol/L) – median* Early follicular: 149 Late follicular: 450 LH peak: 671 Early luteal: 313 Mid-luteal: 495 Late luteal: 327 *Pregnancy (ng/ml)* (De Hertogh et al. 1976) 1st trimester: 0.81–3.30 2nd trimester: 5.60–10.8 3rd trimester: 13.0–17.8 | Virulence Growth | *Pseudomonas aeruginosa*-related pulmonary infection (Beury-Cirou et al. 2013; Chotirmall et al. 2012; Tyrrell and Harvey 2019) *Coxiella burnetii*-related pneumonia (Leone et al. 2004) Coccidioidomycosis (Drutz et al. 1981) Paracoccidioidomycosis (Aristizabal et al. 1998; Muchmore et al. 1973; Shankar et al. 2011) Pulmonary candidiasis (Gujjar et al. 1997; Zhang et al. 2000) |
| | | | |
| E3: estriol | *Pregnancy (ng/ml)* (De Hertogh et al. 1976) 1st trimester: 0.074–0.76 2nd trimester: 2.29–5.07 3rd trimester: 6.45–15.8 | Virulence | *Pseudomonas aeruginosa*-related pulmonary infection (Chotirmall et al. 2012; Tyrrell and Harvey 2019) |
| Undetectable in nonpregnant women | | | |
| **Progesterone** | **Menstrual cycle (pmol/L) – median** Early follicular: 0.64 Late follicular: 0.64 | Growth | *Neisseria gonorrhoeae* and *N. meningitidis* upper respiratory, genital, and neurological infection (Edwards 2010; Morse and Fitzgerald 1974) |
| | | | |

(continued)
potential mechanism that has been put forward to explain these findings includes the role estradiol plays in limiting granuloma formation and tissue infection. *Neisseria gonorrhoeae* and *N. meningitidis*, respectively, cause infections associated with the upper respiratory and genital tracts with the latter associated with meningococcal meningitis (Weyand 2017). Two studies have illustrated the effect of progesterone on growth of these microbes. Progesterone can demonstrate bacteriostatic or bactericidal properties in this setting depending on its concentration. At micromolar levels, it inhibits the growth of both *Neisseria* spp. (Morse and Fitzgerald 1974), while at lower concentrations (nanomolar), *N. gonorrhoeae* growth is promoted (Edwards 2010).

### 13.4.2 Mycobacterium Tuberculosis

Pulmonary tuberculosis is observed in males at greater frequency and severity when compared to females (WHO 2019). A study by Bini EI et al. provides a possible explanation for this phenomena demonstrating testosterone as a susceptibility factor for tuberculosis due to its ability to modify host immunity related to mycobacteria, which in turn affects clearance of the tuberculosis bacilli (Bini et al. 2014).
Fig. 13.2 A pictorial summary of the proposed direct influences from sex steroids on lung microbes during a respiratory tract infection. Sex steroids produced by the testes (males) and ovaries (females), respectively, influence the (1) growth and replication of microbes, (2) the synthesis and metabolism of sex steroids and sex steroid-like molecules, and (3) the production of microbial virulence factors (bacteria, virus, fungi, and/or parasites).
13.4.3 Viral Infection: Influenza and SARS-CoV-2

The 2019 acute respiratory syndrome coronavirus (SARS-CoV-2) pandemic has evolved to reveal important sex and gender differences, where higher intensive care unit (ICU) admissions and deaths have been observed in males (Sharma et al. 2020; Wenham et al. 2020). Angiotensin-converting enzyme 2 (ACE2) represents the entry receptor for the virus in the respiratory tract (Kuba et al. 2005; Shang et al. 2020), and recent work (although limited by a single female donor) highlights the potential regulatory role of estrogen on ACE2 receptor expression in differentiated airway epithelial cells (Stelzig et al. 2020). Independent and prior work has elicited an inhibitory role for estrogen on ACE2 expression in mouse kidneys (Liu et al. 2010).

Influenza causes acute respiratory infection that is influenced by age; however males and pregnant women are most susceptible to poorer outcomes (vom Steeg and Klein 2019). Viral replication occurs primarily in nasal epithelia, and exposure of female epithelial cells to estrogenic compounds has been shown to reduce replication of influenza A (Peretz et al. 2015). Peretz J et al. have demonstrated that estrogen alters metabolic genes important for antiviral effects. In contrast to the protective role offered by estrogen exposure, progesterone is shown to have detrimental effects on influenza’s pathogenesis. Progesterone stimulates production of IL-10, an anti-inflammatory cytokine that associates with poorer outcomes (Davis et al. 2017). In further affirmation of these influenza-related responses to sex hormones, low testosterone levels (in males) reduce viral clearance and result in poorer outcomes (vom Steeg et al. 2016).

