Arch. Immunol. Ther. Exp. (2011) 59:203–213
DOI 10.1007/s00005-011-0124-3

REVIEW

Gender Specific Differences in the Immune Response to Infection

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Received: 29 September 2010 / Accepted: 15 December 2010 / Published online: 26 March 2011

Abstract There are many instances where males and females differ in the susceptibility to infections. The reason for these differences in susceptibility is multifactorial. The primary cause is thought to be due to differences induced by sex hormones and their effects on gene expression as well as the immune system, but may also be due to innate physiological differences between males and females. This review summarizes gender specific differences seen in infections caused by bacteria, fungi, parasites and viruses. Ultimately, gender specific differences appear to be dependent on the microbe causing the infection, as not every infection with a specific microbial type results in increased susceptibility of one gender over the other. This suggests that there is an interaction between gender specific immune differences and the specific immune response to individual microbes.

Keywords Gender differences · Microbial infection · Immune response

Abbreviations

IFN-γ	Interferon γ
IL-4	Interleukin-4
TNF-α	Tumor necrosis factor α
T_H1	T helper 1
DES	Diethylstilbestrol
LTA	Lipotechoic acid
LPS	Lipopolysaccharide
AIDS	Acquired immune deficiency syndrome
HIV	Human immunodeficiency virus
RSV	Respiratory syncytial virus
HSV-2	Herpes simplex virus-2
CMV	Cytomegalovirus
CD38	Cluster of differentiation 38
TLR7	Toll-like receptor 7
CCR5	C-C chemokine receptor type 5

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Introduction

Gender has a significant effect in the outcome of immunity to many infectious microbes (Klein 2004; May 2007). This may be due to a number of factors including different kinetics in men and women regarding infection and progression to disease as well as basic differences in cell response, as seen in embryonic cells that are innately male or female [before production of sex hormones (Penaloza et al. 2009)].

Additionally, hormonal effects are thought to play a significant role in gender-specific differences in the immune response to infection, including skewing of the inflammatory response (T_H1 vs. T_H2). For example, estrogen is thought to induce a T helper 1 (T_H1) inflammatory response to Lyme disease (Jarefors et al. 2006) and infection with the fungus *Paracoccidioides brasiliensis* (Pinzan et al. 2010), but induces a T_H2 protective response during infection with the nematode *Taenia crassiceps* (Guzman et al. 2009).

In general, testosterone is thought to act in an anti-inflammatory fashion while estrogen is more pro-inflammatory in nature (Klein 2004). For example, testosterone has multiple depressive effects on the immune system. It has been shown that testosterone decreases antibody

production, Fc receptor expression, inducible nitric oxide synthase mRNA expression, and eosinophil degranulation while estrogen increases these immune responses (Klein 2004). However, it is also clear that differences in the immune response to specific microbial infections are dependent on the microbe, as not every bacterial or viral infection results in increased susceptibility of one gender over the other overall. Thus, it seems that there may be an interaction between gender specific immune responses and the immune response to a specific microbe.

Bacterial Infections

Bacterial infections encompass a broad range of pathogens and the corresponding immune responses are equally diverse. However, a common theme among many bacterial infections is sexual dimorphism. Examples of gender differences in immune response include the following pathogens: *Mycobacterium* spp., *Treponema pallidum*, *Borrelia burgdorferi*, *Listeria monocytogenes* and *Vibrio vulnificus*.

In several Mycobacterial infections that resemble tuberculosis or lymphadenitis, including *M. lepraemurium, M. marinum,* and *M. intracellulare*, male mice are more susceptible to infection (Brown and Glynn 1987; Curtis and Turk 1984; Sato 1972; Yamamoto et al. 1990). In *M. intracellulare* infections in mice, males have more severe gross lesions in the visceral organs as well as increased numbers of microbes in the lungs, liver, and spleen compared with females (Yamamoto et al. 1990). Examination of peritoneal macrophages from male mice infected with *M. intracellulare* showed more rapid growth of phagocytozed organisms suggesting that female peritoneal macrophages possess more potent antibacterial activity (Yamamoto et al. 1990). Similarly, the footpads of C57BL × BALB/c male mice contain higher numbers of *M. lepraemurium* (Curtis and Turk 1984). Another example of ineffective immunity to mycobacteria in males is the decreased production of anti-lipoarabinomannan immunoglobulin M antibodies in *M. tuberculosis* infections (Demkow et al. 2007).

