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MINIREVIEW

Sex and Gender Differences in Bacterial Infections

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ABSTRACT There is a growing awareness of the importance of sex and gender in medicine and research. Women typically have stronger immune responses to self and foreign antigens than men, resulting in sex-based differences in autoimmunity and infectious diseases. In both animals and humans, males are generally more susceptible than females to bacterial infections. At the same time, gender differences in health-seeking behavior, quality of health care, and adherence to treatment recommendations have been reported. This review explores our current understanding of differences between males and females in bacterial diseases. We describe how genetic, immunological, hormonal, and anatomical factors interact to influence sex-based differences in pathophysiology, epidemiology, clinical presentation, disease severity, and prognosis, and how gender roles affect the behavior of patients and providers in the health care system.

KEYWORDS sex differences, gender differences, bacterial infections

Patient sex is an important determinant in health and disease, and infectious diseases are no exception. Biological sex (defined by sex chromosome complement, sex steroid hormones, and reproductive organs) has been shown to influence susceptibility to infection, pathophysiology, immune responses, clinical presentation, disease severity, and response to treatment and vaccination (1). On the other hand, gender roles (referring to characteristics that are socially constructed) and social norms can influence risk factors and exposure to infection, determine health-seeking behaviors, and impact therapeutic decisions (2). Fig. 1 describes how sex and gender interact to influence differences in bacterial infections.

In this review, we discuss the current knowledge on sex-based differences in bacterial infections, focusing on genetic, anatomical, immunological, hormonal, and behavioral influences and on the epidemiology, pathophysiology, clinical presentation, resolution, and prognosis of selected bacterial diseases.

GENETIC FACTORS

Sex differences begin at conception, with the formation of an embryo carrying XX or XY chromosomes. This establishes a lifelong inequality between male and female cells in the expression of genes encoded in the X and Y chromosomes.

The X chromosome is home to around 1,100 genes and harbors several genes which regulate immune function, such as interleukin-1 (IL-1) receptor-associated kinase 1 (IRAK1), IL-2 receptor-γ chain, IL-3 receptor-α chain, IL-9 receptor, Toll-like receptor 7 (TLR7) and 8, and FOXP3 (3).

Females have two X chromosomes, one of which is randomly silenced in each cell to avoid gene overdosage (4). However, this X chromosome inactivation is only partial, with up to one-third of genes escaping silencing (4). These are often expressed at higher levels in females and can be associated with sex-specific susceptibility to infection and autoimmunity. For example, TLR7 has been shown to escape chromosome X inactivation in immune cells, increasing the risk of autoimmune disease (5).

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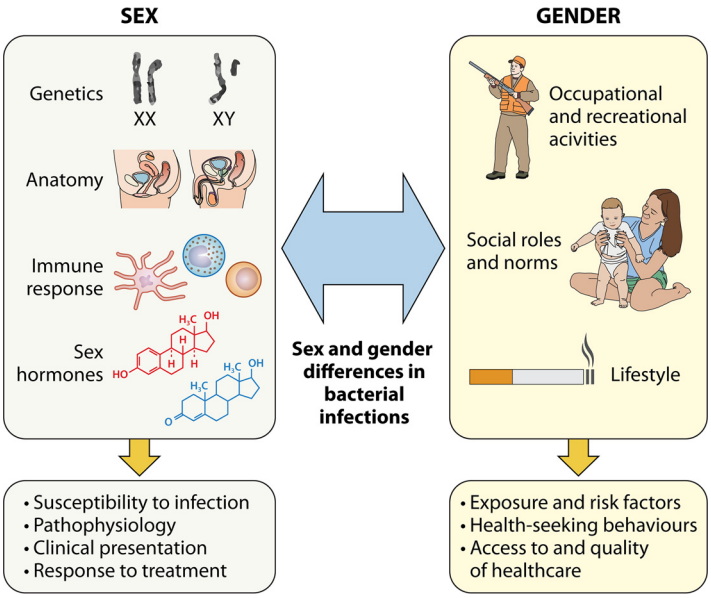

FIG 1 Interaction between sex and gender in bacterial diseases.

Furthermore, because the same chromosome is not expressed in each cell, random inactivation leads to female cell mosaicism, which also provides a survival advantage (6). Males, on the contrary, have only a single copy of each of their X chromosome genes, making them vulnerable to X-linked mutations. This is exemplified by X-linked primary immunodeficiencies, which make affected males susceptible to recurrent bacterial, fungal, and viral infections (7).

In addition to evading the harmful effects of these mutations, females benefit from the added diversity when facing new immune challenges, such as invading pathogens (8). The X chromosome is also richer in microRNAs (miRNAs) compared to the Y chromosome, many of which are known to affect immunity (9). For example, miRNA-223, located in the X chromosome, controls susceptibility to tuberculosis (TB) by regulating lung neutrophil recruitment, and its deletion renders mice highly susceptible to infection (10).

The Y chromosome has the lowest number of genes out of all nuclear chromosomes, and it is significantly shorter than the X chromosome. The notion that its function is restricted to sex determination and spermatogenesis has recently been challenged by the discovery of multiple genes with extragonadal expression, with evidence suggesting that the Y chromosome influences immune responses in males (11). For instance, a murine Y chromosome long-arm deletion is associated with deficiencies in B cell and natural killer (NK) cell development, although the precise molecular mechanisms behind this are unclear (12).

IMMUNE RESPONSE

In general, females have stronger innate and adaptive immune responses than males (Fig. 2) (13). These allow better pathogen clearance and response to vaccination, but also make females more prone to inflammatory and autoimmune diseases.