13.4.4 Fungi: Coccidioidomycosis, Paracoccidioidomycosis, and Candida

Coccidioides immitis remains the key fungi causing coccidioidomycosis, and inhalation of its spores leads to primary pulmonary infection (Barron and Rosenthal 2012). Interestingly, susceptibility to extrapulmonary dissemination is observed most frequently in males and pregnant females suggesting a role for sex steroids. Work performed by Drutz et al. (1981) demonstrate a growth induction from any sex steroid exposure but, importantly, increased maturation and greater endospore release in relation to 17β-estradiol with some correlation to late pregnancy (Drutz et al. 1981). Importantly, however, this work does not explain the higher observed frequency of this infection in males.

Paracoccidioidomycosis is an important infection endemic to Central and South America where the fungus Paracoccidioides brasiliensis resides (Costa et al. 2013). P. brasiliensis induces chronic pulmonary parenchymal damage even with treatment (Costa et al. 2013), and a gender bias exists favoring females (higher male incidence). Available studies illustrate that estrogens (at physiological concentrations) do not affect fungal growth (Shankar et al. 2011) however display inhibition at
supraphysiological concentrations (Muchmore et al. 1973). Other studies however
described reduced fungal load with estrogen exposure, likely explained by inhibitory
effects on yeast transition (its parasitic form), therefore allowing more effective
immune clearance of the fungi (Aristizabal et al. 1998).

*Candida albicans* can colonize mucosal surfaces and commonly coexist with
bacteria. Considered “commensals,” these fungi can become pathogenic and even
lethally invasive when causing disease, seen in particular in immunocompromised
individuals (Pendleton et al. 2017). *C. albicans* causes pulmonary candidiasis that
can become systemic where immune protection is lacking (Bachh et al. 2008).
Airway colonization by *C. albicans* encourages bacterial pneumonia in a rat model
predominantly through an inhibitory effect on the phagocytic ability of alveolar
macrophages (Roux et al. 2013). In the presence of estradiol, however, the growth of
*C. albicans* increases (Zhang et al. 2000), and interestingly the hormone’s β-isomer
induces a greater increase in biomass compared to its α-isomer (Gujjar et al. 1997).
Limited data is available on sex-based differences in *Candida* infection; however,
further work is clearly necessary, because of the growth-related effects induced by
female hormones.

### 13.5 Microbial Synthesis and Metabolism of Sex Steroids
and “Sex Steroid-Like Compounds”

Some studies illustrate that microbes possess the capability to synthesize “sex
steroid-like compounds” to promote their pathogenesis and host survival. These
compounds modulate an individual microbe’s ability to replicate and survive, for
instance, work by Botelho MC et al. (2009) demonstrates that eukaryotic parasites
can synthesize estradiol-related compounds that aid with its parasitic life cycle.
Further follow-up studies demonstrated the antagonistic capability of these com-
plexes on in vivo host estrogen receptor signaling including their expression,
providing further evidence for the importance of such compounds on the host-
pathogen relationship (Botelho et al. 2010).

Fungi also synthesize sex steroid-like compounds, namely, mycotoxins, pro-
duced by *Aspergillus*, *Penicillium*, and *Fusarium*. Mycotoxins have important
roles in pathogenesis and form an additional interface between host and fungi, for
instance, zearalenone (ZEA), produced by *Fusarium*, exhibits estrogenic properties
by binding to host estrogen receptors (Filannino et al. 2011; Gromadzka et al. 2008).
The precise role of endogenous host sex steroid exposure on fungal pathogenesis
however remains largely unknown and necessitates further study.

Sex steroid hormones represent a good carbon source for energy production in
microorganisms (Chiang et al. 2019). Consequently, some have evolved to possess
the capability to metabolize sex steroids into their active forms by specific enzymes
including hydroxysteroid dehydrogenase (Elizabeth García-Gómez and Camacho-
Arroyo 2012; Vom Steeg and Klein 2017). Some pathogens are well known to
metabolize sex steroids to enhance their virulence, for example, *Taenia crassiceps*
reduces host systemic and testicular testosterone concentrations enzymatically,
while the presence of estradiol enhances the parasite reproduction, making females
more susceptible to infection (Larralde et al. 1995; Vom Steeg and Klein 2017).
*Aspergillus fumigatus*, an important cause of aspergillosis (Kosmidis and Denning
2015), demonstrates an ability to metabolize progesterone (Mukherjee et al. 1982;
Smith et al. 1994) and also testosterone (Mahato and Mukherjee 1984) for use as a
carbon source for energy; however pathogenic implications of such metabolism have
yet to be demonstrated.