Syphilis, the sexually transmitted infection caused by *Treponema pallidum*, also demonstrates gender dimorphism. In secondary syphilis, females are more resistant, as they have higher $CD3^+$ cell count (Pope et al. 1994). In fact, both $CD4^+$ and $CD8^+$ T lymphocytes are both elevated in females with secondary syphilis (Pope et al. 1994). Interestingly, females with secondary syphilis have lower natural killer cell numbers compared to males with secondary syphilis (Pope et al. 1994).

In Lyme disease, reinfection in females is common. A study of postmenopausal women who experienced recurrent *Borrelia burgdorferi* infection revealed increased numbers of cells spontaneously secreting interferon (IFN)-γ, interleukin (IL)-4, and IL-10 (Jarefors et al. 2006). The IL-4:IFN-γ and the IL-10: tumor necrosis factor (TNF)-α ratios demonstrated a T_H2, anti-inflammatory immune response in women compared to men (Jarefors et al. 2006). These ratios and responses are opposite the T_H1-dominant response necessary for successful clearance of the *B. burgdorferi* infection (Jarefors et al. 2006).

In the murine model of *Listeria monocytogenes* gastrointestinal infection, treatment with diethylstilbestrol (DES) or estradiol increases susceptibility and mortality in mice (Pung et al. 1984, 1985). In mice infected intraperitoneally with *L. monocytogenes*, estrogen treatment decreases the accumulation of lymphocytes and monocytes in the peritoneal cavity (Pung et al. 1984). DES treatment decreases the numbers of nucleated spleen cells, T lymphocytes, B lymphocytes, and macrophages and increases the number of neutrophils in *L. monocytogenes* infection (Pung et al. 1985). Similarly, DES infected mice have decreased IL-2 production and the IL-2 that is produced does not stimulate concanavalin A proliferation of lymphocytes to the same extent as IL-2 from control infected mice (Pung et al. 1985).

Infection by *Vibrio vulnificus* may lead to gastroenteritis or septicema from eating raw or undercooked seafood as well as wound infection via contact with contaminated seawater. Patients with life-threatening septicemia due to *V. vulnificus* have a 10–60% mortality rate (Kuo Chou et al. 2010; Oliver 2005). In a study of *Vibrio* infection in Florida over 13 years, it was observed that 11% of individuals with *V. vulnificus* wound infections died, all of which were males (Hlady and Klontz 1996; Oliver 2005). In fact, 50–80% of *V. vulnificus* infections occur in males (Kuo Chou et al. 2010).

A rat model using intravenous injection of *V. vulnificus* lipopolysaccharide (LPS) to mimic *V. vulnificus* septicemia reiterates the sexual dimorphism seen in humans. Female rats that had undergone ovarectomy exhibited increased mortality similar to that of males. Estrogen administration to gonadectomized rats of both sexes ameliorated the severity of disease in the *V. vulnificus*-induced endotoxin shock (Merkel et al. 2001).

Bacteremia and septicemia due to other bacteria also show gender-related differences in immune response. For example, *Staphylococcus aureus* and *Pseudomonas aeruginosa* bacteremia is more frequent in males than females (Al-Hasan et al. 2008; Allard et al. 2008; Benfield et al. 2007). Conversely, 60% of *Escherichia coli* bacteremias occur in females, perhaps due to increased *E. coli* urinary tract infections in women (Laupland et al. 2008).