The innate immune system is the first line of immunological defense. There are sex-specific differences in the number and relative distribution of innate immune cells. Males have higher proportions of circulating monocytes (14) and NK cell counts (15), whereas females have higher neutrophil counts in the peripheral blood (16). Antigen-presenting cells (APCs) from females are more efficient in initiating a secondary response from primed lymphocytes compared to APCs from males, and the responsiveness of female cells to alloantigens is superior to that of males (17).

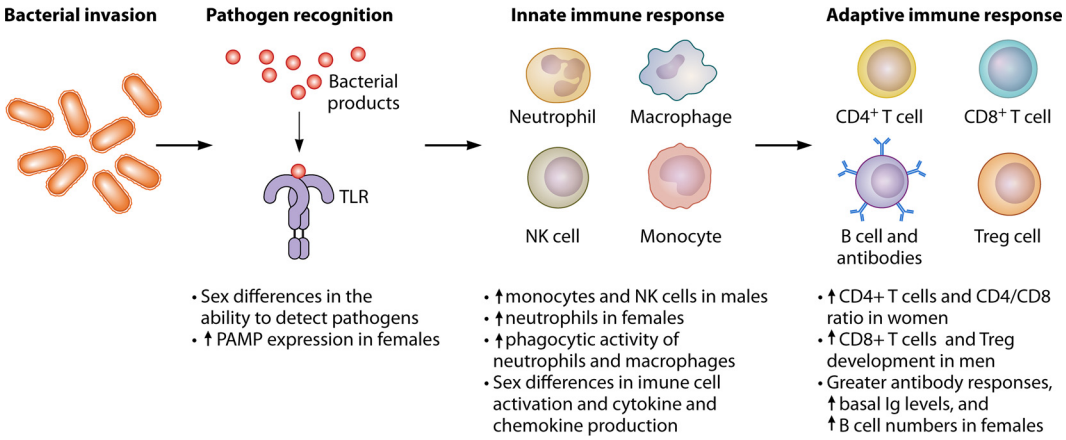

FIG 2 Sex differences in immune responses associated with bacterial infection. Ig, immunoglobulin; PAMP, pathogen-associated molecular patterns; TLR, Toll-like receptor.

In an *ex vivo* study, males had a stronger monocyte-derived cytokine response, including IL-1β, tumor necrosis factor alpha (TNF-α), and IL-6 production in response to lipopolysaccharide (LPS), although these differences disappeared after accounting for differences in monocyte concentration (18). Conversely, genes in the type I interferon (IFN) pathway are upregulated in females compared to males, which promotes enhanced responses to TLR agonists (19).

Furthermore, there are sex differences in the ability to detect pathogens, as females have higher expression of pathogen-associated molecular pattern receptors compared to males (20). Compared to male-derived cells, female rodent-derived resident macrophages express higher TLR2 and TLR3 levels and are more efficient at phagocytosis and bacterial killing, while also limiting excessive cytokine production and neutrophil recruitment (21). Bone marrow-derived macrophages from female mice have a significant increase in TLR8 expression compared to male-derived cells. In addition, TLR7 expression is higher in leukocytes from women (5). On the other hand, neutrophils from human males express higher levels of TLR4 and these are increased following activation with LPS, resulting in greater pro-inflammatory cytokine production, which may underlie increased susceptibility to endotoxic shock (22).

Sex also impacts lymphocyte subset distribution. Females have higher absolute and relative $CD4^+$ T cell numbers and higher CD4/CD8 ratios than males, while males have a higher percentage of $CD8^+$ T cells (23). Sex also influences the development of regulatory T (Treg) cells, which are higher in the peripheral blood of males (24). In addition, there are sex differences in humoral immunity. Adult females have greater antibody responses, higher B cell numbers (15), higher IgM and IgG levels, and lower IgA levels compared with males (25, 26). In children, B cell numbers and IgG and IgM levels are comparable between sexes, but females have lower IgA levels (25).

SEX STEROID HORMONES

Sex steroid hormones have immunomodulatory properties, and changes in their levels over the lifespan influence susceptibility and response to infectious diseases. These differences begin *in utero* with the formation of the testes in male embryos. Once formed, they begin to secrete androgens that cause masculinization and lead to the early development of androgen-dependent sex differences in immunity (27–29). After puberty, concentrations of estrogens and progesterone (P4) in females and androgens in males rise significantly. During this period, there is generally a male bias in infectious diseases, with males being more frequently and more severely affected by bacterial, viral, and parasitic infections, whereas females are more affected by autoimmune disease (30). Differences are also evident during pregnancy, when an increase in the levels of estrogen and, in particular, P4 promote a state of immune tolerance,

making pregnant women more susceptible to many infectious diseases (31). During menopause, estrogen and P4 levels drop rapidly in women, while a gradual decline in androgen levels is observed in aging males (1).

Sex steroids can influence immune responses by binding to specific receptors expressed in immune cells, including lymphocytes, macrophages, and dendritic cells (DCs) (13), and can also have a direct effect over bacterial metabolism, growth, and expression of virulence factors (32).

Estrogen. Estrogens are present in both sexes, but levels are highest in females of reproductive age. The principal endogenous biologically active estrogens are estrone (E1), estradiol (E2), and estriol (E3), the last of these being the main pregnancy estrogen (33). In females, levels vary during the menstrual cycle. They are low before puberty and after menopause and high during pregnancy.

