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REVIEW

Sex differences in the incidence and severity of respiratory tract infections

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Summary
Sex is a significant epidemiological factor for several diseases. However, the role of sex in the development and outcome of various infections has not been extensively studied with the notable exception of urinary tract infections. We searched in the PubMed database to identify articles that could provide relevant data regarding sex differences in the incidence and severity of respiratory tract infections (RTIs). We extracted data from 84 relevant studies that provided information regarding sex differences in the incidence and severity of RTIs. Females are more commonly affected with infections of the upper respiratory tract, specifically sinusitis, tonsillitis, and otitis externa. On the other hand, males are more commonly affected with otitis media, croup, and most important, lower RTIs. It is also evident from the reviewed evidence that the course of most RTIs is more severe in males than in females, leading to higher mortality in males, especially in community-acquired pneumonia. In conclusion, the available data suggest that males are more susceptible than females to most types of RTIs in all age groups (adults and children). Overall, it seems that males develop RTIs more frequently than females, except for sinusitis, otitis externa, and probably tonsillitis. Anatomic, lifestyle, behavioural, and socioeconomic differences between males and females may explain the observed findings. The role of sex hormones in the regulation of the immune system may also contribute to the reported sex differences in the incidence and severity of the various types of RTIs, especially in adolescents and adults.

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Introduction

Sex differences in the incidence and severity of various diseases are considered as basic epidemiologic data in most medical fields. However, sex differences in the development and outcome of diseases are poorly understood primarily due to the fact that, during the past, many studies on pathophysiology and disease prevention included only or mainly males. Social factors that are more common in females (including poverty),[1] participation in the work force, lifestyle characteristics such as smoking habits,[2] and socially defined sex roles may in part explain sex differences in morbidity and mortality due to diseases. In addition, biological factors like oestrogen production,[3] cholesterol levels,[4] insulin deficiency or resistance,[5] and obesity[6] also play a significant role in the pathophysiology of several diseases. There is also evidence that women receive different care than men for common chronic disorders, while they make more visits to physicians for acute, self-limited diseases. Nevertheless, females live longer than males in most populations.[7]

Ischemic heart disease, hypertension, immunologically mediated diseases, osteoporosis, diabetes mellitus, psychological disorders, and substance abuse are disorders that are strongly associated with sex.[1] On the other hand, there has not been much discussion regarding the possible sex differences in the incidence and severity of the various infectious diseases, with the notable exception of urinary tract infections. In this article, we sought to review the available evidence in the literature regarding sex differences in the incidence and severity of respiratory tract infections (RTIs) that constitute a major proportion of infectious disease-related morbidity and mortality in humans.

Literature search and study selection

We searched in the PubMed database for studies reporting data regarding sex differences in the incidence and severity of the upper and lower RTIs. Specifically, the keywords we used in our literature searches were "common cold, pharyngitis, laryngitis, croup, tonsillitis, otitis externa, otitis media, mastoiditis, sinusitis, epiglottitis, bronchitis, bronchiolitis, pneumonia, community-acquired pneumonia (CAP), hospital-acquired pneumonia, nosocomial pneumonia (NP), ventilator-acquired pneumonia, lung abscess, pleural effusion, empyema thoracis" combined with "sex or gender".

The abstracts of the initially identified articles were reviewed in order to select the relevant studies for more detailed review. The decision to include a study was based on whether data regarding our topic was mentioned in the abstract. The complete texts of original articles that were relevant to the focus of our review and we were able to identify were read. When several studies were available, only those with the larger population were included in the review. Reviewed studies were limited to those that referred to humans, were written in English, were published between 1983 and September 2006, and included more than 30 patients. An exception to this rule was made if no study regarding a specific RTI or its complications could meet all the above criteria; in such a case we included data from studies with a smaller number of patients. Studies referring to RTIs of both adults and children were included.

Data extraction

Data regarding the first author, year of publication, type of study, study population, focus of study, male/female ratio of occurrence of RTIs, sex differences in the severity of the infections, suggested cause for the observed differences (if any reported), other factors that may influence the incidence and/or severity of RTIs, and the type of analysis were extracted from the reviewed studies and tabulated.

The term "severity of infection" was defined by short-term or long-term mortality for lower RTIs, while it refers to prolonged course, recurrence, persistence, or complications of disease for upper RTIS.

Sex differences in the incidence and severity of RTIs

In Tables 1 and 2, we present data from the reviewed studies regarding sex differences in the incidence and severity of upper and lower RTIs (URTIs[8–38] and LRTIs),[39–91] respectively.

Pharyngitis: There are limited available data regarding sex differences in the incidence of pharyngitis. In one of the two small studies retrieved,[8] both of which refer to children, the incidence of pharyngitis was a little higher in males than females. The second study[9] reported only cases of subclinical pharyngitis, i.e. cases of asymptomatic

Table 1 Sex differences in the incidence and severity of upper respiratory tract infections.