While limited studies continue to exist focused on the effects and extent of sex
steroid hormone-like production in microbes, including their metabolic potential to
break down host hormones, it is clear that such effects can have pathogenic conse-
quences and drive sex variation. This area of research is, therefore, a key avenue to
pursue to not solely permit a deeper understanding of sex differences in infection
related to specific pathogens but potentially may reveal important pathways and
mechanisms that can be targeted to narrow the “sex-based gap” and provide fresh
approaches in particular for “difficult-to-treat” infections.

### 13.5.1 Sex Steroid-Induced Microbial Virulence:
*Pseudomonas and Candida*

*Pseudomonas aeruginosa* represents a key opportunistic gram-negative bacterium
that colonizes the lungs in patients with cystic fibrosis (CF) and non-CF bronchiec-
tasis. This bacterium possesses multiple virulence mechanisms that include motility,
cytotoxicity, iron scavenging, and elastase production, some of which are regulated
by its quorum-sensing systems (Gellatly and Hancock 2013; Yong et al. 2018).

In relation to CF, females acquire *P. aeruginosa* in advance of males and convert
to the more pathogenic mucoid phenotype earlier, epidemiological observations that
have been described for decades (Chotirmall et al. 2012; Yong et al. 2018). Multiple
studies have been performed to provide a more biological basis for these observa-
tions and, in particular, elucidate estrogen’s influence on *P. aeruginosa* virulence.

Chotirmall and colleagues (2012) illustrated that estrogen-induced alginate pro-
duction in vitro, an important compound conferring mucoid conversion of the
bacteria (Chotirmall et al. 2012). Alginate provides bacterial protection against the
harsh “host” environment by enhancing surface adhesion, facilitating colonization,
and promoting biofilm formation and persistence (Boyd and Chakrabarty 1995;
Stapper et al. 2004). Following prolonged estrogen exposure, *P. aeruginosa* prefer-
entially adopts a mucoid phenotype, driven by mucA mutations, a key part of the
muc operon that dictates alginate biosynthesis. The acquisition of mucA mutations in
an estrogen-rich environment allows “unchecked” overproduction of alginate and
conversion to mucoid status. This mucoid phenotype is associated with poorer CF
prognosis and disease outcomes and represents a key example of the importance of
sex steroids in explaining infection-related phenomena (Alcaraz-Serrano et al. 2019).

The important relationship between estrogens and *P. aeruginosa* in CF extends to the recurrent menstrual cycling that is observed in regularly menstruating females as estrogen levels fluctuate. At high estrogen peaks (the follicular phase), a higher proportion of mucoid bacteria can be isolated and does associate with an increased exacerbation rate when compared to the luteal phase. Follow-up work performed by Tyrrell and Harvey (2019) further demonstrates this estrogenic effect on *P. aeruginosa* virulence, including assessments of swarming motility, pyocyanin production, biofilm formation, and host invasion. Estrogen enhances *P. aeruginosa* adherence to CF bronchial epithelial cells, aiding its invasion and pathogenesis (Tyrrell and Harvey 2019). Importantly, however, at supra-physiological concentrations, estrogen can also act as an inhibitor of quorum sensing (Beury-Cirou et al. 2013).

Deleterious effects from estrogen are not limited to bacteria; the hormone has been shown to influence fungi and, in particular, *C. albicans*. Besides the growth-promoting effect described above, estradiol influences the transition and formation of *C. albicans* to its hyphal form, which in turn affects virulence (Madani et al. 1994; Zhang et al. 2000). Hyphal formation is essential for tissue invasion and destruction (Pukkila-Worley et al. 2009), and increased hyphal morphology stimulates fungal virulence including adherence, biofilm formation, and cellular invasion (Desai 2018).

Taken together, sex steroids can directly influence the virulence and therefore pathogenesis of individual microbes and remain an important aspect of interaction to explain the observed sex differences in infection.

### 13.6 The Interaction of Sex Hormones, Host Immunity, and Respiratory Infection

#### 13.6.1 Innate Immunity

The human respiratory tract is exposed to thousands of liters of inhaled air daily which contains environmental components and airborne pathogens. This constant microbial exposure poses challenges to the innate immune system, which needs to immediately sense pathogen and protect the host from infection through the induction of inflammatory and chemotactic mediators and antimicrobial compounds. X-linked genes and sex steroid hormones can influence this immune response and contribute to different outcomes following respiratory infections between the sexes.

The number, function, and subsequent release of cytokines and chemokines through innate immune mechanisms differ between males and females. These are summarized in Fig. 13.3. In short, females possess neutrophils and macrophages with higher phagocytic activity, and antigen-presenting cells (APCs) present antigens more vigorously, while males exhibit higher NK cell concentrations (Klein and Flanagan
The specific details related to sex and gender differences in specific immune cell types are discussed in the following subsections.