Estrogen receptors (ERs) are ubiquitous in the immune system, and estrogen signals through two different nuclear receptors: ER alpha (ERα) and ER beta (ERβ) (34). Expression of ERs is influenced by age and sex. Monocytes from premenopausal women express ERα at lower levels than monocytes from men and postmenopausal women, whereas no difference was found in ERβ (35). Furthermore, monocytes from men and postmenopausal women contain significantly more ERα than ERβ, suggesting that monocytes from these two groups respond similarly to estrogens (35). On the other hand, ER expression is similar in T or B cells and in plasmacytoid DCs from both sexes (35, 36). *In vitro*, ERα signaling stimulates differentiation of DCs from monocytes, which produce pro-inflammatory cytokines in response to TLR stimulation. ER signaling also promotes the TLR-driven production of type I interferons (IFNs) in mouse plasmacytoid DCs *in vivo* (37). In humans, treatment of postmenopausal women with E2 markedly enhances production of IFN-α by plasmacytoid DCs (38).

E2 can augment or dampen immune signaling pathways and enhances both cell-mediated and humoral immunity in a concentration-dependent fashion. Low E2 concentrations promote a Th1-type response, boost cell-mediated immunity, and stimulate type I IFN responses and production of proinflammatory cytokines and chemokines, including IL-1β, IL-6, and TNF-α (39, 40). At high concentrations, E2 promotes Th2-type and humoral responses, inhibits pro-inflammatory pathways, and promotes production of anti-inflammatory cytokines, such as IL-4 and IL-10 (39, 40). Numbers of antibody-secreting cells have been reported to be significantly higher during the peri-ovulatory period in female rhesus macaques (41). Treatment of mice with physiological levels of estrogen results in retention of high-affinity autoreactive B cells, interfering with tolerance induction (42). On the other hand, E2 increases immunoglobulin class-switch recombination and somatic hypermutation in germinal centers. These changes lead to improved responses to vaccination but also increased propensity to autoimmune diseases in women (43).

E2 stimulates the expansion of Treg cells (44), which are higher during the follicular phase of the menstrual cycle (45). Estrogens also reduce the proliferation of immature T lymphocytes and induce thymic involution in mice (46).

Estrogen has been reported to have a protective effect in several infections, such as *Vibrio vulnificus*, which mostly affects males. In a rat model, ovariectomy was associated with increased mortality and estrogen replacement decreased mortality in both gonadectomized sexes (47). In contrast, in females with cystic fibrosis, estrogen induces conversion of *Pseudomonas aeruginosa* into the more virulent mucoid form, and the majority of infectious exacerbations occur during high circulating E2 levels (48).

Progesterone. P4 is produced by the corpus luteum in the ovaries during the menstrual cycle and by the placenta during pregnancy. Progesterone receptors are present in a variety of cell types, including immune cells such as NK cells, macrophages, DCs, and T cells (49). There are sex differences in PR expression, which can explain sex-based disparities in immune responses. For instance, PR expression is higher in female DCs than in male ones, which could justify the differential suppressive effect of progesterone on these cells in female versus male rats (31, 50).

P4 modulates the immune system in order to achieve a successful pregnancy. Increased maternal P4 levels promote a Th2-dominant cytokine phenotype (51, 52) causing an increase in anti-inflammatory cytokines such as IL-4, IL-5, and IL-10 (53–55)

and a decrease in proinflammatory cytokines such as TNF-α, IFN-γ, and IL-1β (56, 57). P4 also increases the number of Treg cells and inhibits Th17 cells (58, 59). P4 inhibits DC maturation and DC-mediated proliferation of T cells, favoring immature DCs which have a tolerogenic phenotype (56). This state of immune tolerance, while preventing fetal rejection, increases the susceptibility to and severity of many infections during pregnancy (31). Pregnant women are much more susceptible to *Listeria monocytogenes* infection than similarly aged healthy adults (60), and P4 increases susceptibility to *Chlamydia trachomatis* in female rats (61). In contrast, P4 at high doses inhibits the growth of *Neisseria gonorrhoeae* and *N. meningitidis* (62) and the germination of *Clostridioides difficile* spores (63).

Androgens. Androgens occur in higher concentrations in post-pubertal males than in females (13). Testosterone is the principal androgen, secreted from the testes in males and in small quantities from the ovaries in females. The androgen receptor works as a steroid hormone-activated transcription factor which signals through ligand-dependent and independent signaling pathways (64). Both testosterone and its metabolite, dihydrotestosterone (DHT), generally have suppressive effects on both humoral and cellular immune responses, leading to decreased T and B cell proliferation and decreased immunoglobulin and cytokine production (3).

DHT-treated female mice produce more IL-10 and less IL-12 than untreated female mice, and DHT can act on $CD4^+$ T lymphocytes to increase IL-10 gene expression via androgen receptor signaling (65), thereby promoting an anti-inflammatory response. Treatment of lipopolysaccharide or TNF-α-stimulated human endothelial cells with testosterone controls the inflammatory response mediated by NF-κB (66). In males with symptomatic androgen deficiencies, treatment with testosterone lowers proinflammatory cytokines (such as TNF-α, IL-1β, and IL-6) and increases anti-inflammatory cytokines (such as IL-10) (67). Testosterone deficiency in males is associated with increased $CD4^+$ counts and CD4/CD8 ratios, higher immunoglobulin levels, and increased B cell counts compared with controls, and these changes are reversed by hormonal replacement (68, 69).

