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Review

Nosocomial Infections in COVID-19 Patients Treated with Immunomodulators: A Narrative Review

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Abstract

Nosocomial infections pose an imminent challenge to hospitalized Coronavirus disease-19 (COVID-19) patients due to complex interplay of dysregulated immune response combined with immunomodulator therapy. In the pre-pandemic era, immunomodulatory therapy has shown benefit in certain autoimmune conditions with untamed inflammatory response. Efforts to recapitulate these immunomodulatory effects in COVID-19 patients has gained impetus and were followed by NIH COVID-19 expert panel recommendations. The current NIH guideline recommends interleukin-6 inhibitors (tocilizumab and sarilumab) and Janus kinase inhibitors (baricitinib and tofacitinib). Several landmark research trials like COVAVTA, EMPACTA, REMDACTA, STOP-COVID and COV BARRIER have detailed the various effects associated with administration of immunomodulators. The historical evidence of increased infection among patients receiving immunomodulators for autoimmune conditions, raised concerns regarding administration of immunomodulators in COVID-19 patients. The aim of this review article is to provide a comprehensive update on the currently available literature surrounding this issue. We reviewed 40 studies out of which 37 investigated IL-6 inhibitors and 3 investigated JAK inhibitors. Among the studies reviewed, the reported rates of nosocomial infections among the COVID-19 patients treated with immunomodulators were similar to patients receiving standard of care for COVID-19. However, these studies were not powered to assess the side effect profile of these medications. Immunomodulators, by dampening the pyrogenic response and inflammatory markers may delay detection of infections among the patients. This underscores the importance of long-term surveillance which are necessary to discover the potential risks associated with these agents.

Keywords: immunomodulators; COVID-19; nosocomial infections; intensive care unit; critical care; outcomes; pandemic; inflammation

1. Introduction

The novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was first identified in Wuhan, China, in December 2019. Since then, SARS-CoV-2has rapidly evolved into a global health threat and has been declared a pandemic by World Health Organization (WHO) [1–3]. The clinical presentation of Coronavirus Disease-2019 (COVID-19) is heterogeneous, ranging from asymptomatic infection to severe pneumonia involving respiratory failure that could progress to invasive mechanical ventilation or death. The disease is characterized by an initial phase of viral replication followed by a second phase driven by the host inflammatory response [4–9]. Current evidence suggests that a subset of patients with COVID-19 develop severe inflammatory response resembling cytokine release syndrome (CRS) after chimeric antigen receptor (CAR) T-cell, macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH) [10]. This dysfunctional immune response contributes to the development of acute respiratory distress syndrome (ARDS) which is noted in up to 20% of patients [11–18]. The cytokines orchestrating inflammatory damage to the lung include interleukin (IL)-1, IL -6, IL-12, IL-18, tumor necrosis factor α (TNF-α), and interferon-γ (2).

2. Immunomodulators and Raising Concerns for Infection

The optimal approach to the treatment of COVID-19 is continually evolving. In a single-center study from Wuhan, China, which included 15 patients with COVID-19 pneumonia at risk for CRS, treatment with tocilizumab (a recombinant humanized anti-human IL-6 receptor monoclonal antibody) appeared to have a clinical benefit [19, 20]. The accumulating evidence suggests medications targeting dysregulated inflammation comprises a promising therapeutic strategy among critically ill COVID-19 patients. Many immunomodulators have been studied in clinical trials for the treatment of COVID-19. Based on the NIH COVID-19 treatment guidelines, IL-6 inhibitors (Tocilizumab and Sarilumab), Janus Kinase inhibitors (To-