Not all immune responses that exhibit sexual dimorphism are in direct response to the infecting microorganism—some are in response to microbial components. *Streptococcus*

pyogenes, the etiologic agent of pharyngitis and scarlet fever, releases a number of superantigens, including staphylococcal enterotoxin A and streptococcal mitogenic exotoxin Z, which induces an overwhelming cytokine response (Faulkner et al. 2007). In *S. pyogenes* superantigen-sensitive HLA class II mice, females are more susceptible to superantigen than males (Faulkner et al. 2007). Female susceptible mice secrete greater concentrations of serum TNF-α and experience enhanced hepatocyte apoptotic death (Faulkner et al. 2007). Conversely, male mice secrete more soluble TNF-α receptor than females, which acts as a sink for serum TNF-α thereby decreasing inflammation (Faulkner et al. 2007).

In addition to superantigens, cell wall components like endotoxin and lipotechoic acid (LTA) induce strong immune responses with gender differences. In response to stimulation with LPS from *Salmonella abortus equi* and LTA from *Staphylococcus aureus*, male mice secreted larger amounts of pro-inflammatory cytokines including TNF-α, IL-1β, IL-6, and IL-8 (Aulock et al. 2006). IFN-γ secretion was also enhanced when blood from male mice was stimulated with high concentrations of LPS (Aulock et al. 2006). Granulocytes from female mice treated with LPS experience delayed apoptosis and increased overall survival (Aoyama et al. 2009). The same study observed that by 24 h after intraperitoneal LPS exposure, 84% of female mice survived endotoxemia while only 41% of male mice did (Aoyama et al. 2009). Male mice had an increased number of apoptotic neutrophils by 3 h while apoptosis was delayed in females until 18 h post-LPS administration (Aoyama et al. 2009). At the same time-point, males had decreased numbers of myeloid cells and B lymphoblasts (Aoyama et al. 2009). Males also experience a rapid decline in the numbers of peritoneal macrophages with a concurrent increase in neutrophils by 18 h after LPS treatment (Aoyama et al. 2009). In contrast, females had the same decrease in macrophages without the concomitant granulocyte influx (Aoyama et al. 2009).

Fungal Infections

The three major fungal infections that show gender-specific differences are *Cryptococcus neoformans*, *Candida albicans* and *Paracoccidioides brasiliensis*.

Cryptococcus neoformans causes fungal meningitis primarily in patients who are immunosuppressed (i.e. AIDS patients, organ transplant patients, patients undergoing chemotherapy, etc. (Casadevall and Perfect 1998). The literature on gender differences in *C. neoformans* infections is complicated as the majority of studies reported that males have an increased risk of *C. neoformans* infection (Amornkul et al. 2003; Dromer et al. 1996a, b; Hajjeh et al. 1999; Micol et al. 2007; Mitchell and Perfect 1995; Sorvillo et al. 1997) while several studies, reported an increased risk of *C. neoformans* infections in females (Chuang et al. 2008; Jean et al. 2002). A possible explanation for this difference is that most of the patients in these two studies were not infected with human immunodeficiency virus (HIV). It has been noted in the past that males have an increased risk of infection with *C. neoformans* when the patients are also HIV^+ (Bava and Negroni 1992).

One study using BALB/c mice, which are susceptible to *C. neoformans*, as a host system found that males had a significantly higher fungal burden in the spleen than female mice during chronic infection (day 39 post-infection; McClelland and Potts, unpublished data). This data is in concordance with gender differences in human infections. A possible cause of the increased fungal load in male mice was determined by Lortholary et al. (2002) who used outbred mice as a host model for infection with *C. neoformans*. The authors found that at 6-day post-infection female mice had >2-fold higher levels of TNF-α, IL-6, IFN-γ and IL-10 cytokines in the plasma and higher levels of TNF-α and IFN-γ in the spleens. Interestingly, this difference in cytokine levels did not cause a difference in survival or acute fungal burden between the sexes (Lortholary et al. 2002).