In mice, testosterone decreases the expression of TLR4 in macrophages (70). Testosterone suppresses uropathogenic *Escherichia coli* (UPEC) invasion and colonization by inhibiting the JAK/STAT1 signaling pathway in a prostatitis cell model (71, 72) and also inhibits the expression of pro-inflammatory IL-1β, IL-6, and IL-8 cytokines (72). Male patients with TB show impaired production of gonadal androgens, with lower levels of testosterone compared to healthy controls (73).

GENDER

Gender-related occupational and recreational activities can affect exposure to pathogens. Women are more likely to assume caretaking roles, making them more exposed to childhood diseases (74). On the other hand, men wash their hands less often than women (75). Occupational exposure to animals plays a role in male bias in brucellosis (76) and Q fever (77), while male-predominant mine-related silicosis is a risk factor for TB (78).

Access to care also differs between men and women. In some countries, there is a parental preference for boys over girls. Studies in Bangladesh have shown that parents are more likely to bring their male children to the hospital for pneumonia or diarrhea than their female counterparts, and girls have longer delays to diagnosis, more severe illness on admission, and higher in-hospital mortality (79, 80). In adults, sociocultural and religious norms can also constrain access to health care, and poverty and stigma are important factors in limiting access to care for women in low-income countries. Furthermore, men consistently use more intensive care unit (ICU) resources and are more likely than women to be admitted to an ICU and receive advanced life-supporting measures (81).

SEX AND GENDER DIFFERENCES IN BACTERIAL DISEASES

Many bacterial pathogens exhibit a sex preference, and most show a male bias (Table 1). Fig. 3 summarizes differences in the incidence and severity of bacterial diseases across different organ systems.

TABLE 1 Sex bias by specific bacterial species

Bacterial species	Bias	Sex- and gender-based risk factors	Reference(s)
Escherichia coli	Female	Food consumption and handling practices, anatomical differences	245
Streptococcus pneumoniae	Male	Smoking, alcohol use	127
Legionella pneumophila	Male	Smoking, travel	131–134
Mycobacterium tuberculosis	Male	Occupational (e.g., mining), smoking, travel	141
Clostridioides difficile	Female	Antibiotic prescription, exposure to infants	95, 96, 99
Campylobacter spp.	Male	Food-handling practices	246, 247
Helicobacter pylori	Male	Smoking, low estrogen	85, 86
Listeria monocytogenes	Young women, elderly men	Pregnancy, waning cellular immunity	60, 107, 108
Leptospira spp.	Male	Working outdoors or with animals	248, 249
Francisella tularensis	Male	Outdoor activities, contact with animals	250
Borrelia burgdorferi	Male predominance in the U.S., female in Europe	Outdoor activities	220–223
Coxiella burnettii	Male	Contact with animals	77, 232, 233
Brucella spp.	Male	Contact with animals, food consumption habits	76, 251
Chlamydia trachomatis	Female	Screening bias	180, 181
Neisseria gonorrhea	Male	High-risk sexual behaviours	181, 189, 252
Treponema pallidum	Male	High-risk sexual behaviours	144, 252, 253

Gastrointestinal tract infections. Bacterial gastrointestinal infections are a leading cause of illness and death globally and are generally more common and more severe in males (82). This is partly explained by behavioral differences, as men are more likely than women to practice food-handling, preparation, and consumption behaviors that carry a high risk of foodborne diseases (83). Furthermore, differences in the immune response place males at a higher risk of poor outcomes, and sex hormones also play an important role.

(i) *Helicobacter pylori*. *Helicobacter pylori* infection is highly prevalent worldwide and is the strongest risk factor for stomach cancer (84). Infection has a slight male bias (85, 86) and males exhibit more severe inflammation, atrophy, and intestinal metaplasia scores compared to females (87). Gastric cancer is twice as common in men as in women (84).

Epidemiological evidence and animal studies suggest a protective effect of female sex hormones, namely, estrogen. A longer fertility window and the use of oral contraceptives or hormone replacement therapy are associated with a lower risk of gastric

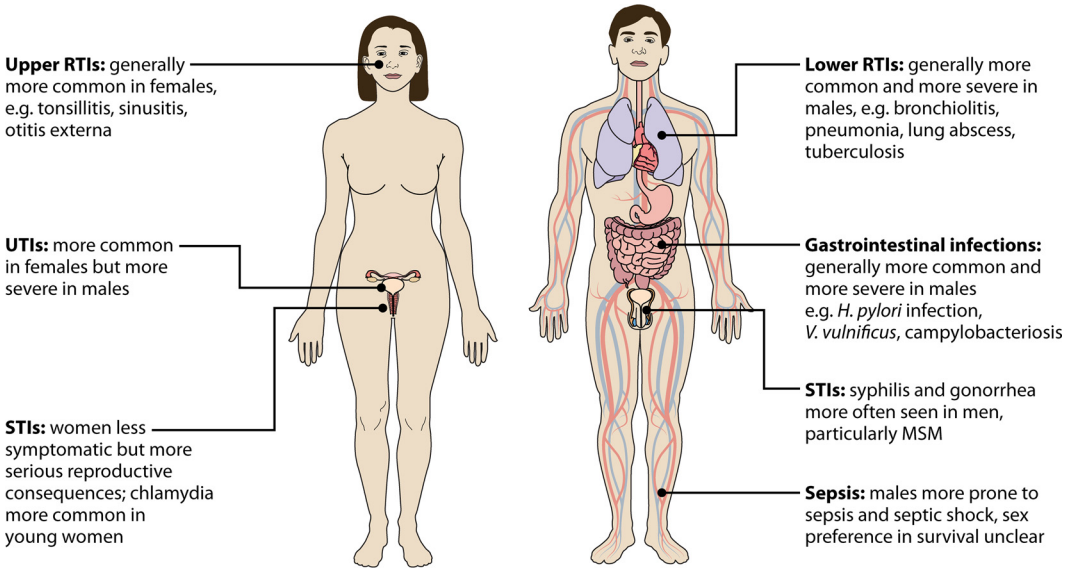

FIG 3 Sex and gender bias in bacterial infections. MSM, men who have sex with men; RTIs, respiratory tract infections; STIs, sexual transmitted infections; UTIs, urinary tract infections.