13.6.2 Toll-Like Receptors (TLRs)

The innate immune system triggers an immediate inflammatory response to control the dissemination of an invading pathogen. Microbial sensing by PRRs, which are located on immune cells, differs between sexes. TLRs are an example of PRRs, and TLR7 and TLR8 genes, encoded on the X chromosome, can escape inactivation leading to an overall higher expression in females (Berghofer et al. 2006). In females, peripheral blood mononuclear cells (PBMCs) induce higher interferon-α (IFN-α) production and also lower concentrations of the immunosuppressive IL-10 in response to TLR7 ligands (Griesbeck et al. 2015). Moreover, higher basal levels of IFN regulatory factor 5 (IRF5) and IFN-α have been detected in TLR7 ligand-stimulated plasmacytoid dendritic cells (pDCs) in female humans and mouse models (Griesbeck et al. 2015). While IRF5 transcription is regulated through ERα signaling in female mice (Griesbeck et al. 2015), no sex differences in IFN-α production results when DCs are stimulated with CpG, a TLR9 ligand not associated with the X chromosome. Sex dimorphism is further revealed by genes involved in the TLR pathway and the type I IFN response by transcriptional analysis. Upon viral challenge in rats, females induce higher TLR and pro-inflammatory gene expression including TLR7, myeloid differentiation primary response gene 88 (MyD88),
retinoic acid-inducible gene-1 (RIG1), IRF7, IFN-β, Janus kinase 2 (JAK2), signal transducer and activator of transcription (STAT3), nuclear factor-kB (NF-kB), and tumor necrosis factor (TNF) in comparison to males (Berghofer et al. 2006). Consistent findings are seen in PBMCs isolated from humans following viral vaccination (Klein et al. 2010).

TLR signaling and subsequent NF-kB activation involve the recruitment of kinases including IL-1 receptor-associated kinase-1 (IRAK-1). IRAK-1 is well-studied in relation to sex dimorphism-associated inflammatory responses (Kawagoe et al. 2008). IRAK-1 is encoded on the X chromosome and escapes chromosome inactivation enhancing transcription of NF-kB-dependent genes in females, which in turn provides an enhanced innate immune response leading to less severe disease in females (Carrel and Willard 2005). Immune cell deficiencies, induced by IRAK-1 mosaicism in mice, improve sepsis outcomes (Chandra et al. 2014). Clinically, the IRAK-1 variant haplotype is functionally significant in sepsis and associates with enhanced nuclear translocation of NF-kB, severe organ dysfunction, and increased mortality (Arcaroli et al. 2006; Toubiana et al. 2010). Nox2, another X-linked gene, encodes the catalytic subunit of the NADPH oxidase complex in phagocytes (Singel and Segal 2016). Nox2 inhibition interestingly ameliorates influenza A virus-induced lung inflammation in mouse models (Vlahos et al. 2011); however, sex dimorphism in Nox2 expression and function has yet to be elucidated.

Besides TLR7, several other studies have reported sex differences in TLR4 expression which results in different immune consequences between sexes (Chamekh et al. 2017). Male mice infected by coxsackievirus express higher TLR4 on splenic monocytes, dendritic cells, and CD3+ and CD4+ lymphocytes compared to females suggesting a higher susceptibility and more severe disease in males (Roberts et al. 2012). A devastating and “out of control” pro-inflammatory response is induced by macrophages isolated from male mice stimulated with LPS. These macrophages demonstrate higher TLR4 expression on their cell surface explaining the experimental findings (Marriott et al. 2006), which in turn is further attested when androgens are removed from male mice (Rettew et al. 2008). Importantly, however, contrasting results are reported in other studies that must be considered: female mice demonstrate significant tissue-resident leukocyte populations and a higher density of pathogen-sensing TLRs in comparison to males, illustrating the complexity of the relationship between sex, innate immunity, and infection and the need for further study in this area (Eisenmenger et al. 2004; Scotland et al. 2011). Finally, it is noteworthy that several groups report the importance of TLR8 gene polymorphism related to the outcomes associated with infection: more severe disease is observed in males, for instance, in response to tuberculosis (Davila et al. 2008; Salie et al. 2015).
13.6.3 Neutrophils

Neutrophils are the most abundant innate immune cells serving as the first line of defense against infection. During respiratory infection, neutrophils infiltrate the lungs of humans and mice and induce pro-inflammatory cytokines and reactive oxygen species to mediate inflammation (Camp and Jonsson 2017). ERα, ERβ, and AR are expressed on neutrophils, and their numbers, life span, and function critically differ between males and females (Bain and England 1975; Chandra et al. 2012; Mathur et al. 1979). Neutrophil numbers increase during pregnancy and in particular in the luteal phase of the female menstrual cycle when progesterone levels increase (Bouman et al. 2005). Neutrophils isolated from healthy women (of reproductive age) demonstrate improved survival and have longer life spans when compared to those of healthy men (Molloy et al. 2003). Sex steroid hormones importantly further contribute to neutrophil function through nitric oxide and superoxide production as well as chemotaxis (Bekesi et al. 2000; Garcia-Duran et al. 1999; Marczell et al. 2016). In murine models, male mice illustrate a higher susceptibility and poorer outcome to S. pneumoniae and/or SARS-CoV infection, attributed to excess neutrophilic inflammation (Channappanavar et al. 2017; Kadioglu et al. 2011). Ovariectomized female mice receiving estradiol are protected from influenza A, illustrating the importance of the interactions between sex steroids, immune cell function, and infecting pathogen (Robinson et al. 2014).