Candida albicans is an opportunistic fungus that is commonly found in the flora and intestines of most healthy humans (Berman and Sudbery 2002). Under instances of immunosuppression, *C. albicans* may become pathogenic and invade host tissues (Ruiz-Herrera et al. 2006). For oral candidiasis infections, the incidence is increased in elderly females (Zegarelli 1993) while *C. albicans* infections are the dominant cause of onychomycosis in females but not males (Aly 1994; Ellabib et al. 2002; Naidu 1993). Additionally, female HIV^+ patients with oral candidiasis have been found to have larger fungal loads than male HIV^+ patients with oral candidiasis (Nebavi et al. 2006), suggesting that estrogen may increase susceptibility to *C. albicans* infection (Diamond 1983; Zhang et al. 2000a). Interestingly, one study showed that more pathogenic genital strains were isolated from females compared to males, which prompted the authors to suggest that the aggressiveness of some *C. albicans* strains is different in males and females (Shi et al. 2007) and supports the fact that estrogen has been shown to increase virulence of *C. albicans* strains (White and Larsen 1997).

Paracoccidioides brasiliensis is a dimorphic fungus that is the cause of Paracoccidioidomycosis, which preferentially affects the lungs followed by the skin, mucous membranes, adrenals, and reticuloendothelial organs (Restrepo et al. 2008). The chronic adult form predominantly causes disease in males compared to females (13:1) (Restrepo et al. 2008), even though males and females are infected at the same rate (Pereira 1988).

A mouse study to determine the immunological basis for this gender difference used C57Bl/6 mice as the host system. After inoculation with *P. brasiliensis*, spleen cells from female mice at day 7 post-infection showed significantly higher levels of the T_H1 cytokines IL-12-p40, TNF-α and IFN-γ, while spleen cells from male mice showed significantly higher levels of the T_H2 cytokine IL-10 (Pinzan et al. 2010). Macrophages from female mice stimulated with *P. brasiliensis* produced higher levels of nitric oxide and eliminated more *P. brasiliensis* than macrophages from male mice (Pinzan et al. 2010). Additionally, male mice showed significantly higher fungal burden in the liver and lungs than female mice (Pinzan et al. 2010).

To demonstrate that sex hormones regulated the immune response in *P. brasiliensis* infection, male and female C57Bl/6 mice were castrated and treated with sex hormones. Male castrated mice treated with estradiol showed a 77% reduction in IL-10 levels compared to intact male mice while female castrated mice treated with testosterone showed a 57% increase in IL-10 levels compared to intact female mice (Pinzan et al. 2010). Thus sex hormones directly regulate the inflammatory cytokine response during *P. brasiliensis* infection.

Parasitic Infections

Parasitic infections encompass a broad range of microbes including protozoa, helminths, and arthropods. Interestingly, sexual dimorphism in parasitic infections is strikingly similar despite the diversity in infecting organisms. In general, males have a higher prevalence and/or severity than females (Klein 2004). Exposure, behavior, and habitat may contribute to this phenomenon; however, studies in humans and rodent models suggest that sex hormone influences on the immune response, particularly cytokine balance, play a significant role as well. Examples of sexual dimorphism in immune response include *Schistosoma, Leishmania*, *Plasmodium*, and *Taenia* (Klein 2004).

The gender difference in immune responses to parasites is best characterized for *Schistosoma,* a flatworm causing chronic disease in humans. Multiple studies in Ethiopia, Kenya, Uganda, and Senegal demonstrated that the prevalence and intensity of *S. mansoni* and *S. haematobia* infections is higher in males than females (Degu et al. 2002). Males secrete greater amounts of T_H1 cytokines, including TNF-α and IFN-γ (Abebe et al. 2001; Degu et al. 2002; Marguerite et al. 1999; Naus et al. 2003; Remoue et al. 2001; Webster et al. 1997). Elevated levels of these pro-inflammatory cytokines lead to many of the pathologies associated with schistosomiasis. Conversely, females secrete greater amounts of the anti-inflammatory cytokines IL-10 and tumor growth factor β as well as almost all antibody isotypes except the protective immunoglobin A, which is higher in males (Remoue et al. 2001).