cancer (88). Transgenic hypergastrinemic mice infected with *H. pylori* develop gastric carcinoma in a male-predominant fashion (89), and estrogen supplementation, but not castration, attenuates gastric lesions (90). Ovariectomized mice develop significantly more severe *H. pylori*-induced gastritis and gastric cancer, and E2 supplementation has a protective effect (91).

On the other hand, female sex is associated with clarithromycin and metronidazole resistance (92) and *H. pylori* eradication failure (93).

(ii) *Clostridioides difficile*. *C. difficile* is a major cause of health care-associated infection, although community-acquired cases are increasingly reported (94). *C. difficile* infection (CDI) is more common in females, who account for 55% to 60% of cases (95, 96). In the United States, females account for 67% of community-acquired CDI (97), potentially due to more frequent antibiotic prescription in women (98). In addition, traditional gender roles result in women generally having more exposure to infants, which is a risk factor for community-acquired CDI (97). Women also account for the majority of hospital-acquired cases and are responsible for 55% of health care-associated CDI in Europe (99). Furthermore, females have an increased risk of recurrent CDI (100) and severe cases have been reported in pregnant and peripartum women (101, 102). On the other hand, male sex is an independent predictor of mortality (103).

(iii) Listeriosis. *L. monocytogenes* is a foodborne pathogen that can cause septicemia and meningitis as well as fetal infection or abortion in pregnant women (104). Pregnant women are about 20 times more likely to contract this infection compared to the general population (60) due to suppressed cellular immunity and the placental tropism of *L. monocytogenes* (104). In pregnant women and mice, increased P4 weakens $CD8^+$ T memory cell-mediated IFN-γ responses, which are crucial to host defense against listerial infection (57). Treating female mice with E2 decreased IL-12, TNF-α, and IFN-γ expression and increased IL-4 and IL-10 expression (105). Estrogen also depressed monocyte and lymphocyte accumulation at infective foci and increased mortality in female mice (106).

Incidence rates of invasive listeriosis are higher in females than in males during reproductive years (likely reflecting pregnancy-related listeriosis). In contrast, in older age groups, rates are 2 to 4 times higher in males (107, 108), with similar case-fatality rates (107). In mice, however, infection with *L. monocytogenes* led to significantly higher lethality rates and bacterial numbers in females than in males (109).

Respiratory tract infections. Generally, males are more susceptible to respiratory tract infections (RTIs) and have a more severe disease course and higher mortality compared with females. Males are more affected by lower RTIs, such as pneumonia, bronchiolitis, or lung abscess, while females more often develop upper RTIs, such as sinusitis, tonsillitis, and otitis externa (110). However, there are some exceptions. Males are more often affected by otitis media (111) and mastoiditis (112), whereas pertussis has a higher incidence rate in females (113).

Anatomical factors can explain some of these differences. For instance, peripheral airways are narrower during the first year of life in males, which may predispose them to lower rates of RTI (114). On the other hand, after puberty, males have significantly larger central airway luminal areas than females, independently of height (115). This could explain why in cystic fibrosis (which affects prepubescent males and females equally), post-pubescent females have increased rates and severity of exacerbations and more rapid declines in lung function after colonization with *P. aeruginosa* compared with males (116). It has also been suggested that females have smaller ostia, making them more susceptible to sinus obstruction and infection (117).

(i) Otitis media. Middle ear infections are a leading cause of medical visits and antibiotic prescription in infants and preschool-aged children. Acute otitis media is more common in boys than in girls (111, 118), and children with more severe disease are more often males (119). Studies also show that male sex is a risk factor for recurrent infection (111), as well as a predictor of chronic otitis media (120).

The reasons for these differences are not well understood; however, it has been proposed that abnormal pneumatisation of the mastoid process (with the smaller

mastoid cell air system in boys compared with girls), could result in more frequent and severe ear infections in male children (121).

(ii) Pneumonia. Pneumonia is a leading cause of hospitalization and death worldwide, and all types of bacterial pneumonia are more common in males (122). In community-acquired pneumonia, male sex is significantly associated with hospitalization and death, with males 1.3 times more likely to die than females (123, 124). Community-acquired pneumonia is also more common in boys than in girls (125), and male sex is associated with bacteremia in children (126).

Streptococcus pneumoniae is the most common bacterial pathogen in both sexes. Pneumococcal pneumonia and invasive pneumococcal disease are more frequent in males than in females (127), and male sex is associated with mortality in bacteremic pneumococcal pneumonia (128). Although older (over 50 years) females generally have lower antibody responses to pneumococcal vaccines than males (129), the 23-valent pneumococcal vaccine is more effective at preventing hospitalizations caused by *S. pneumoniae* in women (130). Legionellosis is also more frequently noted in males, with male:female ratios of 1.7 to 5 reported in Europe, the U.S., Australia, and Japan (131–134).