First author, year of publication, reference no.	Type of study; study population	Focus of study	M/F ratio	Severity	Proposed explanation	Other factors/type of analysis
Pharyngitis						
Lin M.H., 2003[8]	Prospective study; Taiwan, 2001–2002; 252 children, 1–15 years	Group A *Streptococcus*; pharyngitis in children	1.29 (142:110)			Age, month of the year
Gupta R., 1992[9]	Prospective study; New Delhi, 1990–1991; 141 children from whom beta-haemolytic streptococci were isolated	Subclinical group-A; streptococcal throat infection in school children	0.39 (Prevalence 15% of the 639 examined boys: 38.9% of the 118 examined girls) ($P<0.001$)			BV
Tonsillitis–peritonsillar abscess						
Kvestad E., 2005[10]	Retrospective study; Norway, 9479 twins born between January 1967 and December 1979	Heritability of recurrent tonsillitis	Significant predominance of female cases of recurrent tonsillitis. 0.62 (prevalence 8.8 in males vs. 14.1% in females)			
Matsuda A., 2002[11]	Retrospective study; Tokyo, 1988–1999; 724 patients	Peritonsillar abscess	2.96 (541:183)			
Thorp M.A., 2000[12]	Retrospective study; Cape Town, 1991–1995; 7250 tonsillectomies, 111 hospital admissions	Tonsillectomy for recurrent tonsillitis and hospital admission for acute tonsillitis	Tonsillectomy patients: overall M/F ratio 0.69 (2970:4280); F/M ratio in patients >14 years, 3.22 95%CI 2.82–3.68. F/M ratio for admission 1.85		Exposure of the mothers to the URTIs of their children, socio-economic factors, differences in immunity	BV
Sinusitis						
Shashy R.G., 2004[13]	Retrospective study; Olmsted County, Minnesota, 2000; 2405 patients	Prevalence of chronic sinusitis	0.48 (778:1627); prevalence per 100,000 1322:2585			
Chen Y., 2003[14]	Cross-sectional study; Canada, 1996–1997; 3768 patients, >12 years	Epidemiology of chronic rhinosinusitis	0.49 (1231:2537); Prevalence 3.4%: 5.7%		Females have smaller ostia. Increased health care-seeking behaviour, subjective sensitivity to symptoms by women	Low income, allergy history. Smoking significantly associated with rhinosinusitis only in females; MV

Table 1 (*continued*)

First author, year of publication, reference no.	Type of study; study population	Focus of study	M/F ratio	Severity	Proposed explanation	Other factors/type of analysis
Stalman W.A.B., 2001[15]	Prospective study, The Netherlands, 1993–1995; 177 patients, 15–65 years	Determinants for the course of acute sinusitis in adult patients		Female sex was a factor predictive of a prolonged clinical course; BV: HR 0.7 $P<0.01$ MV: HR 0.60 95% CI 0.42–0.83	Women are more likely to share their problems or poor outcomes with their GP	Complaints for more than 14 days before inclusion, headache, cold or cough as reason for encounter, absence of cervical adenopathy; BV and MV
Lieu J.E., 2000[16]	Data from a cross-sectional survey; USA, 1988–1994, 5848 patients, >17 years	Sinusitis and tobacco use	0.66 (actual ratio 2315:3533); BV: unadjusted RR for females 1.19 (CI 1.15–1.24); prevalence 24.7%: 33.2% MV: all race-ethnic groups had a higher prevalence with female sex			Race, higher income status, higher educational level, tobacco use. BV and MV
Croup						
Segal A.O., 2005[17]	Retrospective study; Ontario, 1988–2002; 44,820 patients, 0–4 years	Croup hospitalisations	2.26 (31.057:13.763); In children 0–1 years, boys exhibited a relative risk of 2.08 over girls for croup hospitalisations			Seasonality; MV
Osinusi K., 1999[18]	Prospective study; Nigeria, 30-month period; 35 children, 2–53 months	Acute	laryngotracheobronchitis in Nigerian children	1.7 (22:13)		
Denny F.W., 1983[19]	Prospective study; North Carolina, 1964–1975; 951 croup cases in 903 children, 0–15 years	Croup in a paediatric practice	1.43 (between the ages 6–12 months 1.73) Incidence/100 children/ year 1.82:1.27			
Epiglottitis						
Chan K.O., 2001[20]	Retrospective study Singapore, 1992–1999; 32 patients, of whom 31 adults	Acute epiglottitis in the tropics	3 (24:8)	Male sex was significant predictor for airway intervention (P 0.03) (ratio 11:0 with intervention, 13:8 without)		Age (peak in the 3rd decade) Predictors for airway intervention: stridor, presence of airway compromise on examination, ''thumb sign''; BV
Stanley R.E., 1988[21]	Retrospective study; Singapore General Hospital, 1982–1985; 42 patients, >18 years	Acute epiglottitis in adults	7.4 (37:5)			Age (peak in the 6th decade)

Otitis externa						
Battikhi M.N., 2004[22]	Prospective study; Jordan, 2001–2002; 180 patients	Otitis externa	1.25 (100:80)			Seasonality
Rowlands S., 2001[23]	Retrospective study; UK, 1997 40,661 episodes in 30,412 patients, >5 years	Otitis externa in UK	0.89 [(prevalence higher in females (1.30% vs. 1.16%, $P<0.001$) in all age groups up to the age of 65 years]	Disease persistence more common in women (F/M ratio 1.08 $P=0.06$); Recurrent disease more common in men (F/M ratio 0.90 $P=0.001$)	Greater consultation rate in women 15–74 years Excessive hair washing (likely to be more common in females)	Seasonality; Eczema for recurrent disease; MV
Otitis media						
Acute otitis media						
Hotomi M., 2005[24]	Prospective study; Japan, 308 children, 10–86 months, 277 with severe and 31 with non-severe acute otitis media (AOM)	Treatment and outcome of severe and non-severe AOM	1.22 (169:139)	Children with severe disease were more often males (158:119, 57% males with severe vs. 36% males with non-severe AOM, $P<0.05$)		For severe AOM: colonisation with pathogen (vs. no pathogen); MV
Paradise J.L., 1997[25]	Prospective study; Pittsburg, 1991–1995; follow-up until age 2 years, 2253 children	Prevalence and risk factors of OM during the first 2 years of life	1.1 (1180:1073) Proportions of days with middle-ear effusion higher in boys during 1st and 2nd year, $P<0.05$			1st year: socio-economic status, breastfeeding, number of smokers; 2nd year: socio-economic status, child exposure index MV
Recurrent otitis media						
Engel J.A.M., 2005[26]	Prospective study; The Netherlands, 1999–2003; 73 children with recurrent otitis media with effusion (ROME), 2–7 years	Birth characteristics and ROME in children	Positive association between ROME and male sex OR 1.85, 95%CI 0.56–6.13			Low birth weight, low gestational age, history of incubator care, maternal medication use during pregnancy. MV
Luotonen M., 1998[27]	Prospective study; Finland, 891 children with recurrent otitis media episodes before the age of 3 years, examined at the age of 9 years	Otitis media and school achievement		Lower performance in mathematical skills (risk ratios 1.2–1.4, *P* 0.04–0.02) and classroom concentration (RR 1.4 *P* 0.02) for girls, worse reading skills (RR 1.3 *P* 0.05) and oral performance (RR 1.2 *P* 0.01) for boys	Differences between sexes in the spatial functional organisation and metabolism of the brain for language and behavior	MV
Bennett K.E., 1998[28]	Prospective study; UK, all births in 1 week in 1970, 5 years follow-up (over 13,000 births)	Factors influencing children's middle ear disease (recurrent acute otitis media, RAOM, and otitis media with effusion, OME)		Male sex risk factor for hearing difficulty (reflects OME severity and persistence), adjusted OR 1.26, $P=0.001$ and for conjoint hearing difficulty/ear discharge, OR 1.43, $P=0.014$		Mother's smoking habits, day care attendance; MV
Hardy A.M., 1993[29]	Cross-sectional study; US; children <6 years	Child care arrangements and	1.2 (percentages of children with repeated			Age, race, medical history (repeated tonsillitis, enlarged