Similar to *Schistosoma* infections, *Leishmania donovani* infections in humans are more prevalent in males than females (Goble and Konopka 1973). Males have increased susceptibility to cutaneous, mucosal, and visceral leishmaniasis compared to females. In Mexico, only 10% of *L. mexicana* infections occur in females. This reduction in susceptibility in females appears to be due to increased secretion of granulocyte macrophage colony-stimulating factor in females compared to males (Lezama-Davila et al. 2007b). In Colombia, males are at increased risk for more severe mucocutaneous leishmaniasis due to *L. panamensis* than females (Munoz and Davies 2006). However, in Afghanistan, females are more susceptible to lesions and scars due to *L. tropica* infection (Reithinger et al. 2003). This appears to be due to genetic differences between New World (*L. mexicana*) and Old World (*L. tropica*) parasites.

Similar to leishmaniasis in humans, *L. major* and *L. mexicana* infections in mice and *Leishmania* (*Viannia*) spp. in hamsters are more severe in males (Alexander 1988; Jones et al. 1987; Lynch et al. 1982; Mock and Nacy 1988; Satoskar and Alexander 1995; Satoskar et al. 1998; Shiddo et al. 1995; Weigle et al. 1993). In addition to the increased risk of infection, there appears to be an increased pathogenicity in males compared to females. Travi et al. (2002) found that in male hamsters, leishmania-induced lesions were larger and disseminated to distal sites more frequently than in females. These gender-based differences were found to be directly attributable to sex steroid hormones. Female hamsters given testosterone had larger lesions than males (Travi et al. 2002).

In mice, sexual dimorphism appears to differ based on the genetic background of the parasite. In DBA/2 mice, both sexes develop lesions when infected with *L. major*, but female mice do not resolve their lesions. Conversely, in DBA/2 mice infected with *L. mexicana* females are resistant to infection even at high doses while males are highly susceptible at low doses (Alexander 1988). Resistance to *L. mexicana* in female mice appears to be due to increased secretion of IFN-γ and a delayed type hypersensitivity reaction while males appear to respond to infection with a T_H2-mediated fashion. Female mice infected with *L. mexicana* given neutralizing antibodies to IFN-γ developed lesions similar to male mice. Infected male mice given intralesion IFN-γ exhibited decreased lesion progression compared to control male mice (Satoskar et al. 1998). The effects of sex steroid hormones is further evidenced by studies where estrogen treatment of bone marrow-derived macrophages from mice of both sexes demonstrated increased parasite killing and nitric oxide

production without an increase in proinflammatory cytokines (Lezama-Davila et al. 2007a).

Malaria, caused by the protist *Plasmodium,* in humans differs in intensity between the sexes with males having greater parasite burden and infection severity (Benten et al. 1997, 1993, 1992; Wunderlich et al. 1991; Zhang et al. 2000b). In mice, mortality is higher in males than females and for those male mice that do recover, they do so at a much slower rate (Zhang et al. 2000b). Female mice, which typically have higher anti-*Plasmodium* antibody titers, given testosterone have decreased antibody production and decreased $CD8^+$ T lymphocytes in the spleen (Benten et al. 1993; Zhang et al. 2000b). Female mice secreted higher concentrations of IFN-γ than male mice, a cytokine critical to controlling the malarial infection (Zhang et al. 2000b).

In contrast to the three parasitic infections described above, sexual dimorphism in the immune response to the tapeworm *Taenia* is skewed toward increased inflammation and pathogenicity in females compared to males (Chavarria et al. 2005; Guzman et al. 2009; Kelvin et al. 2009). Human females infected with *T. solium* and female mice infected with *T. crassiceps* developed more cysts and had more inflammation surrounding the cysts than males (Kelvin et al. 2009). In infected women, elevated concentrations of IL-6, IL-5, and IL-10 were measured in the cerebrospinal fluid (Chavarria et al. 2005). In mice given estrogen during the neonatal period, increased IL-4 and IFN-γ levels were observed and correlated with protection later in life (Guzman et al. 2009).

