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SPECIAL ARTICLE

SARS-CoV-2 and *Chlamydia pneumoniae* co-infection: A review of the literature

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Abstract Bacterial co-pathogens are commonly identified in viral respiratory infections and are important causes of morbid-mortality. The prevalence of *Chlamydia (C.) pneumoniae* infection in patients infected with SARS-CoV-2 has not been sufficiently studied. The objective of the present review was to describe the prevalence of *C. pneumoniae* in patients with coronavirus disease 2019 (COVID-19). A search in MEDLINE and Google Scholar databases for English language literature published between January 2020 and August 2021 was performed. Studies evaluating patients with confirmed COVID-19 and reporting the simultaneous detection of *C. pneumoniae* were included. Eleven articles were included in the systematic review (5 case cross-sectional studies and 6 retrospective studies). A total of 18 450 patients were included in the eleven studies. The detection of laboratory-confirmed *C. pneumoniae* infection varied between 1.78 and 71.4% of the total number of co-infections. The median age of patients ranged from 35 to 71 years old and 65% were male. Most of the studies reported one or more pre-existing comorbidities and the majority of the patients presented with fever, cough and

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dyspnea. Lymphopenia and eosinopenia were described in COVID-19 co-infected patients. The main chest CT scan showed a ground glass density shadow, consolidation and bilateral pneumonia. Most patients received empirical antibiotics. Bacterial co-infection was not associated with increased ICU admission and mortality. Despite frequent prescription of broad-spectrum empirical antimicrobials in patients with coronavirus 2-associated respiratory infections, there is a paucity of data to support the association with respiratory bacterial co-infection. Prospective evidence generation to support the development of an antimicrobial policy and appropriate stewardship interventions specific for the COVID-19 pandemic are urgently required.

PALABRAS CLAVE
Infección por SARS-CoV-2;
COVID-19;
Chlamydia pneumoniae;
Coinfección

Coinfección por *Chlamydia pneumoniae* y SARS-CoV-2: Una revisión de la literatura

Resumen Los patógenos bacterianos pueden detectarse en las infecciones respiratorias virales y son una causa importante de morbimortalidad. La prevalencia de *Chlamydia pneumoniae* en pacientes infectados con SARS-CoV-2 ha sido poco estudiada. El objetivo de la presente revisión fue describir la prevalencia de *C. pneumoniae* en pacientes con enfermedad por coronavirus 2019 (COVID-19). Para ello se realizó una búsqueda bibliográfica en Medline y Google Académico, entre enero de 2020 y agosto de 2021. De la revisión surgieron 11 artículos (cinco estudios de casos transversales y seis estudios retrospectivos), que incluyeron un total de 18.450 pacientes. La detección de *C. pneumoniae* varió entre el 1,78 y 71,4% del total de las coinfecciones. La media de edad de los pacientes osciló entre los 35 y 71 años y el 65% fueron hombres. En la mayoría de los estudios se informaron comorbilidades preexistentes y la mayor parte de los pacientes presentó fiebre, tos y disnea. Además, se describió linfopenia y eosinofilopenia en pacientes con COVID-19 coinfectados. La principal manifestación en la tomografía computarizada fue densidad de vidrio esmerilado, consolidación y neumonía bilateral. La mayoría de los pacientes recibió antibióticos de manera empírica. La coinfección bacteriana no se asoció con un aumento de ingresos en cuidados intensivos ni mortalidad. A pesar de la prescripción de antimicrobianos empíricos en pacientes con infecciones respiratorias asociadas a coronavirus existen pocos reportes de detección de coinfección bacteriana. Es necesario generar evidencia para el desarrollo de políticas antimicrobianas e intervenciones de administración apropiadas y específicas en la pandemia de COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was firstly reported in China in December 2019 and is an ongoing pandemic[33]. Although the number of confirmed global cases of COVID-19 now exceeds 4.4 million, several studies have noted that co-infection and superinfection with other respiratory pathogens is relatively common[39], the clinical features of co-infection and its impact on patient outcomes is yet to be clarified.

As the majority of symptomatic patients with SARS-CoV-2 infection develop an atypical pneumonia syndrome with fever, cough, and shortness of breath, bacterial and viral co-infections are likely obscured, therefore, being difficult to make a differential diagnosis only based on clinical presentation[57]. Co-infections and/or superinfections are common in respiratory viral infections[37,42]. It has previously been documented that the mortality rate associated with respiratory viral infections can be influenced by different factors, such as bacterial co-infection[4,26,28,38,46].

Pneumonia is an infection of the lung parenchyma caused by a variety of pathogens such as viruses, bacteria, fungi, and parasites. *C. pneumoniae* is known to be a cause of community-acquired pneumonia (CAP) that spreads from human to human via respiratory droplets without any known animal reservoir[18]. The prevalence of *C. pneumoniae* varied widely in previous studies of patients with CAP. It is important to know its prevalence because this atypical pathogen does not respond to β-lactams and can cause severe complications in some patients. Therefore, we performed a review to describe the updated literature regarding the co-infection or secondary infections between SARS-CoV-2 and this atypical pathogen.

Co-infection in *C. pneumoniae*, SARS, and Middle East respiratory syndrome

Severe acute respiratory syndrome (SARS) was initially reported in Southern China in 2002[63,64]. It received international attention after the individuals exposed to an ill patient in a Hong Kong hotel traveled and infected other persons in 2003[58]. In Toronto other individuals were infected, triggering the first outbreak of SARS in Toronto[45]. The causative agent has since been identified as a novel coronavirus [SARS-associated coronavirus (SARS-CoV)][14,44]. However, a SARS study using serological assays failed to detect atypical respiratory pathogen co-infections, in Hong Kong[10]. Nevertheless, the initial report from China before SARS-CoV, documented ''*Chlamydia-like*'' particles in addition to coronavirus by electron microscopy of respiratory specimens obtained from autopsied SARS patients[24]. Moreover, in the Toronto SARS outbreak, the serological evidence among SARS patients showed the co-infection with *C. pneumoniae* (30%) and *Mycoplasma pneumoniae* (9%)[62].