Table 1 (*continued*)

First author, year of publication, reference no.	Type of study; study population	Focus of study	M/F ratio	Severity	Proposed explanation	Other factors/type of analysis
	old; 1005 children with repeated ear infections in the previous year	repeated ear infections	ear infections in the past year 18%: 15%); OR 1.3 95% CI 1.1–1.5			adenoids, asthma, day care attendance); MV
Otitis media with effusion						
Apostolopoulos K., 1998[30]	Prospective study; Greece, 1996; 332 children, 6–12 years with otitis media with effusion (OME)	The point prevalence of OME among school children	1.4 (194:138); BV analysis: statistically significant relationship between OME and sex, $P<0.028$		Defected pneumatisation of the mastoid process in boys	Age, mother's education, parental smoking, breastfeeding, allergy, previous OM; BV
Chronic otitis media						
Vartiainen E., 1998[31]	Retrospective study; Finland, 1976–1995; 1123 patients operated for chronic OM or its sequels	Changes in the clinical presentation of chronic OM from the 1970s to the 1990s	1.32 (638:485); Male predominance most remarkable among patients with cholesteatoma (64% during 1976–1985, 66% during 1986–1995)		Boys are more prone to acute OM	
Alho O.P., 1995[32]	Retrospective birth cohort with a 2-year follow-up; Finland, births between July 1985 and June 1986 94 children with chronic otitis media with effusion (COME)	Risk factors for COME in infancy	Male sex risk factor for COME OR 2.17, 95%CI 1.37–5.44			Previous acute otitis media, attendance at a day nursery, autumn season MV
Shamboul K.M., 1992[33]	Prospective study; Saudi Arabia, 1988–1989; 117 patients with chronic suppurative otitis media (CSOM)	An unusual prevalence of complications of CSOM in young adults	1.72 (74:43)	Complications of CSOM: female predominance (1:2) (brain abscess, lateral sinus thrombosis, facial palsies)	Late presentation of females because of social reasons or undue susceptibility to the destructive effect of cholesteatoma (abnormal bone metabolism due to low levels of plasma vit. D)	
Mastoiditis						
Spartley J., 2000[34]	Retrospective study; Portugal, 1993–1998; 43 patients	Acute mastoiditis in children	2.31 (30:13)			Age, race, medical history (repeated tonsillitis, enlarged adenoids), day care attendance
Intracranial complications of URTIs						
Quraishi H., 2006[35]	Retrospective study; USA, 1996–2004; 12 patients, <18 years	Intracranial complications of sinusitis in the paediatric population	5 (10:2)			

Kurien M., 1998[36]	Prospective study; India, 1990–1996; 36 patients	Otogenic intracranial abscess	Children: 2.03:1 (67% males); adults: 4:1 (80% males)		
Rosenfeld E.A., 1994[37]	Retrospective study; Chicago, 1980–1992; 9 patients	Infectious intracranial complications of sinusitis in children (abscesses)	3.5 (7:2)		Age (89% >9 years);
Nunez D.A., 1990[38]	Retrospective study; Scotland, 1976–85; 41 patients	Risk of developing an otogenic intracranial abscess	3. $P<0.01$; older males (>40 years) appear to be more at risk		BV

BV: bivariate analysis, CI: confidence interval, F: female, HR: hazard ratio, M: male, MV: multivariate analysis, OR: odds ratio, RR: risk ratio, URTIs: upper respiratory tract infections.

Table 2 Sex differences in the incidence and severity of lower respiratory tract infections.

First author, year of publication	Type of study, study population	Focus of study	M/F ratio	Severity	Proposed explanations	Risk factors/type of analysis
Bronchiolitis						
Nagayama Y., 2006[39]	Prospective study; Japan, 1988–2002; 141 children, < 1year with a first episode	Sex analysis in acute bronchiolitis due to *RSV*	1.76 (90:51); WBC counts and serum CRP levels at acute stage higher in girls ($P<0.05$). Sputum eosinophilia in boys (6/42) exclusively		Sex hormones	BV
Papadopoulos N., 2004[40]	Prospective study; Greece; 81 infants; 0.5–12 months; hospitalised for *RSV* bronchiolitis	*RSV* subtype and severity of acute bronchiolitis in hospitalised infants	1.25 (45:36)	Boys had more severe disease than girls ($P = 0.007$)		More severe disease in infants <3 months and in infants infected with *RSV* subtype A; BV
Lowther S.A., 2000[41]	Retrospective study; Indian Health Service hospital records, 1990–1995; 7641 bronchiolitis-associated hospitalisations, 0–4 years	Bronchiolitis-associated hospitalisations among American Indian and Alaska Native children	1.36 (Hospitalisation rate per 1000 population 12.9:9.5) Hospitalisations higher among males, 4453:3188			
Gupta R., 1996[42]	Retrospective study; Scotland, 1982–1990; 10,058 hospital admissions for bronchiolitis	Sudden infant death syndrome and bronchiolitis	1.6 (6177: 3881)		Peripheral airways disproportionately narrow in the early years of life, more marked in males	
CAP						
Thomsen R.W., 2006[43]	Prospective study Denmark, 1994–2004; 41,793 patients >15 years with a first-time hospitalisation with pneumonia	Hospitalised pneumonia in Denmark	1.12 (53% of the patients were male); Overall incidence rates: 20% higher in men than women, and amongst persons >65 years 50–100% higher in men.	Adjusted mortality rate ratios: 1.15 (95% CI 1.10–1.21) for 30-day mortality and 1.19 (95% CI 1.14–1.24) for 90-day mortality	Socio-economic and lifestyle-related risk factors	For incidence: age For mortality: age, comorbidity; MV
O'Meara E.S., 2005[44]	Prospective study; USA, 1989–1993, follow-up for 10 years; 582 patients, >65 years	Hospitalisation for pneumonia in community-dwelling older adults	287:295; 1.47 (rate per 1000 person-years 13.7:9.3); male sex risk factor for hospitalisation for pneumonia, RR 1.96, 95% CI 1.59–2.42, $P<0.001$ (related to the control population)			Age, comorbidity, lower FEV-1, smoking, DM MV
Vrbova L., 2005[45]	Retrospective study; Ontario, 1995–2001; 60,457 patients, >65 years	Socioeconomic status and mortality subsequent to admission for CAP		Women had lower odds of dying for both 30-day (OR 0.78 $P<0.0001$) and 1 year mortality (OR 0.68 $P<0.0001$)		Age, comorbidity; MV