13.6.4 Alveolar Macrophages

Alveolar macrophages (AMs) are key phagocytic resident cells in the lung which protect against respiratory infection through secretion of soluble mediators (Goritzka et al. 2015). AMs express ERα, ERβ, ARs, and PRs (Khan et al. 2005; McCrohon et al. 2000; Murphy et al. 2009). Following viral infection, AMs clear virus and release chemokines including the production of type I IFNs (Goritzka et al. 2015). Female mice demonstrate higher macrophage numbers in their pleural and peritoneal cavities with higher levels of TLR expression and phagocytic capacity, which in turn associate with stronger acute inflammatory responses (Scotland et al. 2011). Sex steroid hormones can further influence TLR-mediated inflammation: responses are enhanced by estrogen and diminished by testosterone (Calippe et al. 2008; Chao et al. 2000; Corcoran et al. 2010; Rettew et al. 2008). Critically, however, the direct consequences of sex hormone exposure on AM function during respiratory infections have yet to be fully expounded.
13.6.5 Monocytes and Monocyte-Derived Cells

Monocytes can differentiate into macrophages or myeloid lineage dendritic cells and secrete cytokines and chemokines in response to microbial infection. ERα and ERβ are expressed in monocytes (Komi and Lassila 2000; Laffont et al. 2014; Murphy et al. 2009; Pioli et al. 2007), and exogenous estradiol administration at physiological levels decreases CCR2 and CXCR3 expression on murine monocytes, indicating that ER signaling potentially diminishes monocyte recruitment to tissues (Janis et al. 2004). Interestingly, the number of monocytes including their CCL2 induction decreases when systemic estradiol is administered to ovariectomized mice during influenza A infection (Robinson et al. 2014). Male mice infected with SARS-CoV demonstrate increased Ly6C⁺ CD11b⁺ monocyte-derived cells with greater inflammatory consequences compared to female mice, while lethal infection may be partially rescued by depleting monocyte-derived cell populations (Channappanavar et al. 2017). Male mice are more susceptible to SARS-CoV and critically were not protected following orchidectomy, in contrast to female mice who demonstrate protection through ovarian hormones and ER signaling. In COVID-19, higher levels of CD14⁺CD16⁺ monocytes are identified in females, while males demonstrate a greater CD14lowCD16⁺ monocyte subset (Takahashi et al. 2020). Taken together, these data imply that estrogens rather than androgens regulate “pathogenic” responses in monocytes.

Sex steroid hormones directly influence monocyte counts and associated cytokine production; however, findings between studies have been inconsistent. Higher monocyte counts are observed in the luteal phase of the female menstrual cycle when progesterone levels peak (Mathur et al. 1979), and monocyte numbers are elevated in the postmenopausal compared to the premenopausal state (Ben-Hur et al. 1995). Furthermore, pregnancy is associated with higher monocyte counts, while IL-12 and TNFα production diminish (Elenkov et al. 2001). An LPS challenge to peripheral monocytes isolated from healthy males induces less IL-6 compared to females (O’Connor et al. 2007), and work evaluating the effect of estrogens on monocyte-induced cytokine production reveals conflicting results (Janis et al. 2004; Kramer et al. 2004; Miyagi et al. 1992). Relationships with testosterone are however more clear-cut: diminished amounts of pro-inflammatory cytokine production are coupled to increases to the anti-inflammatory response (IL-10) in monocytes after testosterone exposure (Angele et al. 1999; D’Agostino et al. 1999; Li et al. 1993).

13.6.6 Natural Killer Cells

Natural killer cells are cytotoxic innate immune lymphocytes that produce IFN-γ during early infection to limit viral burden (Lam and Lanier 2017). Human and murine NK cells express ERs and PRs (Laffont et al. 2014; Pierdominici et al. 2010). Males have higher numbers and cytotoxic activity of NK cells compared to females.
Abdullah et al. 2012; Chng et al. 2004); however, such sex bias is reversed with age (Al-Attar et al. 2016). NK cell numbers are regulated by sex hormones that fluctuate over monthly menstrual cycles in females and change with advancing age in males (Souza et al. 2001; Yovel et al. 2001). In tandem with the increased estradiol and progesterone concentrations during pregnancy, greater numbers of NK cells are observed in the uterine mucosa (Carlino et al. 2008; King et al. 1996). However, the influence that these hormones have on direct NK cell activity remains controversial, despite several studies reporting on this relationship (Hao et al. 2007; Hou and Zheng 1988; Phan et al. 2017; Sulke et al. 1985).