Viral Infections

For viral infections, females are thought to be more likely to develop T_H1 responses in mouse studies (Villacres et al. 2004) and, thus, in infections where a T_H1 response is protective, such as vesicular stomatitis virus (Barna et al. 1996) or herpes simplex virus (HSV) (Han et al. 2001), female mice are more resistant to disease. Whereas in infections where T_H1 responses are more pathogenic, such as in lymphocytic choriomeningitis virus infection, female mice develop enhanced pathology (Muller et al. 1995). However, in humans, females show a predominant T_H2 cytokine profile after stimulation of lymphocytes with the polyclonal activator phytohemagglutinin (Giron-Gonzalez et al. 2000). This data and the fact that women show increased susceptibility to many viral infections, suggests that the immune response to viral infections in humans and mice are different, and perhaps opposite. Regarding memory T-helper responses, both men and women appear to have a predominant T_H1 response (Villacres et al. 2004). Thus, in general there is a disparate immune response to most viral antigens in men and women. A few of them are delineated below.

Respiratory syncytial virus (RSV) is the most frequent cause of acute viral bronchiolitis in children (Wainwright 2010). Male children have a greater risk of more severe illness when infected with RSV. More severe disease is also associated with defects in innate immunity. Infection with RSV leads to activation of the nuclear factor κB pathway and induction of a variety of cytokines and chemokines as well as recruitment of other innate immune cells into the airways. The increased risk of more severe disease with hospital admission seen in male children may be related to airway mechanics and the fact that males have smaller airways than females (Wainwright 2010). Additionally, it has been seen that males have higher blood and sputum eosinophilia than females, while females had higher white blood cell counts, serum C reactive protein levels (Nagayama et al. 2006), and eosinophilic cationic protein levels than males (Colocho Zelaya et al. 1994), which may explain the susceptibility seen in males. However, the roles of the sex hormones in RSV infection have not been explored.

In contrast, the role of sex hormones play a pivotal role in the immune response to HSV-2. HSV infections are among the most common sexually transmitted genital infections with transmission occurring primarily through symptomatic lesions and asymptomatic shedding following genital infection (Nazli et al. 2009). There are a number of studies illustrating that there is a higher prevalence of HSV-2 in females compared to males (Glynn et al. 2008; Howard et al. 2003; Rabenau et al. 2002). This may be due to increased levels of progesterone in females as prolonged exposure to progesterone has been shown to increase susceptibility to HSV-2 and decrease the induction of a protective immune response in mice (Gillgrass et al. 2003; Kaushic et al. 2003). In concordance with this finding, ovariectomized mice injected with estradiol and then treated with estradiol, progesterone or saline alone showed complete protection against challenge while ovariectomized mice injected with progesterone or saline alone showed increased susceptibility to challenge (Gillgrass et al. 2005). Additionally, ovariectomized mice injected with estradiol showed higher survival rates, reduced pathology and lower viral shedding after challenge compared to mice treated with progesterone or a placebo (Bhavanam et al. 2008).

Interestingly, the opposite results are seen when using a model of ex vivo human genital epithelium cells in HSV-2 infection. Treatment with estradiol increases HSV-2 infection in human endometrial epithelium cells and viral shedding is decreased following treatment with progesterone (MacDonald et al. 2007). This suggests that the effects of sex hormones on the immune response to HSV-2 in humans and mice are different, and perhaps opposite, and may explain the prevalence of HSV-2 infection in human females.

For hepatitis C virus, a major cause of liver damage, young females are also more likely to be infected than males (European Paediatric Hepatitis C Virus Network 2001; Tovo et al. 1997, 2005; Zanetti et al. 1998). This may be due to increased levels of lymphocytes and neutrophils in the blood of young females compared to males after vertical transmission with hepatitis C virus (Pembrey et al. 2008). Interestingly, in adult chronic hepatitis C virus infection, males were more likely to have increased fibrosis than females (Poynard et al. 1997) and males with the cytotoxic T lymphoctye antigen-4 haplotype −318C +49A were more likely to have an unfavorable outcome (Schott et al. 2007). This data suggests that the immune response to hepatitis C varies depending on age and whether the infection is acute or chronic. Additionally, genes encoded on the sex chromosomes or skewing of X-chromosomal activation may result in differential immune regulation.