Marrie T.J., 2005[46]	Prospective study; Canada, 2000–2002; 3065 low-risk patients with CAP	Low-risk patients admitted with CAP	0.96 (1498:1567 patients with CAP) hospitalised 240:346, OR (female vs. male) 1.34 95% CI 1.06–1.69 $P = 0.015$			Respiratory rate, substance abuse, psychiatric illness, comorbidities, site of care; MV
Jackson M.L., 2004[47]	Retrospective study; Washington, 1998–2001; patients >65 years; 1266 patients with hospitalisation for CAP and 1881 with outpatient visits for CAP	The burden of CAP in seniors	1.25 (no. of cases of CAP per 1000 person-years 32.2:25.6) Male sex: HR 1.23 (95%CI 1.15–1.33)(all CAP) 1.34 (hospitalisations for CAP), 1.19 (outpatient visits)			Age, current smoking, DM, congestive heart failure, lung cancer, COPD; MV
Marrie T.J., 2003[48]	Retrospective study; Canada, 1991–1999 11,684 hospitalisations among 10,466 patients, 18–55 years	Factors associated with death among adults <55 years hospitalised for CAP	0.93 (5640:6044 patients hospitalised for CAP)	Male sex risk factor for CAP-associated death: Overall deaths 152 females: 224 males (F/M OR 0.7). During the 10 days of hospitalisation F/M OR 0.64		Urban residence, aspiration CAP, comorbidity, age, bigger hospitals; MV
Aliyu Z.A., 2003[49]	Retrospective analysis; Maryland, Jan–Dec 2000; 296 patients, 18–49 years	Determinants for hospitalisation in low-risk CAP	Females 2.94 times more likely to be admitted than males $P = 0.0018$; (82% f vs. 18%m hospitalised, 61%f vs. 39%m discharged)		Women are more likely to rate their health poor and accept hospitalisation	Race, insurance coverage, temperature, pulse rate BV
Mortensen E.M., 2003[50]	Prospective study; USA, 1991–1994; 1419 of 1555 pneumonia patients survived for >90 days	Assessment of mortality after long-term follow-up of patients with CAP		Male sex significantly associated with long-term mortality. 63% of males: 70.2% of females survived. Male sex: HR 1.5 95% CI 1.2–1.8		Age, do-not-resuscitate orders, poor nutritional status, comorbid illnesses, lack of feverishness, nursing home residence; MV
Kaplan V., 2002[51]	Retrospective study USA, 1997; 623,718 cases >65 years	Hospitalised CAP in the elderly	1.2 (incidence rate 19.4 vs. 15.6 cases per 1000 population, $P<0.001$), actual numbers; 289,249(46.4%): 334,469(53.6%)	Men had higher mortality, 11.6% vs. 9.8%, $P<0.001$, adjusted OR 1.15. Men more likely to suffer from gram-negative infections (14.3% vs. 11.5%, $P<0.001$); Men were more likely to have a complex course (24.4% vs. 20.8%, $P<0.001$)	Biological factors, differences in the access to care, sex bias in the admission decision.	Factors for mortality: age, residence in a nursing home, comorbidity. MV
Baine W.B., 2001[52]	Retrospective study; USA, 1991–1998; 273,143 pneumonia hospitalisations, patients, >65 years	Hospitalisation of elderly Medicare patients for pneumonia	Age-adjusted discharge rates for men invariably exceeded those for women (e.g., Pneumonia, organism unspecified: annual hospital discharges per 100,000 persons 65–89 years: 1311 m vs. 884f for black race ($P<0.001$) and 1293 m vs. 920f for white ($P<0.001$)		Male sex is risk factor for cigarette smoking in elderly Americans	Age, race; BV

Table 2 (*continued*)