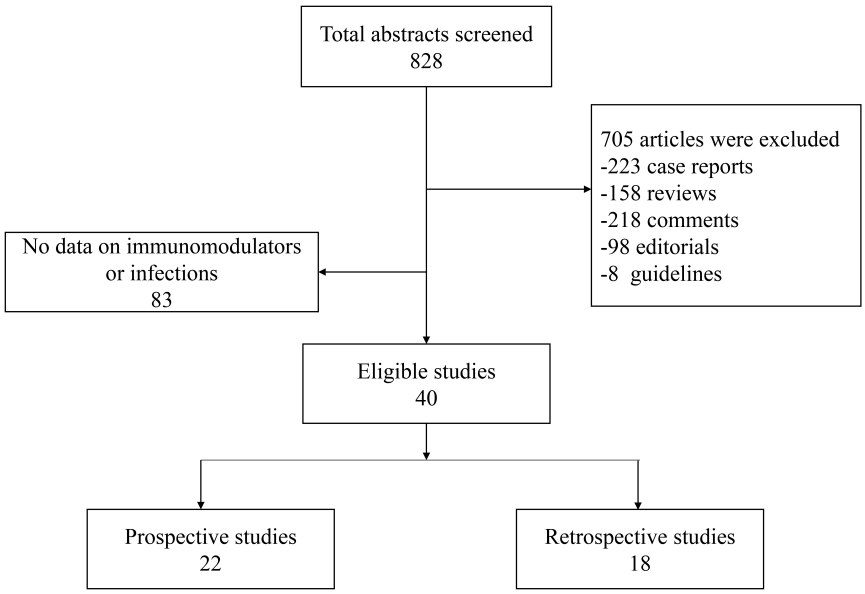

Fig. 1. Schema for literature review.

facitinib and Baricitinib), and Steroids (Dexamethasone) are currently approved, immunomodulatory agents [21]. This approach has been useful to reduce pulmonary inflammation in patients suffering from COVID-19 [22], but the historical evidence of increased infection among patients receiving immunomodulators for autoimmune conditions, raised concerns regarding concomitant administration of immunomodulators and corticosteroids in COVID-19 patients [23,24].

3. Pathogenesis of Cytokine Release Syndrome and Mechanism of Action of IL-6 Inhibitors

COVID-19 primarily infects type II pneumocytes and cells expressing angiotensin-converting enzyme (ACE-2), which serves as a receptor and entry point for the virus [4, 25]. The viral replication and its cytopathic effects activate cells of innate immunity (monocytes and macrophages) by stimulating Toll-like receptors and leading to the synthesis of pro-inflammatory cytokine responsible for Cytokine Release Syndrome (CRS) [5,6]. Among those cytokines, several studies suggest that IL-6 plays a central role in CRS pathogenesis in COVID-19. It works by binding to transmembrane IL-6 (mIL-6R) and IL-6 soluble receptor (sIL-6R). The complex then binds to signal transducer (gp130) and triggered gene expression leading to cellular proliferation, differentiation, and oxidative stress. CRS, marked by the uncontrolled release of the pro-inflammatory cytokine, may affect the alveolar gas exchange, reducing pulmonary tissue oxygenation [11,26]. Tocilizumab and sarilumab are the monoclonal antibodies that prevent IL-6 from binding to its receptors (both membrane-bound and soluble receptors) and inhibit its interaction with gp130, thus hindering the downstream activation of the inflammatory cascade. On the other side, suppression of IL-6 may also impair B-cell proliferation, T-cell differentiation, and cytotoxicity, which are essential for immune clearance of bacterial and fungal pathogens [27]. This is supported by the reduced ability of interleukin-6 deficient mice to clear systemic candida infection when compared with IL-6 positive controls [28,29].

4. JAK Inhibitors: Mechanism of Action and Current Evidence in COVID-19 Treatment

Baricitinib is an inhibitor of JAK 1 and 2 receptors with high oral bioavailability. Similarly, Tofacitinib inhibits JAK 1 and 3 receptors. JAK inhibitors affect multiple cytokines orchestrating CRS such as IL-2, IL-6, IL-10, and interferon-gamma, unlike other biological drugs which are predominantly inhibitors of one cytokine. Data suggests that in addition to immunomodulatory effect, Baricitinib, may have antiviral action by interfering with viral entry into the cell. It binds to ACE2 receptors (angiotensin-converting enzyme) thereby inhibiting the entry of the virus into the cell and its intracellular coupling by binding to GAK (cyclin G-associated kinase), which regulates endocytosis and acts on AAK1 (Associated protein kinase 1), consequently interfering with viral replication [30]. These observations pivoted attention towards the JAK inhibitors as a promising strategy in the treatment of COVID-19.