Moreover, the co-infection of the Middle East respiratory syndrome coronavirus (MERS-CoV) and *C. pneumoniae* was reported[3]. In this multicenter retrospective cohort study in Saudi Arabia of 349 critically ill patients with MERS, the authors identified atypical bacterial co-infection in 5/349 (1%) on admission. Atypical organisms identified were *Mycoplasma* spp. (3/5), *Legionella* sp. (1/5) and *Chlamydia* sp. (1/5). However, 6 out of 17 patients were investigated for atypical organisms and these may reflect physician screening preferences based on clinical presentation[3].

The literature on CAP documents reported a dual pathogen infection incidence between 3% and 40%, predominantly with pathogens causing atypical pneumonia[62]. These findings raised the question of whether co-infection with *Chlamydia* in SARS-CoV-2-infected patients played a role in disease severity and mortality. However, there are limited studies reporting this clinical phenomenon.

Methods

Literature review

On August 13, 2021, we searched Medline and Google Scholar for articles describing the clinical features of patients infected with SARS-CoV-2, using the search terms ''*Chlamydia pneumoniae* and COVID 19'' or ''2019-nCoV and *Chlamydia*'' or ''COVID 19 coinfection'' or ''COVID-19,'' ''coronavirus and bacterial infection'', ''SARS-CoV-2 co-infection'' or ''SARS-CoV-2 and bacterial co-infection'' or ''SARS-CoV-2 and *Chlamydia pneumoniae*''. We also searched using the same terms in Spanish. We included articles written in English or Spanish (the primary languages of the investigators). We also reviewed the reference lists for review articles identified by our search, and those of any included studies. We also included all studies using culture, polymerase chain reaction (PCR) or serology, to identify *C. pneumoniae*.

We principally sought to analyze the proportion of patients with confirmed COVID-19 disease who were co-infected simultaneously with *C. pneumoniae* and other pathogens, and to describe the co-infecting pathogens. Separate analyses were conducted for studies reporting laboratory-confirmed bacterial and viral co-infections. Laboratory-confirmed co-infections were those identified in blood, or through antigen detection methods or PCR detection of respiratory pathogens.

Data abstraction

All investigators reviewed each abstract to identify articles that should be reviewed in full. Any article selected for full review was examined by all investigators. For each included article, study characteristics and data regarding detection were abstracted by the authors. For detection data, definite cases were included and possible cases were excluded. For each report, we documented the type of surveillance used, number of cases reported and total population studies.

Results

The recognition of SARS-CoV-2 infection is important as it enables the implementation of appropriate infection control measures; however, clinicians should not neglect the possibility of SARS-CoV-2 co-infection. Therefore, this study aimed to better understand the prevalence of *Chlamydia* co-infection among COVID-19 patients.

Table 1 summarizes the current evidence of *Chlamydia* co-infection in patients admitted to hospital with coronavirus. Eleven studies reported the prevalence of COVID-19 and co-infection or secondary infections for *C. pneumoniae*, five of which were cross-sectional studies.

Two of the abovementioned studies were conducted in China[16,34], while, two others were conducted in the United States[48], and one in Russia[52]. Six of the studies were retrospective, three of which were conducted in China[15,54,66], two in Italy[12,41] and one in Saudi Arabia[2].

The laboratory-confirmed COVID-19 cases were identified in these studies, and the study population ranged from 42 to 10 222 cases. In the study of 182 patients in Italy, 3.8% (n = 7) were coinfections or secondary infections, and the antibodies for *C. pneumoniae* were detected in 5 of the 7 patients[41]. By contrast, Schirmer et al.[51] showed that 1 (1.78%) of 56 patients with co-infections had *C. pneumoniae* in a study of 10 222 COVID-19 patients in USA (1/10 222 = 0.01%)[51]. Among the remaining 9 studies, the prevalence of COVID-19 co-infected with *C. pneumoniae* or secondary infections ranged from 2.5% to 52.6%. Eight studies reported the occurrence of bacterial co-infections, and *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Haemophilus influenzae*, *Escherichia coli*, *Acinetobacter baumannii*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bordetella pertussis* and *Klebsiella pneumoniae* were identified as co-pathogens[2,15,34,41,48,52,54,66]. Eight studies reported viral co-infections; influenza A and influenza B virus, respiratory syncytial virus and adenovirus were the most common co-pathogens, and rhinovirus/enterovirus, coronavirus, Epstein–Barr virus, herpes simplex virus, human bocavirus, adenovirus, parainfluenza, metapneumovirus, and non-COVID-19 coronavirus, were also reported as co-pathogens[2,15,16,34,48,51,54,66]. In three studies also fungal

Table 1 Summary of studies that reported the incidence of *C. pneumoniae* co- and secondary infection in COVID-19 patients.

Reference	City, country	Type of study	Type of pts. Age[a]	No. of pts. with COVID-19 studies	No. of pts. COVID-19 con-firmed	Overall rate of co-infection	No. of patients with *C. pneumomiae* coinfections (%)	Diagnostic methods of coinfection	Treatment	COVID patient Outcome	Outcome of COVID with coinfections (respiratory pathogens identified)
Richardson et al., 2020[48]	New York, EEUU	Case series of patients with COVID-19 admitted to 12 hospitals in New York City, between March 1, 2020, and April 4, 2020	Adults 63 years (52–75)	5700	5700	42/1996 (2.1%)	2/42 (4.76)	RT-PCR (Respiratory pathogen panel)	NR	553 died.	NR
Wang et al., 2020[54]	Wuhan, China	Retrospective. Patients hospitalized between January 16 to January 29, 2020.	Adults 42 years (35–62)	69	69	9/57 (15.7%)	2/9 (22.2) *Chlamydia sp.*	Serology (IgG)	Mostly moxifloxacin 66 (98.5%)	5 died.	NR
Du et al., 2020[15]	Wuhan, China.	Retrospective. 85 COVID-19 patients who died between January 9, 2020, and February 15, 2020.	Adults. 65 years (14–86)	85	33	NR	12/35 (34.1)	Serology	Mostly moxifloxacin (47.1%) and Meropenem (44.7%)	All patients selected were fatal cases.	NA
Oliva et al., 2020[41]	Roma, Italy	Retrospective. All the patients admitted to Azienda Ospedaliero-Universitaria Policlinico Umberto I of Rome between 1 March and 30 April 2020	Adults 68 years (45–79)	182	182	7/182 (3.8%)	5/7 (71.4)	Serology	Azithromycin	1 died	1 died
Sharov 2020[52]	Moscow, Russia.	COVID patients assays were collected in twelve Russian cities/provinces in a time range from 2 March to 5 May 2020.	Pediatric and Adults NR (12–94)	1204	1204	636/1204 (52.8%)	38/636 (5.97)	Serology (IgM) and multiplex RT-PCR.	NR	89 died.	17 died (bacterial and viral pathogens). 57 died (bacterial pathogens).
Zhu et al., 2020[66]	Jiangsu, China.	Retrospective. Patients enrolled between January 22 to February 2, 2020.	Pediatric and Adults 51 years (2–99)	257	257	243/257 (94.2%)	6/243 (2.5)	RT-PCR	Azithromycin	All recov-ered	NA