Hospital-acquired pneumonia is also more common in men (122, 135), and male sex is a risk factor for aspiration pneumonia in older patients (136). Furthermore, males are 1.6 times more likely to develop ventilator-associated pneumonia (137), although women have more severe disease and higher mortality (122, 138).

Animal models suggest that sex hormones are involved in pneumonia caused by different pathogens. In some instances, estrogen appears to have a protective role. In a mouse model of pneumococcal pneumonia, E2 promoted control of macrophage inflammatory activity and resolution of lung inflammation (139). In contrast, in a murine model of *Acinetobacter baumannii* pneumonia, female mice were more susceptible to infection, and treating male mice with E2 increased their susceptibility (140).

(iii) Tuberculosis. TB is the leading cause of death from a bacterial disease among adults worldwide. TB rates are significantly higher in men than in women. According to the World Health Organization, men accounted for 56% of all TB cases in 2020 versus 33% in adult women, with children accounting for the remaining 11% (141). However, the reasons for this bias are not entirely clear. It has been proposed that it could result from systematic underreporting and underdiagnosis of TB in women. Women may be less likely to seek appropriate medical care (142) and present difficulties in diagnostic testing, such as poorer-quality sputum samples (143). In addition, men undergo chest imaging sooner and are more likely to have a sputum smear sample performed (144). However, male bias persists when survey prevalence, rather than notification rates, is analyzed (141), and male predominance is seen even in low-burden countries where differences in access to health care should be negligible (78).

Both gender- and sex-related factors play a role. Men have more social contacts and more often participate in activities that place them at higher risk for TB, such as traveling, smoking, drinking, spending time in settings conducive to transmission (e.g., bars), and engaging in hazardous careers (e.g., mining) (78). However, other risk factors, such as household contacts and HIV infection, are not male-biased.

Both human and animal studies have shown that protective immune responses against *M. tuberculosis* are largely mediated by $CD4^+$ Th1 cells, which secrete IFN-γ, and this response is mediated by IL-12 (145). However, excessive inflammation can exacerbate lung infection and lead to early death. In a mouse model, elevated *M. tuberculosis* loads in males were associated with an early exaggerated pulmonary inflammatory response resulting in accelerated disease progression and increased mortality (146). B cells also play a role, and smaller B cell follicles have been reported in male compared with female lungs in mice and are associated with greater disease progression (147).

Male bias does not appear until puberty, suggesting a role for sex steroid hormones. Female and castrated male mice express significantly higher TNF-α, IFN γ, and IL-12 levels than uncastrated males (148), and treatment with testosterone increases their susceptibility to *Mycobacterium intracellulare* and *Mycobacterium marinum* infection (149).

Conversely, estrogen appears to have a protective role, as ovariectomized mice have a higher susceptibility to *Mycobacterium avium*, which is lessened by treatment with E2 (150). This is paralleled in humans by postmenopausal women, who are more susceptible to *M. avium* complex disease (151).

Certain X-linked gene mutations and polymorphisms confer increased risk of TB. Mutations in CYBB result in X-linked chronic granulomatous disease in males and increase susceptibility to mycobacterial disease (152), and TLR8 polymorphisms are linked to tuberculosis susceptibility in males (153).

From a clinical standpoint, women are usually less symptomatic than males. Men are more likely to be smokers, have more comorbidities, and present with hemoptysis, weight loss, and pleural effusion (154). Men also have more advanced radiological findings than women (155) and begin treatment earlier (144), and in a prospective observational study, male sex was associated with worse treatment outcomes (154). Males also have higher treatment dropout rates (156) and are at higher risk of recurrence (157).

For unknown reasons, female sex is a risk factor for developing extrapulmonary TB; studies in the U.S. (158) and Nepal (159) found women to be 1.7 times more likely to develop extrapulmonary TB relative to males. In addition, a prospective cohort study in eight countries showed that significantly more women than men had extensively drug-resistant TB (160).

Urinary tract infections. Urinary tract infections (UTIs) also exhibit a sex-based preference, with a bias toward women. Etiology is influenced by patient sex, as *E. coli*, *Klebsiella pneumoniae*, and *Streptococcus agalactiae* are more frequently isolated in females than in males, while the opposite is true for *Enterococcus faecalis*, *Proteus mirabilis*, and *P. aeruginosa* (161). The most common causative agent in both sexes is UPEC (162).

Male UTI shows a bimodal distribution at the extremes of age, whereas the burden of infection in women is durable over a lifetime (162). During the first few months of life, the incidence of UTI in boys exceeds that in girls (163), but afterwards, females of all ages are more prone to UTIs than males and around half of all women will experience at least one UTI during their lifetime (164). This gap significantly decreases with age as the incidence of benign prostatic hyperplasia, urinary retention, and incontinence increases in the male population.

The increased female susceptibility to UTI is due to several factors. The female urethra is shorter than its male counterpart, which has been proposed to make it easier for ascending bacteria to reach the bladder (165). Physical proximity of the urethral opening to the rectum and vagina is another important risk factor, as it can lead to colonization of the periurethral mucosa with enteric bacteria (166), and vaginal dysbiosis is associated with an increased risk of UTI (167). A dryer environment at the urethral opening and the anti-bacterial properties of prostate secretions are additional protective features in men (168).