First author, year of publication	Type of study, study population	Focus of study	M/F ratio	Severity	Proposed explanations	Risk factors/type of analysis
Akbar D.H., 2001[53]	Retrospective study; Saudi Arabia, 1998–1999; 354 pneumonia (CAP and HAP) patients of whom 125 diabetics	Bacterial pneumonia, comparison between diabetics and non-diabetics	3:1 in diabetics vs. 1.2:1 in non-diabetics, $P<0.001$			
Georges H., 1999[54]	Retrospective, 1987–1992, and prospective study, 1993–1995; ICUs in France; 505 patients with severe CAP, 137 of whom with pneumococcal CAP	Prognosis of severe community-acquired pneumococcal pneumonia	1.97 (335:170 with severe CAP) Male sex was independently predictive of pneumococcal pneumonia, 3.03 (103:34 patients), $P = 0.01$;			Lack of antimicrobial agents before ICU admission, septic shock, non-aspiration pneumonia MV
Gordon H.S., 1999[55]	Retrospective study 30 hospitals in Northeast Ohio, 1991–1993; 17,982 pneumonia patients	The relationship of sex and in-hospital death for 6 common nonsurgical diagnoses		Death rates higher in men than women for pneumonia (OR 1.16 95%CI 1.02–1.32 *P* 0.002)	Higher prevalence of unmeasured risk factors in men; sex-related variation in the utilisation of hospital services; biological differences	MV
Watanakunakorn C., 1997[56]	Retrospective study; Ohio, 1992–1996; 108 patients (no HAP)	Adult bacteremic pneumococcal pneumonia	0.69 (44:64)			
Hedlund J., 1997[57]	Prospective study; Sweden, 1991–1995; 653 patients, 50–85 years	Recurrence of pneumonia after hospital treated CAP, aetiology and predisposing conditions	0.92 (313:340)	Male sex significantly associated with higher mortality (HR 2.71 95% CI 1.48–4.94 $P = 0.01$)		Age, congestive heart failure, other chronic diseases; MV
Jokinen C., 1993[58]	Prospective and retrospective study; Finland, 1981–1982; 546 cases in 543 persons	Incidence of CAP in Finland	1.45 (323:223), the male predominance particularly strong among children <5 years and the elderly; incidence per 1000 inhabitants per year: 13.9 in males, 9.4 in females	Mortality higher in men aged >60 years than in women of the same age (mortality per 1000 inhabitants per year >60 years: 4.4 for males, 0.8 for females)		
Nursing-home acquired pneumonia						
Sund-Levander M., 2003[59]	Prospective study; Sweden, 2000–2001; 32 patients with pneumonia, >66 years	Nursing-home-acquired pneumonia in a Swedish population	OR 3.2 $P<0.05$; (males 16/78, females 16/156)			COPD, ADL status (activities of daily living) MV

Hutt E, 2002[60]	Retrospective study USA; 124 patients with pneumonia during 1994	Precipitants of emergency room visits and acute hospitalisation in short-stay Medicare nursing-home residents	Males had increased odds for hospitalisation for pneumonia; OR 2.74 95% CI 1.10–6.87 $P<0.005$			Do not resuscitate orders negatively associated with hospitalisation; Comorbid congestive heart failure positively associated; MV
Loeb M., 1999[61]	Prospective study; Ontario, 1993–1996; 155 episodes of pneumonia in 113 residents	Risk factors for pneumonia and other LRTIs in elderly residents of long-term care facilities	Male sex risk factor for pneumonia OR 1.9 95% CI 1.1–3.5 $P=0.03$			Age, swallowing difficulty, inability to take oral medication, influenzae vaccination (protective); MV
Nosocomial pneumonia						
Sopena N., 2005[62]	Prospective study; Spain, 1999–2000; 165 patients	Multicenter study of HAP in non-ICU patients	2.37 (116:49)			Comorbidity, antibiotic therapy, histamine type 2 blockers, steroids, antacids, thoracic surgery
Gastmeier P., 2005[63]	Surveillance study; ICUs in Germany, 1997–2002; 1851 patients with *S. aureus* pneumonia	Nosocomial *Staphylococcus aureus* infections in ICUs	1.84 (64.8%: 35.2%)			MV
Lee S.C., 2005[64]	Surveillance study; Taiwan, 1999–2000; 132 patients with nosocomial pneumonia	Risk factors of mortality for nosocomial pneumonia	2.38 (93:39)			
Napolitano L.M., 2001[65]	Prospective study; Maryland, 1983–1995; 848 patients with pneumonia after blunt trauma, 18–65 years	Sex differences in adverse outcomes after blunt trauma	4.1 (61:15) in the age 45–65 years and ISS >30 subgroup. Males had a higher incidence of pneumonia, with the strongest association in the age 45–65 years and ISS >30 subgroup ($P<0.01$)	Females with pneumonia were at significantly higher risk for mortality (in the 18–45 years–ISS 15–29 subgroup OR 2.76, in the 46–65 years-ISS >30 2001 subgroup OR 5.58)	Sex hormones may play an important role in the regulation of post-traumatic immunosuppression	For the incidence or pneumonia: age, ISS; MV
Arozullah A.M, 2001[66]	Prospective study Veterans Affairs medical centres, 1997–1999; 2466 patients with postoperative pneumonia of 160,805 undergoing major surgery	Predicting postoperative pneumonia after major noncardiac surgery	2411:55 (98% men) of the study group (95% men) had postoperative pneumonia $P<0.001$			BV
Vanhems P., 2000[67]	Surveillance study; ICUs in France, 1994–1996; 628 patients with nosocomial pulmonary infection (NPI)	NPI by antimicrobial-resistant bacteria of patients hospitalised in ICUs	2.39 (443:185)			BV

Table 2 (*continued*)