Table 1 *(Continued)*

Reference	City, country	Type of study	Type of pts. Age[a]	No. of pts. with COVID-19 studies	No. of pts. COVID-19 con-firmed	Overall rate of co-infection	No. of patients with *C. pneumomiae* coinfections (%)	Diagnostic methods of coinfection	Treatment	COVID patient Outcome	Outcome of COVID with coinfections (respiratory pathogens identified)
Ma et al., 2021[34]	Wuhan, China.	All patients diagnosed with COVID-19, clinic at Wuhan Union Hospital between Jan 19, 2020, and Feb 26, 2020.	Adults 35 years (27–63)	250	250	39/250 (15.6%)	13/39 (33.3) 4/39 (10.2) *M. pneumoniae* + *C. pneumoniae*	Serology (IgM) Chemiluminescence immunoassays.	Azithromycin	3 died.	1 died (bacterial pathogens)
Fang et al., 2021[16]	Guangdong, China.	42 patients with COVID-19 were enrolled during January 26, 2020 to February 25, 2020.	Adults. 51 years (38–63)	42	42	19/42 (45.2%)	10/19 (52.6)	Serology (IgA). Protein microarray technology.	NR	NR	NR
Schirmer et al., 2021[51]	USA	Patients from all 50 states as well as the District of Columbia and Puerto Rico from September 29, 2019 through May 31, 2020.	Adults	174 746	10 222	56/3757 (1.5%)	1/56 (1.78)	Multiplex respiratory pathogen panels.	NR	512 died	10 died. (viral pathogens).
De Franchesco et al., 2021[12]	Italy	Retrospective. Patients enrolled between 6 March 2020 and 12 May 2020 in three Hospitals.	Adults 70 years	721	443	242/443 (54.6%)	179/242 (73.9) 63/242 (26) *M. pneumoniae* + *C. pneumoniae*	Serology (IgA/IgM/IgG) Chemiluminescence immunoassays and immunoenzymatic assays.	Azithromycin	102 died.	58 died. (bacterial pathogens).
Alosaimi et al., 2021[2]	Saudi Arabia.	Retrospective. Patients admitted to one Hospital in Saudi Arabia.	Adults 52 years	48	48	34/48 (71%)	13/48 (27) 4/48 (8.3) Influenza H1N1 + *C. pneumoniae*	Multiplex PCR assay.	NR	9 died.	6 died. (bacterial and viral pathogens).

[a] Median age and range.

co-infections were reported (*Candida, Aspergillus, Mucor* and *Cryptococcus*)[15,54,66].

Data regarding co-infections and/or secondary respiratory infections in the severe diseases caused by SARS-CoV-2 coronavirus are limited due to the still ongoing spread of the disease worldwide. Epidemiological and clinical characteristics of COVID-19 patients and co-infections are listed in Table 2. Of the eleven studies that reported co-infections with *C. pneumoniae*, nine were included in this review, because demographic data, co-morbidities, treatments and patient outcomes were not reported in the remaining two studies. SARS-CoV-2 as unique pathogen and COVID-19 co-infection populations did not show any differences.

The median age of co-infected COVID patients ranged from 35 to 71 years old and most of them were male[2,12,15,16,41,51,66]. A single study analyzing the ethnicity of COVID-19 patients reported higher odds of COVID-19 co-infection in White, Black or African American individuals and >80% of COVID-19 patients with co-infections came from urban areas[51].

Most studies reported one or more pre-existing comorbidities, mostly hypertension, cardiovascular disease, diabetes and hyperlipidemia[2,12,15,16,34,41,54]. Similarly to what has been reported in the literature, the majority of the patients presented with fever, cough and dyspnea[12,15,34,41,54].

Patients with SARS-CoV-2 and *Chlamydia* had lower level of lymphocytes[12,15,54] and De Franchesco et al., 2021[12] reported higher leukocyte counts (Table 2). Eosinopenia was also described in COVID-19 co-infected patients[15,54]. An increased ALT serum level was found in patients with SARS-CoV-2 and *C. pneumoniae*[12,15]. Furthermore, Du et al. (2020)[15] reported increased levels of creatine kinase and lactate dehydrogenase in the patients. Different degrees of impaired renal function with elevated blood urea nitrogen or serum creatinine, C-reactive protein[54] and procalcitonin levels above the normal ranges were described[12,15]. Additionally, Alosaimi et al.[2] found that troponin T was strongly associated with disease severity; therefore, troponin T could be used as a predictor for disease severity.

The most common chest CT scan manifestation is ground glass density enhancement along the outer bands of both lungs, consolidation and bilateral pneumonia[12,15,41,54].

Antibiotic use was only reported in five studies[12,15,34,41,54]; however, in several COVID-19 reports most patients received empirical antibiotics. In China, for COVID-19 patients in whom bacterial co-infection could not be ruled out, empirical antibiotics, such as amoxicillin, azithromycin or fluoroquinolones were recommended for mild cases. Moreover, broad-spectrum antibiotics covering all possible pathogens were suggested for severe cases[27].