While more common in women, UTIs are more persistent and have higher morbidity and risk of complications in men. Other organs, namely, the prostate, are often involved (168), and male UTIs are usually treated with antibiotics for a longer period compared with female UTIs (169). In UPEC-infected mice, more males than females are unable to clear bacteria and remain chronically infected, and male mice more frequently develop advanced pyelonephritis and kidney abscesses compared with females (170, 171). Furthermore, there is a strong and rapid increase in proinflammatory cytokine expression in female mice which is not observed in males and a larger infiltration by immune cells (170, 171), which may contribute to better bacterial clearance.

Sex hormones are also likely involved. Treatment of UPEC-infected female mice with testosterone leads to persistent bacteriuria and chronic cystitis (170), and castrated male mice have significantly lower bacterial burdens than sham-operated controls (171). After menopause, decreased estrogen levels contribute to physiologic and structural changes which increase the risk of UTI in postmenopausal women, such as reduced urinary flow, increased postvoid residual volume, and incontinence (172) along with a rise in vaginal pH, loss of commensal lactobacilli, and increased vaginal

colonization by enteric organisms (165). Furthermore, randomized controlled trials have shown that vaginal estrogen administration reduces UTI recurrence rates in postmenopausal women (173).

Sexually transmitted infections. Despite being curable, bacterial sexually transmitted infections (STIs) are associated with a significant burden of disease. STI-related morbidity disproportionately affects women, with important implications for women of reproductive age.

In many societies, more restrictive sociocultural norms regarding sexual behavior in women may limit their sexual freedom, restrict their access to information, and reduce their ability to practice safe sexual behaviors (174). Male-to-female transmission of STIs is also thought to be more efficient than female-to-male transmission, possibly due to retention of the infected ejaculate within the vagina and greater tissue injury during intercourse (175).

In addition, STIs are more often asymptomatic in women than in men. Undiagnosed and untreated STIs can result in important long-term reproductive complications, including pelvic inflammatory disease (PID), ectopic pregnancy, and infertility (176, 177). Furthermore, infections in pregnant women are associated with maternal morbidity as well as adverse fetal and perinatal outcomes (178).

(i) Chlamydia. Chlamydia is the most common bacterial STI globally (179). Persons between 15 and 24 years report the highest infection rates, and young women are twice as affected as men (180, 181), although this partly reflects screening programs which primarily target women.

The infection is asymptomatic in a large proportion of cases in both sexes, especially in women (182), but if left untreated can cause severe damage, particularly to the female reproductive tract, and chlamydia is an important cause of PID (176). In men, urethritis can be complicated by epididymitis and male infertility (183). *C. trachomatis* is the most common genitourinary trigger of reactive arthritis, and *Chlamydia*-induced arthritis is most often seen in men (184).

The mechanisms by which sex hormones affect *C. trachomatis* infections are not entirely clear. The likelihood of developing chlamydial or gonococcal salpingitis has been reported to be highest during the estrogen-dominant proliferative phase of the menstrual cycle (185), and a positive correlation was shown between chlamydial load and E2 levels in women (186). *In vitro* studies have also demonstrated that estrogen enhances chlamydial adherence and intracellular development (187). In contrast, other studies have found increased detection of *C. trachomatis* during the secretory phase when P4 is higher (188).

(ii) Gonorrhea. Gonorrhea is the second most common bacterial STI (179) and rates of reported infections continue to increase, particularly among men. Rates are highest among adolescents and young adults, and men—especially men who have sex with men (MSM)—are currently more often affected than women in high-income countries (181, 189). In 2018, the male-to-female ratio was 3.2 in Europe and 1.4 in the United States (181, 189).

Urethritis is the most common manifestation of gonococcal infection in men, whereas the endocervical canal is the primary infection site in women (190). Most women show no symptoms of infection (182), while males are often symptomatic (191). Rectal gonorrhea occurs in both sexes and is usually asymptomatic in women, whereas cases in MSM can be associated with complaints of overt proctitis (192). Complications in men include epididymitis, infertility, prostatitis, and seminal vesiculitis (190). Similarly to chlamydial infection, PID is the main complication of gonorrhea in women (176). Disseminated gonococcal infection is the most common systemic complication in both sexes, and probably occurs more frequently in women (190). Estrogen likely plays a role, as E2-treated mice show an enhanced susceptibility to disseminated gonococcal infection (193).

The molecular mechanisms used by the gonococcus to initiate infection, and the resulting inflammatory response, also differ between sexes. In men, interaction with the urethral epithelial cells triggers the release of pro-inflammatory cytokines, promoting an inflammatory response and contributing to the symptomatic nature of

gonococcal disease in men (194). Similarly, ascending gonococcal infection of the uterus and fallopian tubes also results in inflammation. In contrast, gonococcal cervicitis is mostly asymptomatic because the gonococcus can evade host immune function by subverting the alternative pathway of complement and does not elicit strong immune responses during uncomplicated genital infections in women (194).

Emergence of gonococcal antimicrobial resistance is a major public health threat, and one study found that men infected with *N. gonorrhoeae* had 4-fold higher expression of gonococcal antimicrobial resistance genes compared with women (195), which could have implications for sex-specific treatment.

Sepsis. Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection (196), and it is a major global health problem (197). If not identified and treated promptly, it can lead to septic shock, multiple organ failure, and death (196). The most common sources are the respiratory tract in males and the urinary tract in females (198, 199). Most studies report higher rates of sepsis and septic shock in males, who account for 55% to 64% of cases (200–202), and male sex has been identified as a predictor of sepsis after trauma (203) and surgery (204). Experimental studies have consistently shown a survival advantage and a protective effect of sex hormones in females. In humans, however, reports on sex and mortality have shown conflicting results. Some have found higher mortality in women (199, 205), others in men (198, 206), whereas others reported no differences (207, 208).