For other viral infections, such as cytomegalovirus (CMV), which is a major cause of brain damage and hearing loss in congenitally infected children (Istas et al. 1995) and the main cause of blindness in AIDS patients (Hoover et al. 1996), there is a higher prevalence of CMV infection in HIV^+ women (Fleming et al. 1993). When the memory T-helper response was examined after stimulus with CMV, in healthy CMV-seropositive men and women, there was a higher frequency of IL-2 responders, higher levels of IL-2 secretion, and an increased frequency of IL-2 secreting cells in women compared to men (Villacres et al. 2004). This data is in concordance with a study of Amish families that showed that there was an increased frequency of antibody responders in females compared to males after serum challenge with CMV antigen (Hsia et al. 1977).

There have also been gender-specific differences noted for Influenza A virus, the common cause of seasonal flu (Taubenberger and Kash 2010). When stimulated with Influenza A virus, men had significantly higher levels of TNF-α compared to women (Villacres et al. 2004). This is in agreement with a recent study that reported an association with male gender and severity of influenza infection leading to hospitalization in children (Quach et al. 2003). Additionally, there have also been a number of studies showing that females have an increased local inflammatory reaction at the injection site after vaccination with various types of influenza vaccines (Cook 2009), suggesting that the female inflammatory response may be more robust than in males, which could explain the increased susceptibility seen in males.

Gender-specific differences in HIV infection also exist. Females without treatment usually have significantly shorter survival times than men (Lemp et al. 1992; Moore et al. 1991; Rothenberg et al. 1987). Almost universally, females also have significantly lower viral loads then men (Anastos et al. 2000; Farzadegan et al. 1998; Rezza et al. 2000; Sterling et al. 1999, 2001). Interestingly, one study found that the differences in viral load between females and males was greatest soon after seroconversion and then diminished over time. This resulted in the convergence of the viral load trajectories of patients and controls within 5–7 years as the viral load in females increased more rapidly than in males (Sterling et al. 1999). This suggests that the viral dynamics between males and females are significantly different.

With respect to whether females show a significant increase in progression to AIDS, there are some disparities. There are studies describing an increase in progression to AIDS in females (Farzadegan et al. 1998; Meier et al. 2009) or an increased risk of death in females (Melnick et al. 1994), while there are a number of other studies showing no difference in progression to AIDS between females and males (Chaisson et al. 1995; Cozzi Lepri et al. 1994; Friedland et al. 1991; Lemp et al. 1992; Melnick et al. 1994; Rothenberg et al. 1987; Turner et al. 1994). These differences may reflect variation in access to health care (Gandhi et al. 2002).

A possible explanation for the observed gender differences in HIV infection may be due to increased immune activation in females compared to males. Females had increased immune activation, as measured by increased CD38 expression on both $CD4^+$ and $CD8^+$ T cells compared to males (Camara et al. 2010; Meier et al. 2009). Levels of CD38 expression are a strong predictor of HIV disease progression (Fahey et al. 1990, 1998; Giorgi et al. 1999; Meier et al. 2009) while immune activation is critical to susceptibility of HIV-1 transmission (Lawn et al. 2001). Subjects with increased immune activation show increased in vitro susceptibility to HIV-1 and higher in vivo replication (Shapira-Nahor et al. 1998; Stanley et al. 1996). This is in line with a study that found that HIV-1 infected females had significantly higher levels of $CD8^+$ T cell activation than males after adjusting for viral load (Meier et al. 2009). The same study found that plasmacytoid dendritic cells from females produce significantly more IFN-α in response to stimulation with HIV-1 derived Toll-like receptor (TLR)7 ligands than plasmacytoid dendritic cells from males (Meier et al. 2009). Since levels of IFN-α are an important prognostic indicator for HIV clinical progression (Eyster et al. 1983; Fahey et al. 1990; Krown et al. 1991; Mildvan et al. 1992), and IFN-α has been shown to up-regulate CD38 expression on $CD8^+$ T cells (Rodriguez et al. 2006), this could explain the increased immune activation and increased mortality in females. Additionally, plasmacytoid dendritic cell function is modulated by progestin (Hughes et al. 2008), suggesting that sex hormones may be able to modulate the ability of plasmacytoid dendritic cells to produce IFN-α in response to TLR7 stimulation.