13.6.7 Plasmacytoid Dendritic Cells (pDCs)

Plasmacytoid dendritic cells are innate immune cells that localize to primary and secondary lymphoid organs and sense a wide range of PAMPs including viral single strain RNA (through TLR7) and bacterial CpG DNA (via TLR9) (Chistiakov et al. 2014). ERs are expressed on pDCs (Laffont et al. 2014) which provide the principal source of type I IFNs and IFN-induced proteins that exert antiviral capabilities (Chistiakov et al. 2014). Significantly more IFN-α is produced by females especially when stimulated with viral nucleic acids or synthetic TLR7 ligands which correlate directly with higher levels of ERα-regulated IRF5 in female pDCs (Berghofer et al. 2006; Meier et al. 2009). X chromosome inactivation of both TLR7 and estrogen signaling pathways promotes sex dimorphism in human pDCs’ IFN-α production (Laffont et al. 2014). Postmenopausal women treated with estradiol, for instance, demonstrate higher IFN-α production (Seillet et al. 2012), while female rats subjected to hantavirus infection similarly demonstrate higher type I IFN gene expression, including viral nucleic acid sensors, when compared to males (Hannah et al. 2008). Conversely, progesterone inhibits pDCs’ IFN-α production (Hughes et al. 2008), and, in response to TLR7 and TLR8 agonists, IFN-α production in male infants was also significantly dampened due to elevated testosterone after birth (Wang et al. 2012). Together, these findings propose an important sex difference in antiviral response: female pDCs produce more type I IFNs and exert a stronger immune response in females, albeit with accompanying and associated immunopathology.

13.6.8 Adaptive Immunity

The thymus produces a peripheral T-cell pool critical for the development of adaptive immunity, which importantly is further influenced by sex (Table 13.3). Studies in animal models reveal that males have larger thymus glands, greater T-cell counts, and a different distribution of T-cell subsets compared to females (Leposavic et al. 1996; Leposavic et al. 2011). Females, on the other hand, have higher
populations of CD4+ T cells, greater CD4+/CD8+ T-cell ratios, higher Th2 abundance, and greater cytotoxicity and proliferation of T cells. Males, besides exhibiting more CD8+ and Treg cells with a Th1 preponderance, also demonstrate lower B-cell counts and basal immunoglobulin levels that result in overall weaker antibody-related responses compared to females (Pennell et al. 2012).

### Table 13.3 Sex differences in adaptive immunity

| Component | Feature | Sex differences |
|------------|---------|-----------------|
| Thymus     | Size    | Larger in males (Leposavic et al. 1996, 2011) |
| T cells    | CD4+ T-cell counts | Higher in females (Abdullah et al. 2012) |
|           | CD8+ T-cell counts | Higher in males (Lee et al. 1996; Lisse et al. 1997) |
|           | CD4+/CD8+ T-cell ratio | Higher in females (Lee et al. 1996; Lisse et al. 1997) |
|           | Number of activated and proliferating CD4+ T cells | Higher in females (Sankaran-Walters et al. 2013) |
|           | IFN-γ levels (produced by CD4+ T cells) | Higher in females (Roberts et al. 2001) |
|           | IL-17 levels (produced by CD4+ T cells) | Higher in males (Hewagama et al. 2009) |
|           | Number of activated and proliferating CD8+ T cells | Higher in females (Hewagama et al. 2009) |
|           | Treg cell counts | Increased in males (Afshan et al. 2012) |
|           | Th1 cell function | Greater in males (Girón-González et al. 2000) |
|           | Th2 cell function | Greater in females (Girón-González et al. 2000) |
|           | Th1 versus Th2 cell bias | Th2 cell bias in females, Th1 cell bias in males (Girón-González et al. 2000) |
| B cells    | B-cell counts | Higher in females (Abdullah et al. 2012; Furman et al. 2014; Teixeira et al. 2011) |
| Immunoglobulins | Basal immunoglobulin levels | Higher in females (Abdullah et al. 2012; Furman et al. 2014; Teixeira et al. 2011) |
|           | Antibody production | Higher in females (Abdullah et al. 2012; Furman et al. 2014; Teixeira et al. 2011) |
|           | Antibody response | Higher in females (Abdullah et al. 2012; Furman et al. 2014; Teixeira et al. 2011) |