In animal models, estrogen exerts a protective effect by maintaining adequate immune responses and cardiac function. Ovariectomized females show depressed macrophage and splenocyte functions after trauma-hemorrhage, which are associated with significantly increased mortality from subsequent sepsis (209, 210), and addition of E2 normalizes immune functional capacities (210). Sepsis-induced cardiac dysfunction is also less pronounced in female mice than in males (211). In contrast, in humans, circulating E2 levels are increased in non-survivors compared to survivors (212). Testosterone levels are generally low in male patients with sepsis (213), and androgen depletion appears to be protective in animals. Testosterone receptor blockade after trauma-hemorrhage in male mice restores depressed immune functions and improves survival following subsequent sepsis (214). Males also show an inappropriate inflammatory response to sepsis and produce significantly higher levels of pro-inflammatory cytokines (including TNF-α, IL-6, IL-8, IL-1β, and procalcitonin) following endotoxemia induction or sepsis than females (22, 215, 216), which could render them more susceptible to septic shock.

Sex-based differences in health care have also been reported. Women experience significantly longer delays to initial antibiotic administration than men (217, 218), and in a nationwide cohort study, a complete 1-h emergency department sepsis care bundle was fulfilled 38% more often in men (218). In the UCI, women are less likely to receive deep venous thrombosis prophylaxis, hemodialysis catheters, invasive mechanical ventilation (199, 205), or vasopressor support (207), and have a shorter length of stay (206) compared with men.

Other infections. (i) Lyme borreliosis. Lyme borreliosis is the most common human vector-borne infection in Europe and the U.S. (219). It has a slight male predominance in the U.S., with around 57% of cases being male (220), presumably due to higher occupational risks and outdoor recreational activities. However, in Europe, 55% to 60% of affected patients are female (221–223). Furthermore, females have been reported to attract 33% more tick bites than males, despite spending less time outdoors (224).

One study in Sweden found that erythema migrans in women was less likely to have the classic "bull's eye" appearance, and the duration from treatment until disappearance of the lesion was significantly longer in women than in men (224).

In the U.S., 70% of patients with Lyme carditis and 60% of cases of Lyme arthritis are male (220). A retrospective study in Slovenia reported that 75% of patients with Lyme arthritis were men, and men accounted for 60% of cases of neuroborreliosis (225). Acrodermatitis chronica atrophicans, a late cutaneous manifestation of Lyme disease, was more common in females, who represented nearly 70% of cases (225). Women may also be at higher risk of developing post-treatment Lyme disease syndrome (226). Reinfection rates are higher in

women, particularly postmenopausal women (227), which could be due to falling estrogen levels and differences in the immune response (228).

Sex also impacts diagnosis, because the recommended two-tier testing is male biased. The magnitude of enzyme-linked immunosorbent assay (ELISA) and IgG serologic responses is greater in men (229) and men have on average six reactive bands on the IgG immunoblot, whereas women have only four (230). Current Centers for Disease Control and Prevention criteria require five bands for a positive test, likely underestimating the true number of female cases (230).

(ii) Q fever. Q fever is a zoonosis caused by *Coxiella burnetii* (231). Seroprevalence is higher in men, a study in Australia reporting a male-to-female ratio of around 1.6 (77). An even greater proportion of men are diagnosed with the disease (sex ratio of 2 to 5) (232, 233), suggesting that men develop symptomatic Q fever more often than women (234). In contrast, boys and girls are almost equally represented (231), suggesting that sex hormones could be involved.

In *C. burnetii*-infected mice, bacterial loads and granuloma numbers were lower in intact females than in males and ovariectomized females, and treatment with E2 reduced bacterial loads and granuloma numbers in ovariectomized mice (235). P4 inhibits *C. burnetii* replication in infected placenta-derived cells (236) and bacterial loads increase toward parturition (237) when P4 levels decrease. However, both animals and humans exhibit an increased risk of persistent infection and unfavorable outcomes during pregnancy (231), likely due to impaired cellular immunity.

(iii) Meningitis. Bacterial meningitis is an infection of the membranes that cover the brain and spinal cord caused by a bacterial pathogen. *S. pneumoniae*, *N. meningitidis*, and *Haemophilus influenzae* are the most frequently isolated bacteria. Some studies have reported similar rates of bacterial meningitis in men and women, while others have found a slight male bias (238–241). Male sex has been identified as a predictor of poor outcomes in children (242, 243) and adults (238, 241), despite females having a higher disease severity and higher inflammation markers on admission (238). This may be in part related to a better female response to anti-inflammatory treatment with corticosteroids (244). Sex steroid hormones may also play a role.

CONCLUSIONS

Many bacterial infections exhibit sex and gender differences in pathophysiology, incidence, clinical presentation, disease course, response to treatment, and outcome. Both biological and gender factors come into play and their recognition is essential to improving patient care. Behavioral differences play an important role in the exposure to pathogens, whereas sex differences in the immune response are directly influenced by sex chromosome complement and concentrations of sex steroid hormones.

Nevertheless, these observations have not been systematically integrated into research practices or resulted in changes to medical guidelines, which are mostly not sex-specific. This needs to change, and funding agencies and medical journals should promote scientific research that is sex-conscious and provides sex-disaggregated data. Incorporating implementation science methods to translate existing evidence into sex-specific guidelines is essential to promote improved and more personalized patient care.

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