Another hypothesis to explain the observed gender differences in HIV infection is outlined in the review by Gandhi et al. (2002) and is related to levels of estrogen produced by females since HIV viral loads have been shown to vary with ovulation (Greenblatt et al. 2000). Estrogen also decreases levels of TNF-α (Shanker et al.

Table 1 Gender susceptibility by microbe

Microbe	Species	Susceptibility in males	Susceptibility in females
Bacteria			
Mycobacterium lepraemurium	*Mus musculus*	Yes	
Mycobacterium marinum	*Mus musculus*	Yes	
Mycobacterium intracellulare	*Mus musculus*	Yes	
Treponema pallidum	*Homo sapiens*	Yes	
Borrelia burgdorferi	*Homo sapiens*		Yes
Listeria monocytogenes	*Homo sapiens*		Yes
Vibrio vulnificus	Homo sapiens	Yes	
Vibrio vulnificus	*Rattus norvegicus*	Yes	
Streptococcus pyogenes superantigens	*Mus musculus*		Yes
Salmonella abortus equi LPS	*Mus musculus*	Yes	
Staphylococcus aureus LTA	*Mus musculus*	Yes	
Fungi			
Cryptococcus neoformans	*Mus musculus*	Yes	
Cryptococcus neoformans	*Homo sapiens*	Yes	
Candida albicans	*Homo sapiens*		Yes
Paracoccidioides brasiliensis	*Mus musculus*	Yes	
Paracoccidioides brasiliensis	*Homo sapiens*	Yes	
Parasites			
Shistosoma mansoni	*Homo sapiens*	Yes	
Shistosoma haematobia	*Homo sapiens*	Yes	
Leishmania donovani	*Homo sapiens*	Yes	
Leishmania major	*Mus musculus*		Yes
Leishmania mexicana	*Mus musculus*	Yes	
Leishmania mexicana	*Homo sapiens*	Yes	
Leishmania (*Viannia*) *panamensis*	*Homo sapiens*	Yes	
Leishmania (*Viannia*) *panamensis*	*Mesocricetus auratus*	Yes	
Leishmania (*Viannia*) *guyanensis*	*Mesocricetus auratus*	Yes	
Leishmania tropica	*Homo sapiens*		Yes
Plasmodium chabaudi	*Mus musculus*	Yes	
Plasmodium chabaudi	*Homo sapiens*	Yes	
Taenia solium	*Homo sapiens*		Yes
Taenia crassiceps	*Mus musculus*		Yes
Viruses			
Vesicular stomatitis	*Mus musculus*	Yes	
Lymphocytic choriomeningitis	*Mus musculus*		Yes
Respiratory syncytial	*Homo sapiens*	Yes	
Herpes simplex	*Mus musculus*		Yes
Herpes simplex	*Homo sapiens*		Yes
Hepatitis C	*Homo sapiens*		Yes
Chronic hepatitis C	*Homo sapiens*	Yes	
Cytomegalovirus	*Homo sapiens*		Yes
Influenza A	*Homo sapiens*	Yes	
Human immunodeficiency	*Homo sapiens*		Yes

1994), which directly affects HIV expression (Mellors et al. 1991). Additionally, human lymphocytes express a glucocorticoid receptor that binds progesterone, which has been shown to inhibit CCR5 expression on activated T cells (Vassiliadou et al. 1999). Since CCR5 density is lower in female $CD4^+$ T cells than males (Portales et al. 2001) and there is a strong correlation between HIV load and $CD4^+$ CCR5 density (Reynes et al. 2000), this could explain the lower viral loads in females.

Conclusion

Clearly gender-specific differences in many infections are quite complex, but ultimately whether males or females are more susceptible depends on which microbe is causing the infection (Table 1). This seems to be true whether the infection is caused by bacteria, fungi, parasites, or viruses. Generally, there are more cases where estrogen acts to increase the immune response while testosterone acts to decrease the immune response. Depending on the microbe, this may result in either increased immune responses leading to clearance, immunopathology, or decreased immune responses leading to increased infection. Perhaps the best explanation is that there is an interaction between gender specific immune responses and immune responses to specific microbes.

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