De Franchesco et al.[12] showed that the proportions of critical COVID-19 patients with atypical pathogen co-infection were higher than those of patients only infected with SARS-CoV-2. Furthermore, requirement and use of a nasal cannula, high flow oxygen support and non-invasive ventilation were significantly higher in co-infected patients than in only SARS-CoV-2 positive patients.[12] In addition, Fang et al.[16] found that the seroprevalence of SARS-CoV-2 and other respiratory pathogens such as *C. pneumoniae* was associated with severity. Meanwhile, other studies reported that less than 10 patients required ICU care[2,41,51,66]. There was also no statistical difference comparing death to COVID-19 mono-infected and COVID-19 co-infected individuals[51]. In the same way, Zhu et al. (2020)[66] did not find a specific relationship between co-infection and ICU admission, as well as the occurrence of death. The median duration of hospitalization ranged from 7 to 28 days[15,34,41,51].

Discussion

Although numerous studies were focused on viral and bacterial co-infections, there is scant information about human coronaviruses. In the present review we described all the reports of described patients infected with SARS-CoV-2 and *Chlamydia pneumoniae* published so far. This last microorganism can affect adults and children, usually causing mild infections and only occasionally could represent life-threatening conditions[18].

The percentage within the total number of co-infections ranges between 1.78 and 71.4% for *C. pneumoniae* in the eleven analyzed studies, and this wide difference may be associated with the used diagnostic technique, since the positivity increased in the studies that used serology[12]. Furthermore, the reasons accounting for the discrepancies may be multifactorial, for example, different study populations, small sample sizes and high sensitivity of molecular assay detection. Moreover, the diagnosis of co-infections may mostly be performed only with serology, as the molecular analyses of respiratory samples of SARS-CoV-2 patients for the diagnosis of *C. pneumoniae* need especial biosafety conditions. In fact, serology might be limited by possible false positive results and another additional limitation is represented by the lack of paired samples to confirm prior serological results for the diagnosis of atypical pathogens. Also, in the analyzed studies not all the patients with SARS-CoV-2 infection were tested for *C. pneumoniae;* therefore the real incidence of co-infection cannot be truly established. Routine testing for pathogens other than SARS-CoV-2 will be necessary.

Despite low rates of bacterial co-infections reported in the molecular studies of COVID-19 patients, high rates of antimicrobial prescriptions were reported. For example, in a study in China, 101 patients (99%) from critical and non-critical care, received antibacterial therapy[7]. No bacterial co-infections were reported in this study. Guan et al.[19] reported that 637 of 1099 (58%) patients admitted to critical and non-critical care settings in China, received antibacterial agents and also no bacterial pathogens were reported in this study[18]. Similar data was repeated in several studies[25,30,40,61]. These results showed the importance of using a broad-spectrum molecular diagnostic panel for the rapid detection of the most common respiratory pathogens to improve the evaluation and clinical management of patients with a respiratory syndrome consistent with COVID-19[6].

Potential stewardship interventions to support reduced antimicrobial prescribing during the COVID-19 pandemic require consideration[47]. The traditional markers used to support antimicrobial decisions, such as vital signs; blood tests (white blood cell count and C-reactive protein); and imaging tend to be abnormal in SARS-CoV-2 infection[1,65]. This makes decision making surrounding the requirement for empiric antibacterial coverage challenging.

Table 2 Clinical, epidemiological, laboratory and radiologic features of patients with bacterial coinfection and SARS-CoV-2.

Author	Age, mean (years)	Gender, no./total (%)	Laboratory findings	Image	Comorbidities	Pts. with MV (%)	Pts. treated in the ICU (%)
Wang et al., 2020[54]	42	Male 32/69 (46)	Lymphopenia. Eosinopenia. Elevated lactate dehydrogenase, c reactive protein, and erythrocyte sedimentation rate.	Most common manifestation is ground glass density enhancement along the outer bands of both lungs, and consolidation.	Hypertension, cardiovascular disease and diabetes.	NR	NR
Du et al., 2020[15]	65	Male 62/85 (72.9)	Elevated procalcitonin level. Eosinopenia. Lymphocytopenia.	Bilateral pneumonia, multiple mottling and ground-glass opacities.	Hypertension, diabetes, and coronary heart disease.	18 (21.2)	NR
Oliva et al., 2020[41]	67	Male 3/5 (60)	NR	Bilateral peripheral infiltrates, ground glass and subpleural consolidation.	Congestive heart failure, bronchial asthma, chronic renal failure. Hypertension, diabetes.	0	1 (14.2)
Zhu et al., 2020[66]	52	Male 138 (53.7)	NR	NR	NR	NR	3 (1.16)
Ma et al., 2021[34]	35	Male 9/21 (42.8)	Higher IL-2, IL-4 and TNF-α levels. Decreased T-cells and NK-cells.	NR	Hypertension, Coronary Heart Disease, Diabetes.	NR	NR
Fang et la, 2021[16]	51	Male 27/42 (64.2)	NR	NR	Hypertension, chronic obstructive pulmonary disease. Diabetes.	NR	NR
Schirmer et al., 2021[51]	68	Male 55/56 (98)	NR	NR	Obesity.	NR	10 (26)
De Franchesco et al., 2021[12]	71	Male 173/242 (71.4)	Leukocytosis Lymphopenia	Bilateral lung involved.	Hypertension, cardiovascular disease, diabetes and hyperlipidemia.	14 (6.8)	NR

Table 2 (*Continued*)

Author	Age, mean (years)	Gender, no./total (%)	Laboratory findings	Image	Comorbidities	Pts. with MV (%)	Pts. treated in the ICU (%)
Alosaimi et al., 2021[2]	52	Male 37/48 (77)	Higher d-dimer, lactate dehydrogenase and Troponin.	NR	Diabetes, cardiovascular disease, chronic kidney disease. Lobar pneumonia, cancer, acute kidney failure, and rheumatoid arthritis.	NR	14 (29)

ICU: intensive care unit; MV: mechanical ventilation. NR: not reported.