### 13.6.9 B Cells

ERα, ERβ, and ARs are all expressed on B cells (Grimaldi et al. 2002; Smithson et al. 1998) whose activation is influenced by activated Th2 cells that in turn increase
systemic IgE. Enhanced antibody responses are characteristic in females who also exhibit higher basal immunoglobulin levels and B-cell numbers compared to males independent of age group (Furman et al. 2014; Teixeira et al. 2011). B-cell gene expression analyses reveal a higher level of basal gene expression in females (Fan et al. 2014), and estradiol is shown to stimulate B-cell antibody production at physiological concentrations (Pauklin et al. 2009). This relationship is further demonstrated in animal models where antibody responses to inactivated influenza vaccination, administered to BALB/c mice, can be enhanced with estradiol treatment (Nguyen et al. 2011). In influenza infection mouse models, female mice display more robust humoral and cellular immune responses even though vaccination provides comparable protection between the sexes. B cells isolated from female mice also express higher TLR7, and the enhanced antibody response observed in female mice is impaired by TLR7 knockout (Fink et al. 2018).

13.6.10 T Cells

Lymphocytes account for 30% of the white blood cell population in vivo where up to 90% of them represent T lymphocytes. Almost all (95%) of the T-cell population expresses αβ-T-cell receptors (TCRs), while the minority have γδ-TCRs. Important work illustrates that the number of γδ-T cells increases during pregnancy, and while total T-lymphocyte number is consistent between sexes, males demonstrate lower overall percentages of T lymphocytes when considering the total lymphocyte population. CD4+ T cells polarize toward a Th1-mediated immune response, increased IFN-γ production, and greater IL-12 responsiveness through STAT-4 activation and T-cell proliferation during the luteal phase of the menstrual cycle. In contrast, CD4+ T cells sustain Th2-mediated responses during the follicular phase of the menstrual cycle and pregnancy. Th17 responses are importantly also stimulated by estrogen and, collectively with other factors, induce IL-17 production (Arsenovic-Ranin et al. 2017). An increased number of activated T cells including terminally differentiated CD8+ T cells have been identified in females with COVID-19, while a less robust T-cell-mediated immunity in males could explain their overall poorer COVID-19 outcomes (Takahashi et al. 2020). Overall, females exhibit strongly activated and proliferating CD4+ and CD8+ T-cell populations, characterized by IFN-γ production and high cytotoxicity, while males exhibit more IL-17-producing T cells (Zhang et al. 2012).

13.7 MicroRNAs (miRNAs)

miRNAs are small noncoding RNAs (of approximately 22 nucleotides) that are involved in posttranscriptional gene regulation. They are key negative gene regulators implicated across a diverse range of biological processes through different
mechanisms including RNA degradation and translational repression (Baltimore et al. 2008; Selbach et al. 2008). Abnormal miRNA expression is also attributed to a wide range of inflammatory diseases (Dai and Ahmed 2011; Johnnidis et al. 2008). Expression of miRNA-encoding genes can be influenced by single nucleotide polymorphisms (SNPs) and consequently affects disease susceptibility including respiratory infection. miRNAs are enriched in the X chromosome when compared to Y with a twofold density difference on human and mouse autosomes (Laffont et al. 2014). Several studies have elucidated the roles of X-linked miR-106a and miR-223 in innate immune cell differentiation particularly at the earliest stages of infection.

MiR-223 is identified to have a role in Mycobacterium tuberculosis infection in mice. Higher susceptibility to infection is observed in miR-223 knockout mice with excess neutrophil accumulation in the lungs leading to tissue damage. Neutrophil recruitment is reduced in miR-223 KO mice with downregulation of CXCL2 and CCL3 (Dorhoi et al. 2013). As miR-223 is X-linked, it may escape silencing or be subject to effects of skewed inactivation, which in turn results in its differential expression and effects between sexes. The sex differences observed in tuberculosis may be attributed to the pathological accumulation of neutrophils resulting from the silencing escape or the preferential expression of one gene copy by skewed inactivation, which downregulates their recruitment. Following LPS treatment, miR-223 KO mice develop severe inflammatory symptoms with reduced expression of TNF-α, CXCL1, and CXCL2 (Moschos et al. 2007). Neutrophil oxidative burst is also increased following Candida albicans infection in miR-223 KO mice (Johnnidis et al. 2008). Acute lung injury, induced by either mechanical ventilation or S. aureus infection, can be dampened through pulmonary overexpression of miR-223 in mice (Neudecker et al. 2017). MiR-223 is upregulated in mouse lungs following H1N1 (Li et al. 2010) and H5N1 influenza infection (Rogers et al. 2012). In humans, miR-223 is associated with granulopoiesis (Zardo et al. 2012), and a marked decrease of miR-223 expression is detected in sepsis (Wang et al. 2010). Collectively, these findings emphasize the importance of X-linked miR-223 in regulating the immune-inflammatory response through the control of neutrophil recruitment. Conversely, X-linked miR-106a negatively regulates monocyte differentiation and maturation (Fontana et al. 2007). MiR-106a knockdown illustrates benefit in ovalbumin-sensitized murine asthma models through enhancement of the anti-inflammatory cytokine IL-10 and reduced Th2 responses which alleviate airway hyperresponsiveness (AHR) (Sharma et al. 2012).