First author, year of publication	Type of study, study population	Focus of study	M/F ratio	Severity	Proposed explanations	Risk factors/type of analysis
Crabtree T.D., 1999[68]	Prospective study Virginia, 1996–1999; 892 patients in the surgical units with 1470 infectious episodes—326 pneumonia patients	The role of sex among hospitalised patients treated for infection	1.69 (205:121)	Mortality higher in women (men 18%-women 34%, *P* 0.002) Multivariate: female sex risk factor for mortality due to pneumonia (OR for death 2.25 95%CI 1.17–4.32 *P* 0.02)	Intrinsic sex differences in the pathogenesis of disease and the host's response to infection; Difference in respiratory tract colonisation in critically ill patients	For pneumonia-associated mortality: increased APACHE II score, preexisting malignancy, DM, time from admission to diagnosis of infection of >7 days, organ transplantation, increased age; MV
Kropec A., 1996[69]	Prospective study; Germany, 1991–1993 129 patients >18 years with NP	Nosocomial pneumonia (NP) in ICUs	Male sex risk factor for NP; RR 2.7 95% CI 1.2–6.3 *P* 0.021			No infection on admission, thorax drainage, antacids, urgent surgery, neurological diseases; MV
Gomez J., 1995[70]	Retrospective case-control study; Spain, 1989–1993; 104 patients with NP	Risk factors and prognosis in non-ventilated patients with nosocomial pneumonia	56:48 vs. 76:28 in the control group [female sex risk factor for NP ($P = 0.01$)]			Hospital stay >14 days, other admission in the previous month, use of antibiotics during the previous 6 months; BV
Carratala J., 1994[71]	Prospective surveillance study; Spain, 1985–1990; 286 patients with nosocomial pneumonia	Risk factors for nosocomial *Legionella pneumophila* pneumonia	4.2 (231:55 patients with nosocomial pneumonia)			
Leu H.S., 1989[72]	Surveillance study; Virginia, 1979–1983; 890 patients with nosocomial pneumonia	Hospital-acquired pneumonia	1.87 (580:310)			
VAP						
Shorr A.F., 2004[73]	Prospective study; ICUs at USA, 2000–2001; 311 patients with VAP	VAP and red blood cell transfusion	1.99 (66.6% 33.4%); OR 1.54 (95%CI 1.15–2.07), $P = 0.0042$;			Total parenteral nutrition, red blood cell transfusion, admission after trauma, continuous sedation; MV
Bornstain C., 2004[74]	Prospective study France, 1998–2000; 80 patients, >16 years	Early-onset VAP	Male sex risk factor for VAP; OR 2.06 95%CI 1.18–3.63 *P* 0.0034			Logistic organ dysfunction score at day 2, actual GCS value, use of sucralfate MV
Rello J., 2002[75]	Retrospective study; ICUs at USA, 1998–1999; 842 patients with VAP	VAP in a large US database	1/79 (540: 302); OR 1.58, $P<0.001$		Male sex may be marker for other risk factors that predispose patients to either colonisation with pathogenic bacteria or aspiration	Admission after trauma, severity of illness on admission MV

Cook D.J., 1998[76]	Prospective study; ICUs in Canada 177 patients with VAP	Risk factors for VAP in critically ill patients	2 (118:59); Male sex risk factor for VAP, RR 1.43 (95% CI 1.05–1.96) *P* 0.02	Age, primary admitting diagnosis, location before ICU admission (emergency department), absence of exposure to antibiotics, low GCS score, aspiration. BV
Kollef M.H., 1997[77]	Prospective study; St. Louis, Mar–Jul 1996; 77 VAP patients	Patient transport from ICU increases the risk of developing VAP	1.96 (51:26); Adjusted OR 2.02 95% CI 1.50–2.71 *P* 0.017	Transport out of the ICU, reintubation, tracheostomy, administration of aerosols; MV
Papazian L., 1996[78]	Prospective case-control study; ICU in France, 1989–1993; 85 patients with VAP	Effect of VAP on mortality and morbidity	2.04 (57:28)	
Rello J., 1993[79]	Prospective study; ICU at Spain; 129 VAP patients	Impact of previous antimicrobial therapy on the aetiology and outcome of VAP	2.4 (91:38)	BV
Rello J., 1992[80]	Prospective study ICU at Spain, 1988–1990; 91 patients with VAP	Pneumonia due to *Haemophilus influenzae* among mechanically ventilated patients	2.25 (63:28 patients with VAP)	
Aspiration pneumonia				
Isbister G.K., 2004[81]	Retrospective study; Australia, 1997–2002; 71 patients	Aspiration pneumonitis (AP) in an overdose population	1.56; (61% of patients with AP were men, compared with 39% of overdose patients without AP being men, $P<0.001$). Female sex associated with a decreased risk for AP, OR 0.49 95% CI 0.29–0.82	Age, GCS, emesis, seizure, tricyclic antidepressants co-ingestion; MV
Aslanyan S., 2004[82]	Prospective study; Multicenter 198 patients developed aspiration pneumonia	Pneumonia and UTIs after acute ischaemic stroke	Male sex risk factor for aspiration pneumonia; OR 1.71 95% CI 1.22–2.39	Higher baseline National Institute of Health Stroke Scale, age, history of diabetes, stroke subtype; MV
Kozlow J.H., 2003[83]	Retrospective study; Maryland, 1999–2000; 2636 patients with AP	Aspiration pneumonia (AP) in patients undergoing surgery	Male sex risk factor for AP, OR (for females) 0.5 95% CI 0.5–0.6	Age, race, admission from the emergency room, dementia, COPD, DM, renal disease; MV
Lung abscess				
Hagan J.L., 1983[84]	Retrospective study; Hospital of University of Mississippi; 1960–1982; 184 cases	Lung abscess	4.26 (149:35)	Proximal obstructive carcinoma, alcoholism, DM, seizure disorders, post-traumatic; BV
Empyema thoracis				
Hacimustafaoglou M., 2006[85]	Prospective study; Turkey; 80 children >2 months with parapneumonic effusion	Evaluation of parapneumonic effusion in childhood	1.42 (47/33)	BV

Table 2 (*continued*)

First author, year of publication	Type of study, study population	Focus of study	M/F ratio	Severity	Proposed explanations	Risk factors/type of analysis
Angelillo-Mackinlay T.A., 1996[86]	Retrospective (1985–1991) and prospective (1992–1994) study; Argentina; 64 patients	Loculated post pneumonia empyema	2.04 (43:21)			BV
Fajardo J.E., 1987[87]	Retrospective study; USA, Military Hospitals, 1978–1982; 104 patients 0–18 years	Pleural empyema in children (nontuberculous)	2.15 (71:33)	Mortality (8 patients) 6:2		Predisposing factors: pneumonia, multiple trauma, leukaemia, severe burns
LRTIs						
Hak E., 2004[88]	Retrospective study; The Netherlands, 1998–2000; 455 patients >60 years with a first LRTI episode	Community-acquired LRTIs among the elderly, factors for serious morbidity and mortality	0.82 (45%: 55%);	Male sex risk factor for serious morbidity and mortality, OR 3.12 95% CI 1.66–5.87 $P<0.001$	There is not valid information on smoking behaviour of the patients	Age, heart failure, dementia/ stroke, antidepressants, diagnosis pneumonia; MV
Lovering A.M., 2001[89]	Prospective study; UK, 1994–1996; 704 LRTI episodes in 613 patients	Patients hospitalised for LRTIs	Hospital stays in days significantly longer for men (16.1 for men: 12.6 for women)			Marital status, diabetic status, type of infection; MV
Dharmage S.C., 1996[90]	Case control study; Sri Lanka; 100 patients <5 years	Risk factors of acute LRTIs in children (lobar pneumonia, bronchopneumonia, bronchiolitis)	Male sex increased the risk of acute LRTI, OR 2.5 $P = 0.04$			History of wheezing, low birth weight, passive smoking, delivery by caesarean section; MV
Kofteridis D.P., 2004[91]	Prevalence study-cross sectional; Greece, 1999 and 2000; 200 nos. LRTIs	Nosocomial LRTIs in 14 Greek hospitals	Male gender risk factor OR 1.37 95% CI 1.03–1.83 $P<0.05$			Age, mechanical ventilation, intratracheal tube, tracheostomy; MV