Furthermore, with fears surrounding prolonged patient contact and aerosol generation, the number of patients undergoing routine microbiological investigation may be reduced.

In terms of antimicrobial prescribing for bacterial co-infection of the respiratory tract; some patients presenting SARS-CoV-2 infection have a clinical picture that is not dissimilar from that of atypical bacterial pneumonia[31]. SARS-CoV-2 infection may also be difficult to be distinguished from hospital-acquired and ventilator-associated pneumonia in hospital inpatients[54,65,66]. Moreover, patients present febrile with respiratory symptoms, such as a dry cough, associated with bilateral chest X-ray changes[54,65,66]. Given the suggested use of broad-spectrum agents and macrolides[20,49,59]; it is important to prevent unintended consequences of antimicrobial therapy including toxicity, antibiotic-associated diarrhea, and the propagation of antimicrobial resistance through the increased usage of antimicrobial agents within the healthcare systems[23]. Finally, according to the recommendations of the National Institutes of Health, there are insufficient data to recommend the use of empiric broad-spectrum antimicrobial therapy in the absence of another indication in patients with COVID-19 and severe or critical illness[40].

Several studies did not find the presence of *C. penumoniae*[5,9,11,17,22,29,55,56,60]. A clinical study assessing features of COVID-19 in more than 20 000 hospitalized patients in the United Kingdom[13] does not include any reference to secondary infections despite being an item included in the ISARIC World Health Organization questionnaire used by the investigators. This may reflect the fact that co-infections are largely not considered relevant during any large infectious epidemic in which the focus is set in the sole pathogen driving the outbreak and the identification of comorbidities to identify groups of patients at risk. These analyses, arising from the earliest cases of the SARS-CoV-2 pandemic, suggest that bacterial co-infections may be less prevalent in COVID-19 patients than in patients with influenza. In the 2009 influenza pandemic, 1 out 4 severe or fatal cases of influenza A (H1N1) had a bacterial infection, with an apparent association with morbidity and mortality[26,28,35,43,46]. The possibility exists that severe COVID-19 patients could be subsequently or co-incidentally infected by bacteria. The median hospital stage of COVID-19 patients is 7 days[13] but can reach up to 28 days or even longer[34,41], and the risk of hospital-associated pneumonia increases significantly with the length of the hospitalization period. Moreover, more than 80% of nosocomial pneumonia is associated with mechanical ventilation, being this intervention one of the therapeutics used in COVID-19 patients admitted to the ICU[36]. However, inverse association or not statistical difference were observed between bacterial co-infection and disease severity[2,34,41,51,66]. This association indicates a lower likelihood of ICU admission with bacterial co-infection which may be attributed to the empirical use of antibiotics during the early onset of COVID-19.

Previous studies found that nearly half of patients with COVID-19 mono-infection were over the age of 50 years, and that men are more likely to be infected than women[59,61,65]. Also COVID-19 and *C. pneumoniae* co-infection were more prevalent in male patients over the age of 50 years (Table 2). The most common comorbidities of the patients with COVID-19 and co-infection were hypertension and diabetes, which is similar to the findings in the COVID-19 mono-infected patients of previous studies[25,50,53].

Similarly to what has been reported in the literature, the majority of the patients presented with fever, cough and/or shortness of breath, showed bilateral infiltrates in the lung CT and were treated with azithromycin. The blood test showed mostly lymphopenia, and increased C-reactive protein, serum lactate dehydrogenase, procalcitonin, D-dimer level and troponin. In a study by Zhou et al.[65] of 191 patients, 54 of whom died, authors found that D-dimer >1 mg/ml and elevated procalcitonin level >0.5 could assist in the early identification of patients who may have a poorer prognosis and were associated with a higher chance of death[65]. Another laboratory abnormality found in patients with bacterial co-infection was a decrease in total lymphocyte count, which is consistent with the conclusions of existing research indicating that lymphocytopenia is more often observed in non-survivors of SARS-CoV-2 infection[54].

Ma et al.[34] also found high IL-2, IL-4 and TNF-α levels and decreased T-cells and NK-cells. Chen et al.[8] found an increased expression of IL-2 and also IL-6 in serum, proposing that it might predict the severity of COVID-19 pneumonia and bad prognosis of patients.

Bacterial co-infection in the setting of viral pneumonia is known as a major cause of mortality[21]. Co-infection is possible among COVID-19 patients. Clinicians can neither rule out co-infection with other respiratory pathogens when diagnosing SARS-CoV-2 infection nor rule out COVID-19 by detecting non-SARS-CoV-2 respiratory pathogens. However, those findings were based on a limited number of studies. A further large-sample and well-designed studies are warranted to investigate the prevalence of COVID-19 co-infection, risk of co-infection, microbiological distribution, and impact of co-infection on the clinical outcomes of COVID-19 patients. After obtaining more data regarding SARS-CoV-2 co-infection, empirical antimicrobial agents in suspected COVID-19 cases can be recommended.

The absence of standardized criteria to define the presence of co-infections does not allow us to estimate the problem of co-infection worldwide. The enormous heterogeneity of the results does not allow for synthesis measures. Likewise, the frequency of co-infection depends to a great extent on the country where the study is conducted. The results cannot be extrapolated between the different countries. No studies were identified in Latin America; therefore, more information is necessary at the regional level.

Co-infection may considerably inhibit the host's immune system, increase antibacterial therapy intolerance and be detrimental to the prognosis of the disease[32]. To truly define the role that these co-infecting pathogens play in the pathogenesis of COVID-19 is exceedingly difficult, considering the fact that bacterial co-infections commonly occur during other viral respiratory infections. This type of co-infection is very difficult to prevent and can complicate the course and treatment of the underlying viral infection.

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Conflict of interest

The authors declare that they have no conflicts of interest.