13.8 Sociocultural and Behavioral Factors

Sociocultural factors in the context of gender differences in respiratory infection are recognized but not completely studied. There are however studies elucidating the role of social status in the susceptibility to respiratory infection (Cohen 1999; Cohen et al. 1997). For instance, adults and children from lower socioeconomic backgrounds are more prone to respiratory infections. This has been attributed to higher
exposure risks due to poverty, overcrowding, inadequate hygiene and sanitation, illiteracy, malnutrition, and lack of access to vaccinations. Adults with inadequate social support systems have also been shown to be more prone to community-acquired pneumonias (Fernandez et al. 2010). In addition, men in many global societies have a culturally dominant role: males, whether men or boys, may receive greater amounts of nutrition as sole breadwinners of the family in some jurisdictions, placing women at an immune disadvantage (Vlassoff 2007). Furthermore, in some societal settings, women make up a large proportion of primary caregivers and therefore spend the most time in the household environment. This in turn increases their proximity to young children, household smoke, dust, and mites during daily activities such as cooking and cleaning, which in turn potentially makes them more susceptible to respiratory infection.

Gender differences have been widely studied in tuberculosis, where higher infection rates are observed in men (Nhamoyebonde and Leslie 2014; Rao 2009; The Lancet Infectious 2002). Besides their physiological and immunological disadvantages as described above, behavioral traits including social contact, more frequent travel, smoking, alcohol consumption, and occupational risks may further place males at higher overall risk for infection. These findings hold, even after considering confounding linked to health-seeking behaviors (Nhamoyebonde and Leslie 2014).

Smoking has been strongly implicated in the increased susceptibility to respiratory infection (Arcavi and Benowitz 2004; Brown et al. 1987; Haenle et al. 2006; Marcy and Merrill 1987). Cigarette smoke exposure alters pulmonary anatomy and physiology and impairs the host immune response including ciliary defenses. Smokers are also at substantially higher risks to bacterial and viral infections including tuberculosis and influenza when compared to nonsmokers (Arcavi and Benowitz 2004; Marcy and Merrill 1987). Relationships between smoking and gender have been assessed across several studies: females, irrespective of age, demonstrate greater lung function decline and report more respiratory symptoms compared to males (Boezen et al. 2004; Chen et al. 1991; Gold et al. 1996; Holmen et al. 2002; Langhammer et al. 2003; Xu et al. 1994). Despite males smoking at higher frequencies, females remain more vulnerable to the adverse effects of smoking and consequently are more prone to respiratory infections.

Interestingly, disease severity is perceived differently between the genders. Women generally seek healthcare for mild illnesses such as pharyngitis and tonsillitis, potentially explaining their increased prevalence in women. Conversely, underreporting of infections may also occur due to socioeconomic factors including poverty, limited access to healthcare, and limited health insurance coverage that prevents some women from seeking healthcare (Falagas et al. 2007).

While sociocultural and behavioral aspects that differ between the genders are less widely studied in relation to respiratory infections, they may have important roles in addressing the observed gender differences. Clinical trials need to recruit more equitably between the genders, and gender-specific studies (including sub-analysis) are required to better understand these if “perceived” gender
differences in respiratory infection truly impact diagnosis, presentation, and treatment response.

### 13.9 Conclusion

Current evidence suggests that “sex and gender gaps” do exist in the context of respiratory infection. Differences in susceptibility, disease progression, and infection outcomes are described, and while the study of chronic respiratory diseases has taken the lead in understanding sex and gender differences in lung health, a similar focus on respiratory infection is now necessary. A focus on sex and gender variation in the incidence, severity, and treatment response in the context of respiratory infection is necessary, and an improved understanding of the underlying mechanisms and complex interplay between sex hormones, immunity, inflammation, and infection will likely lead to better therapeutic outcomes for both genders.

**Acknowledgments** This study was supported by the Singapore Ministry of Health’s National Medical Research Council under its Clinician-Scientist Individual Research Grant (MOH-000141) (S.H.C) and the NTU Integrated Medical, Biological and Environmental Life Sciences (NIMBELS) [NIM/03/2018] (S.H.C). The authors would like to acknowledge the Academic Respiratory Initiative for Pulmonary Health (TARIPH) for collaboration support.

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