APACHE: acute physiology and chronic health evaluation, BV: bivariate analysis, CAP: community-acquired pneumonia, CI: confidence interval, COPD: chronic obstructive pulmonary disease, DM: diabetes mellitus, F: female, GCS: Glasgow Coma Scale, HR: hazard ratio, ICU: intensive care unit, ISS: injurie severity score, LRTIs: lower respiratory tract infections, M: male, MV: multivariate analysis, NP: nosocomial pneumonia, OR: odds ratio, RR: risk ratio, VAP: ventilator-associated pneumonia.

children who had beta haemolytic streptococci isolated from the throat.

Tonsillitis: No study is available regarding the incidence of a first episode tonsillitis. On the other hand, the data regarding the course, severity, and complications of tonsillitis are contradictory. Thus, females seem to suffer more episodes of recurrent tonsillitis[10] and therefore undergo more tonsillectomies.[12] On the other hand, males seem to suffer more episodes of peritonsillar abscesses.[11]

Sinusitis: Data on both acute and chronic sinusitis are available. It seems that both entities are more prevalent in females.[13,14,16] The clinical course of the disease also seems to be longer in females.[15]

Croup and epiglottitis: The studies regarding croup include children, whereas those regarding epiglottitis include adult patients. A large retrospective study on hospitalised children with croup[17] reported that male patients were significantly more than female patients (69.3% of all hospitalisations for croup were males). Although age was also a significant factor for acquisition of croup, males suffered more episodes of the infection in both studied age groups (children 0–1 and 1–4 years old). On the other hand, there are limited data regarding sex differences on the development and severity of epiglottitis. However, the two retrieved studies[20,21] reported that epiglottitis was more common in males.

Otitis externa, otitis media and mastoiditis: Two studies[22,23] were available for patients with otitis externa. The results of the bigger one[23] (approximately 30,000 patients) suggest that otitis externa is more common in females. In addition, persistent infection was marginally more common in females ($P = 0.06$), but males exhibited more episodes of recurrent infection ($P = 0.001$). On the other hand, the incidence of otitis media was higher in males in all the available studies, all but two of which include children populations.[24–33] This was evident for both acute and chronic form of the infection. These studies also suggest that male sex is also a risk factor for more severe infection, more episodes of recurrent acute otitis media, and higher probability for transition to chronic disease. Finally, limited data are available for sex differences in patients with mastoiditis; the single available study[34] reported that the male to female ratio for this infection was 2.31 in children.

Intracranial complications of URTIs: Four studies[35–38] reported outcomes of intracranial complications of URTIs. All four of them included a small number of patients. However, all of them reported that these complications were more common in males than in females. The male to female ratio in these studies ranged from 2 to 5.

Bronchiolitis: Children between 0 and 4 years were enrolled in the available studies[39–42] that examined the prevalence and severity of bronchiolitis. The data from these studies suggest that bronchiolitis is more frequent in boys than in girls. Boys were also more commonly hospitalised than girls.[41] A small study that enrolled infants also concluded that the disease was more severe in males.[40]

Community-acquired pneumonia (*CAP*): Several studies[43–58] were performed regarding the potential risk factors for development of CAP. Most of them enrolled hospitalised patients. In most of these studies (and especially in the larger ones), men were statistically more frequently enrolled and in some of them male sex was a risk factor for CAP or hospitalisation for CAP. Moreover, a study showed that diabetic males are at increased risk for acquisition of CAP than diabetic females, while this was not so evident between non-diabetic males and females.[53] In addition, male sex was a predictor of worse outcome in terms of duration of hospitalisation, more complex course of CAP, and mortality. Interestingly, more women were enrolled and/or hospitalised more frequently in studies that were performed on patients with milder cases of CAP.[46,49]

Nursing home-acquired pneumonia (*NHAP*): Three studies were available for nursing home residents. Two of these studies reported that male sex was a risk factor for development of NHAP.[59,61] The third study reported that males were more commonly hospitalised for this condition.[60]

Nosocomial pneumonia (*NP*): Several studies[62–72] examined the factors that are associated with development and outcome of NP. In almost all of them NP developed more frequently in men, while several studies also reported that male sex was a risk factor for development of NP. The study by Arozullah et al.[66] was conducted in military hospitals and therefore enrolled 98% men. The male to female ratio regarding NP in this study was 2.19. Interestingly, the outcomes of one single study[70] were exactly the opposite; female sex was the risk factor for development of NP. On the other hand, two studies[65,68] that studied predictors of mortality in patients with NP reported that female sex was an independent risk factor for mortality.

Ventilator-associated pneumonia (*VAP*): Several studies[73–80] were designed to identify factors that are associated with the development of VAP and the available data suggest that males develop VAP more frequently than females. Some of these studies also reported that male sex was a risk factor for VAP. Unfortunately, no data are available regarding the severity of VAP (in terms of mortality or duration of hospitalisation due to VAP) according to males and females.