References

1. Adebisi YA, Alaran AJ, Okereke M, Oke GI, Amos OA, Olaoye OC, Oladunjoye I, Olanrewaju AY, Ukor NA, Lucero-Prisno DE 3rd. COVID-19 and antimicrobial resistance: a review. Infect Dis (Auckl). 2021;14, 11786337211033870.
2. Alosaimi B, Naeem A, Hamed ME, Alkadi HS, Alanazi T, Al Rehily SS, Almutairi AZ, Zafar A. Influenza co-infection associated with severity and mortality in COVID-19 patients. Virol J. 2021;18:127.
3. Arabi YM, Deeb AM, Al-Hameed F, Mandourah Y, Almekhlafi GA, Sindi AA, Al-Omari A, Shalhoub S, Mady A, Alraddadi B, Almotairi A, Al Khatib K, Abdulmomen A, Qushmaq I, Solaiman O, Al-Aithan AM, Al-Raddadi R, Ragab A, Al Harthy A, Kharaba A, Jose J, Dabbagh T, Fowler RA, Balkhy HH, Merson L, Hayden FG. Saudi Critical Care Trials group. Macrolides in critically ill patients with Middle East Respiratory Syndrome. Int J Infect Dis. 2019;81:184–90.
4. Beadling C, Slifka MK. How do viral infections predispose patients to bacterial infections? Curr Opin Infect Dis. 2004;17:185–91.
5. Blasco ML, Buesa J, Colomina J, Forner MJ, Galindo MJ, Navarro J, Noceda J, Redón J, Signes-Costa J, Navarro D. Co-detection of respiratory pathogens in patients hospitalized with Coronavirus viral disease-2019 pneumonia. J Med Virol. 2020;92:1799–801.
6. Bordi L, Nicastri E, Scorzolini L, Di Caro A, Capobianchi MR, Castilletti C, Lalle E, On Behalf Of Inmi COVID-Study Group and Collaborating Centers. Differential diagnosis of illness in patients under investigation for the novel coronavirus (SARS-CoV-2), Italy, February 2020. Eurosurveillance. 2020;25, 2000170.
7. Cao J, Tu WJ, Cheng W, Yu L, Liu YK, Hu X, Liu Q. Clinical features and short-term outcomes of 102 patients with corona virus disease 2019 in Wuhan, China. Clin Infect Dis. 2020;71:748–55.
8. Chen L, Liu HG, Liu W, Liu J, Liu K, Shang J, Deng Y, Wei S. Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia. Zhonghua Jie He He Hu Xi Za Zhi. 2020;43:203–8.
9. Chi Q, Dai X, Jiang X, Zhu L, Du J, Chen Y, Zheng J, Huang J. Differential diagnosis for suspected cases of coronavirus disease 2019: a retrospective study. BMC Infect Dis. 2020;20:679.
10. Choi KW, Chau TN, Tsang O, Tso E, Chiu MC, Tong WL, Lee PO, Ng TK, Ng WF, Lee KC, Lam W, Yu WC, Lai JY, Lai ST, Princess Margaret Hospital SARS Study Group. Outcomes and prognostic factors in 267 patients with severe acute respiratory syndrome in Hong Kong. Ann Intern Med. 2003;139:715–23.
11. Contou D, Claudinon A, Pajot O, Micaëlo M, Longuet Flandre P, Dubert M, Cally R, Logre E, Fraissé M, Mentec H, Plantefève G. Bacterial and viral co-infections in patients with severe SARS-CoV-2 pneumonia admitted to a French ICU. Ann Intensive Care. 2020;10:119.
12. De Francesco MA, Poiesi C, Gargiulo F, Bonfanti C, Pollara P, Fiorentini S, Caccuri F, Carta V, Mangeri L, Pellizzeri S, Rizzoni D, Malerba P, Salvetti M, Muiesan ML, Alberici F, Scolari F, Pilotto A, Padovani A, Bezzi M, Chiappini R, Ricci C, Castellano M, Berlendis M, Savio G, Montani G, Ronconi M, Bove S, Focà E, Tomasoni L, Castelli F, Rossini A, Inciardi R, Metra M, Caruso A. Co-infection of *chlamydia pneumoniae* and *mycoplasma pneumoniae* with SARS-CoV-2 is associated with more severe features. J Infect. 2021;82:e4–7.
13. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, Holden KA, Read JM, Dondelinger F, Carson G, Merson L, Lee J, Plotkin D, Sigfrid L, Halpin S, Jackson C, Gamble C, Horby PW, Nguyen-Van-Tam JS, Ho A, Russell CD, Dunning J, Openshaw PJ, Baillie JK, Semple MG. ISARIC4C investigators. Features of 20133 UK patients in hospital with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. 2020;369:m1985.
14. Drosten C, Günther S, Preiser W, van der Werf S, Brodt HR, Becker S, Rabenau H, Panning M, Kolesnikova L, Fouchier RA, Berger A, Burguière AM, Cinatl J, Eickmann M, Escriou N, Grywna K, Kramme S, Manuguerra JC, Müller S, Rickerts V, Stürmer M, Vieth S, Klenk HD, Osterhaus AD, Schmitz H, Doerr HW. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med. 2003;348:1967–76.
15. Du Y, Tu L, Zhu P, Mu M, Wang R, Yang P, Wang X, Hu C, Ping R, Hu P, Li T, Cao F, Chang C, Hu Q, Jin Y, Xu G. Clinical features of 85 fatal cases of COVID-19 from Wuhan. A retrospective observational study. Am J Respir Crit Care Med. 2020;201:1372–9.
16. Fang ZF, Sun BQ, Zhu AR, Lin LC, Zhao JC, He S, Huang SK, Zhong NS, Liu ZG. Multiplexed analysis of circulating IgA antibodies for SARS-CoV-2 and common respiratory pathogens in COVID-19 patients. J Med Virol. 2021;93:3257–60.
17. Favier P, Piñeiro F, Serio E, D'amico N, De Izarbe M, Pinilla F, Muñoz C, Arteaga A, Kumar L, Primost I, Gallino I, Pérez J, Raffo C, Carrillo J, Hermida L, Luna C, Padilla MJ, Montiel G, Ripoll P, Kovac A, Andreani M, Gorbaran V, Rodríguez O, Guelfand L, Abusamra L, Sisto A, Prieto M, Vilar G, Lara C, Motter A, Nusblat L, Moncalero S, Rolón MJ, Cadario ME. Prevalence of atypical pathogens in SARS-CoV-2 coinfection in Argentina: finding what

we were not looking for. In: Comunicación presentada en el 31st European Congress of Clinical Microbiology & Infectious Diseases, Vienna, Austria. July 2021.
18. Gautam J, Krawiec C. *Chlamydia pneumonia*, 2020. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021. PMID: 32809709.
19. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS. China Medical Treatment Expert Group for COVID-19. Clinical characteristics of Coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708–20.
20. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, Doudier B, Courjon J, Giordanengo V, Vieira VE, Tissot Dupont H, Honoré S, Colson P, Chabrière E, La Scola B, Rolain JM, Brouqui P, Raoult D. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;56:105949.
21. Guo L, Wei D, Zhang X, Wu Y, Li Q, Zhou M, Qu J. Clinical features predicting mortality risk in patients with viral pneumonia: the MuLBSTA score. Front Microbiol. 2019;10:2752.
22. Hazra A, Collison M, Pisano J, Kumar M, Oehler C, Ridgway JP. Coinfections with SARS-CoV-2 and other respiratory pathogens. Infect Control Hosp Epidemiol. 2020;41:1228–9.
23. Holmes AH, Moore LS, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, Guerin PJ, Piddock LJ. Understanding the mechanisms and drivers of antimicrobial resistance. Lancet. 2016;387:176–87.
24. Hong T, Wang JW, Sun YL, Duan SM, Chen LB, Qu JG, Ni AP, Liang GD, Ren LL, Yang RQ, Guo L, Zhou WM, Chen J, Li DX, Xu WB, Xu H, Guo YJ, Dai SL, Bi SL, Dong XP, Ruan L. *Chlamydia-like* and coronavirus-like agents found in dead cases of atypical pneumonia by electron microscopy. Zhonghua Yi Xue Za Zhi. 2003;83:632–6.
25. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506.
26. Jia L, Xie J, Zhao J, Cao D, Liang Y, Hou X, Wang L, Li Z. Mechanisms of severe mortality-associated bacterial co-infections following influenza virus infection. Front Cell Infect Microbiol. 2017;7:338.
27. Jin YH, Cai L, Cheng ZS, Cheng H, Deng T, Fan YP, Fang C, Huang D, Huang LQ, Huang Q, Han Y, Hu B, Hu F, Li BH, Li YR, Liang K, Lin LK, Luo LS, Ma J, Ma LL, Peng ZY, Pan YB, Pan ZY, Ren XQ, Sun HM, Wang Y, Wang YY, Weng H, Wei CJ, Wu DF, Xia J, Xiong Y, Xu HB, Yao XM, Yuan YF, Ye TS, Zhang XC, Zhang YW, Zhang YG, Zhang HM, Zhao Y, Zhao MJ, Zi H, Zeng XT, Wang YY, Wang XH. for the Zhongnan Hospital of Wuhan University Novel Coronavirus Management and Research Team, Evidence-Based Medicine Chapter of China International Exchange and Promotive Association for Medical and Health Care (CPAM). A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Mil Med Res. 2020;7:4.
28. Katsurada N, Suzuki M, Aoshima M, Yaegashi M, Ishifuji T, Asoh N, Hamashige N, Abe M, Ariyoshi K, Morimoto K, Adult Pneumonia Study Group-Japan. The impact of virus infections on pneumonia mortality is complex in adults: a prospective multicentre observational study. BMC Infect Dis. 2017;17:755.
29. Kim D, Quinn J, Pinsky B, Shah NH, Brown I. Rates of co-infection between SARS-CoV-2 and other respiratory pathogens. JAMA. 2020;323:2085–6.
30. Langford BJ, So M, Raybardhan S, Leung V, Soucy JR, Westwood D, Daneman N, MacFadden DR. Antibiotic prescribing in patients with COVID-19: rapid review and meta-analysis. Clin Microbiol Infect. 2021;27:520–31.
31. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect. 2020;81:266–75.
32. Li XX, Zhou XN. Co-infection of tuberculosis and parasitic diseases in humans: a systematic review. Parasit Vectors. 2013;6:79.
33. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: the mystery and the miracle. J Med Virol. 2020;92:401–2.
34. Ma L, Wang W, Le Grange JM, Wang X, Du S, Li C, Wei J, Zhang JN. Coinfection of SARS-CoV-2 and other respiratory pathogens. Infect Drug Resist. 2020;13:3045–353.
35. MacIntyre CR, Chughtai AA, Barnes M, Ridda I, Seale H, Toms R, Heywood A. The role of pneumonia and secondary bacterial infection in fatal and serious outcomes of pandemic influenza a(H1N1)pdm09. BMC Infect Dis. 2018;18:637.
36. Maes M, Higginson E, Pereira-Dias J, Curran MD, Parmar S, Khokhar F, Cuchet-Lourenço D, Lux J, Sharma-Hajela S, Ravenhill B, Hamed I, Heales L, Mahroof R, Soderholm A, Forrest S, Sridhar S, Brown NM, Baker S, Navapurkar V, Dougan G, Bartholdson Scott J, Conway Morris A. Ventilator-associated pneumonia in critically ill patients with COVID-19. Crit Care. 2021;25:25.
37. McArdle AJ, Turkova A, Cunnington AJ. When do coinfections matter? Curr Opin Infect Dis. 2018;31:209.
38. Metzger DW, Sun K. Immune dysfunction and bacterial coinfections following influenza. J Immunol (Baltimore, MD: 1950). 2013;191:2047–52.
39. Musuuza JS, Watson L, Parmasad V, Putman-Buehler N, Christensen L, Safdar N. Prevalence and outcomes of co-infection and superinfection with SARS-CoV-2 and other pathogens: a systematic review and meta-analysis. PLoS One. 2021;16:e0251170.
40. National Institutes of Health (NIH).
41. Oliva A, Siccardi G, Migliarini A, Cancelli F, Carnevalini M, D'Andria M, Attilia I, Danese VC, Cecchetti V, Romiti R, Ceccarelli G, Mastroianni CM, Palange P, Venditti M. Co-infection of SARS-CoV-2 with *Chlamydia* or *Mycoplasma pneumoniae*: a case series and review of the literature. Infection. 2020;48:871–7.
42. Paget C, Trottein F. Mechanisms of bacterial superinfection post-influenza: a role for unconventional T cells. Front Immunol. 2019;10:336.
43. Palacios G, Hornig M, Cisterna D, Savji N, Bussetti AV, Kapoor V, Hui J, Tokarz R, Briese T, Baumeister E, Lipkin WI. *Streptococcus pneumoniae* coinfection is correlated with the severity of H1N1 pandemic influenza. PLoS One. 2009;4:e8540.
44. Peiris JS, Lai ST, Poon LL, Guan Y, Yam LY, Lim W, Nicholls J, Yee WK, Yan WW, Cheung MT, Cheng VC, Chan KH, Tsang DN, Yung RW, Ng TK, Yuen KY, SARS study group. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet. 2003;361:1319–25.
45. Poutanen SM, Low DE, Henry B, Finkelstein S, Rose D, Green K, Tellier R, Draker R, Adachi D, Ayers M, Chan AK, Skowronski DM, Salit I, Simor AE, Slutsky AS, Doyle PW, Krajden M, Petric M, Brunham RC, McGeer AJ. National Microbiology Laboratory, Canada; Canadian Severe Acute Respiratory Syndrome Study Team. Identification of severe acute respiratory syndrome in Canada. N Engl J Med. 2003;348:1995–2005.
46. Quah J, Jiang B, Tan PC, Siau C, Tan TY. Impact of microbial Aetiology on mortality in severe community-acquired pneumonia. BMC Infect Dis. 2018;18:451.
47. Rawson TM, Moore LSP, Castro-Sanchez E, Charani E, Davies F, Satta G, Ellington MJ, Holmes AH. COVID-19 and the potential long-term impact on antimicrobial resistance. J Antimicrob Chemother. 2020;75:1681–4.
48. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, the Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J,

Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020;323:2052–9.

49. Rizzi Malattie Infettive M, Francesco Castelli Malattie Infetive B, Nicola Latronico Anestesia Rianimazione B, et al. and Gruppo collaborativo – Terapia COVID-19 Lombardia. Vademecum per la cura delle persone con malattia da COVI-19 Versione 2.0. 13 marzo 2020. 2 SIMIT Società Italiana di Malattie Infettive e Tropicali SEZIONE REGIONE LOMBARDIA Gruppo collaborativo-Terapia COVID-19 Lombardia Coordinamento redazionale Emanuele Focà Malattie Infettive, Brescia; 2020.
50. Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, Hosein Z, Padda I, Mangat J, Altaf M. Comorbidity and its impact on patients with COVID-19. SN Compr Clin Med. 2020;25:1–8.
51. Schirmer P, Lucero-Obusan C, Sharma A, Sohoni P, Oda G, Holodniy M. Respiratory co-infections with COVID-19 in the Veterans Health Administration, 2020. Diagn Microbiol Infect Dis. 2021;100:115312.
52. Sharov KS. SARS-CoV-2-related pneumonia cases in pneumonia picture in Russia in March–May 2020: secondary bacterial pneumonia and viral co-infections. J Glob Health. 2020;10:020504.
53. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet. 2020;395:470–3.
54. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with Coronavirus disease 2019 in Wuhan, China. Clin Infect Dis. 2020;71:769–77.
55. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical characteristics of 138 hospitalized patients with 2019 Novel Coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323:1061–9.
56. Wang M, Wu Q, Xu W, Qiao B, Wang J, Zheng H, Jiang S, Mei J, Wu Z, Deng Y, Zhou F, Wu W, Zhang Y, Lv Z, Huang J, Guo X, Feng L, Xia Z, Li D, Xu Z, Liu T, Zhang P, Tong Y, Li Y. Clinical diagnosis of 8274 samples with 2019-novel coronavirus in Wuhan. medRxiv. 2020, http://dx.doi.org/10.1101/2020.02.12.20022327 [online ahead of print].
57. World Health Organization. Clinical management of COVID-19, interim guidance; 27 May 2020 https://www.who.int/publications/i/item/clinical-management-of-covid-19
58. World Health Organization. Global surveillance for severe acute respiratory syndrome (SARS). Wkly Epidemiol Rec. 2003;78:100–19 https://apps.who.int/iris/handle/10665/232131
59. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;180:934–43.
60. Xing Q, Li G, Xing Y, Chen T, Li W, Ni W, Deng K, Gao R, Chen C, Gao Y, Li Q, Yu G, Tong J, Li W, Hao G, Sun Y, Zhang A, Wu Q, Li Z, Pan S. Precautions are needed for COVID-19 patients with coinfection of common respiratory pathogens. medRxiv.; 2020, http://dx.doi.org/10.1101/2020.02.29.2002769 [online ahead of print].
61. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8:475–81.
62. Zahariadis G, Gooley TA, Ryall P, Hutchinson C, Latchford MI, Fearon MA, Jamieson FB, Richardson S, Kuschak T, Mederski B. Risk of ruling out severe acute respiratory syndrome by ruling in another diagnosis: variable incidence of atypical bacteria coinfection based on diagnostic assays. Can Respir J. 2006;13:17–22.
63. Zhao Z, Zhang F, Xu M, Huang K, Zhong W, Cai W, Yin Z, Huang S, Deng Z, Wei M, Xiong J, Hawkey PM. Description and clinical treatment of an early outbreak of severe acute respiratory syndrome (SARS) in Guangzhou, PR China. J Med Microbiol. 2003;52:715–20.
64. Zhong NS, Zheng BJ, Li YM, Poon, Xie ZH, Chan KH, Li PH, Tan SY, Chang Q, Xie JP, Liu XQ, Xu J, Li DX, Yuen KY, Peiris, Guan Y. Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003. Lancet. 2003;362:1353–8.
65. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054–62.
66. Zhu X, Ge Y, Wu T, Zhao K, Chen Y, Wu B, Zhu F, Zhu B, Cui L. Co-infection with respiratory pathogens among COVID-2019 cases. Virus Res. 2020;285:198005.