Aspiration pneumonia (*AP*): The role of sex for the development of AP was studied in different patient populations (patients with stroke, patients undergoing surgery).[81–83] However, all of these studies concluded that male sex is a risk factor for the development of AP.

Lung abscess and empyema thoracis: The single available study[84] suggested that lung abscess develops more often in men than in women. The studies that examined patients with empyema thoracis[85–87] came up to the same conclusions.

Evaluation of the reviewed evidence

Overall, the available data suggest that males develop RTIs more frequently than females, except for sinusitis, otitis externa, and probably tonsillitis. In addition, male sex was frequently found to be a risk factor (and for specific infections like CAP a significant risk factor) for the development of RTIs. Moreover, the available data suggest that male sex is not only a predictor of worse outcome for CAP (as concluded in the meta-analysis by Fine et al.[92]) but also for several other RTIs. The available data also suggest that the higher prevalence of RTIs in males is more obvious

for the devastating and life-threatening infections like pneumonia (CAP, NP, and VAP) and croup. On the contrary, mortality of NP is higher in females. Finally, it seems that the intracranial complications of the URTIs are probably commoner in males than in females.

Possible explanatory mechanisms of the observed differences

It should be mentioned that in trying to investigate the role of sex in the incidence and severity RTIs, population-based studies might be less susceptible to various sources of biases, including selection bias. We think that several factors may play a role in the development and the course of RTIs. Anatomic differences of the respiratory tract may partially explain the different prevalence of specific infections between males and females. More specifically, females have smaller ostia of the paranasal sinuses and therefore may be more susceptible to sinusitis.[14] On the other hand, the defected pneumatisation of the mastoid process may explain the more frequent and severe ear infections in male children.[30] There is also evidence that the peripheral airways are disproportionately narrower during the early years of life in males, which may predispose for lower RTIs.[42]

Several socioeconomic and behavioural factors probably also play a role in the development of infections and may partially explain the observed differences.[93] A significant proportion of women work in low salary, part-time, non-union jobs that do not provide health insurance. Moreover, a lot of them lose their health insurance after a divorce or the death of their husband. The available evidence suggest that currently almost one-third of the families headed by women in the United States live in poverty; and the fraction is higher for African-American women and women of Latin origin.[7] These economic differences can either explain the observed variations in the development of RTIs or give rise to false conclusions. In the first case, the access to health care is limited for women who live in poverty and therefore the probability for enrolment to studies becomes smaller. In the second case, poverty is associated with poor hygiene, limited knowledge of and access to disease prevention (vaccination and transmission) and thus, higher probability of exposure to infectious micro-organisms.

In addition, lifestyle factors, for example, smoking is a habit that is more common in males, although the prevalence in women rises continuously.[94–96] Smoking is associated with several diseases of the respiratory tract (e.g. cancer, chronic obstructive pulmonary disease, etc.) that predispose to infections. In addition, smoking activates a process that destroys the epithelium of the upper airways, a fact that eliminates the normal washout of potential pathogens.

Socially defined sex roles can also provide explanation for the findings. The perception of disease severity is different between males and females. Women may seek more easily health care for mild diseases, such as tonsillitis and pharyngitis, which can explain the higher prevalence of these diseases in females. Furthermore, women traditionally tend to spend more time than men with their children, thus exposing themselves to the URTIs that are commonly found in children.

Special attention should be paid to biological differences and mainly to sex hormones. Steroid sex hormones are responsible for a variety of actions during the activation of the immune system. In general, estrogens at physiological concentrations are thought to play an immune-stimulating role by upregulating both cellular and humoral immunity, whereas androgens have an anti-inflammatory impact.[97] Most of the available data on this issue come from patients with autoimmune diseases. In both sexes, adrenal hormones, that is, glucocorticoids, dehydroepiandrosterone (DHEA), and androgens, are inadequately low in patients with autoimmune diseases when compared to healthy controls.[98] In addition, female animals appear to have more vigorous immune response.[7] In humans, the administration of 17β-estradiol stabilises or increases immune stimuli-induced secretion of TNF, IL-2, IL-4, IL-6, IL-10, and IFNγ from the peripheral blood leucocytes of healthy males in relation to testosterone. Testosterone, in contrast, inhibits (IL-2, IL-4, IL-10) or tends to inhibit stimulated secretion of these cytokines (TNF, IFNγ).[97]

Although these differences in circulating sex hormones could explain (at least in part) the reported differences in the incidence and severity of RTIs between males and females, the apparent differences between boys and girls remain without an answer, since the role and the concentration of sex hormones are not so prominent in the early years of life. Another fact that may question the findings is that several chronic diseases like diabetes mellitus or autoimmune diseases, and chronic conditions like obesity that compromise the function of the immune system are more commonly found in women. Although the epidemiology of cancer and other chronic diseases of the respiratory tract have changed during the last decades (mainly as a consequence of smoking habits and exposure to air pollutants), their role should also be significant in the development and outcome of RTIs.

Limitations in interpreting the reviewed evidence

It should be acknowledged that there are various sources of limitations in interpreting the findings of this review. The studies included in our review used various methodologies. In addition, the source of the study populations was not always clarified. It should also be mentioned that someone could have used a different scheme for the classification of the infections in URTIs and LRTIs; although the glottis is anatomically considered the point of separation between the upper and lower respiratory tract, we classified croup in the URTIs as it is done in most infectious diseases textbooks. Another noteworthy limitation in the interpretation of the findings of our review is that the studies included in our article were heterogeneous to some degree regarding disease definitions, geographical differences, and the age of study populations.

Conclusion

There are significant sex differences in the development, course, and outcome of RTIs. Compared to females, males seem to suffer more commonly from most types of RTIs.

In addition, most RTIs take a more severe course in males, leading to higher mortality. Clinicians should be aware of these differences and take them under consideration when managing patients with RTIs, for example by being alert to diagnose an intracranial complication, which seems to be more often in males, after a URTI episode, or when treating patients with CAP they should keep in mind the higher mortality of male patients. Also, it seems prudent that future studies on the incidence and severity of RTIs should pay more attention to a traditionally important epidemiological characteristic of patients: the sex.

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