5. Materials and Methods

In this narrative review, we aimed to summarize the information from seminal articles on the presentation of nosocomial infections among the COVID-19 patients treated with immunomodulators. We have focused our discussion pertinent to NIH-approved IL-6 inhibitors and Janus kinase inhibitors. We searched the PubMed and Med-

Table 1. Study demographics and rates of nosocomial infection in COVID-19 patients receiving IL-6 inhibitors.

	Reference study	Country	Study type	No. of patients (Treatment arm /Control)	Age (mean ± SD)	Gender	Common comorbidities	Study drug	Concomitant use of systemic steroids	Rates of any infections (Treatment arm vs Control)	Rates of Bacterial pneumonia	Mortality
1	Rosas *et al.* (COVACTA) [32]	Multinational	RCT	294/144	60.9 ± 14.6	M: 205 (70%) F: 91 (30%)	DM: 105 (36%) HTN: 178 (61%)	Tocilizumab	54.1%	38.3% vs 40.6%	5.4% vs 7%	19.7% vs 19.4%, $p = 0.94$
2	Salama *et al.* (EMPACTA) [31]	Multinational	RCT	249/128	56.0 ± 14.3	M: 150 (60%) F: 99 (40%)	NR	Tocilizumab	80.3%	10.0% vs 12.6%	NR	10.4% vs 8.6%
3	Hermine *et al.* (CORIMUNO-TOCI-1) [33]	France	RCT-Open label	63/67	64 (IQR: 57–74)	M: 44 (70%) F: 19 (30%)	DM: 20 (33%) Cardiac disease 20 (33%)	Tocilizumab	33%	3.1% vs 16.4%	NR	11% vs 11.9%
4	Salvarani *et al.* (RCT-TCZ-COVID-19) [34]	Italy	RCT-Open label	60/66	60 (IQR: 53–73.2)	M: 40 (67%) F: 20 (33%)	DM: 10 (16.7% Obesity: 16 (28%) HTN: 27 (45%)	Tocilizumab	NR	1.7% vs 6.3%	NR	3.3% vs 1.6%
5	Stone *et al.* (BACC BAY Tocilizumab) [35]	USA	RCT	161/81	61.6 (IQR: 46.4–69.7)	M: 96 (60%) F: 65 (40%)	HTN: 80 (50%) Obesity: 80 (50%)	Tocilizumab	11%	8.1% vs 17.1, $p = 0.03$	NR	3.7% vs 2.4%
6	Soin *et al.* COVINTOC [36]	India	RCT open label	91/88	56 (IQR: 47–63)	M: 76 (84%) F: 15 (16%)	HTN: 36 (40%) DM: 31 (34%)	Tocilizumab	91%	7% vs 6%	NR	12% vs 17%, $p = 0.35$
7	Alaa Rashad *et al.* [37]	Egypt	RCT	46/63	60.5 (IQR: 49–67)	M: 26 (56%) F: 20 (44%)	HTN: 26 (56%) DM: 16 (35%)	Tocilizumab vs Dexamethasone	NR	30.4% vs 25.4%, $p = 0.356$	NR	69.6% vs 52.4%, $p = 0.05$
8	Rosas *et al.* (REMDACTA) [38]	Multinational	RCT double blind	430/210	60.1 ± 13.3	M: 266 (62%) F: 164 (38%)	HTN: 267 (62.1%) DM: 172 (40%)	Tocilizumab	83.2%	30.5% vs 33.3%	NR	22.6% vs 25.7%, $p = 0.39$
9	Farias *et al.* (TOCIBRAS) [39]	Brazil	RCT open label	65/64	57.4 ±15.7	M: 44 (68%) F: 21 (32%)	HTN: 30 (46%) DM: 22 (34%) Obesity: 15 (23%)	Tocilizumab	25%	15% vs 16%, $p = 0.98$	7.6% vs 10.9%	
10	Declercq *et al.* (COV-AID) [40]	Belgium	2X2 Factorial design RCT-Open label	227/115	65 (IQR: 54–73)	M: 175 (77%) F: 52 (23%)	HTN: 115 (51%) DM: 59 (26%)	Ant interleukin vs Usual care	62%	9% vs 8%	NR	17.6% vs 12%
11	Lescure *et al.* [41]	Multinational	RCT Double blinded	332/84	58 (IQR: 51–67)	M: 206 (62%) F: 126 (38%)	HTN: 138 (42%) DM: 92 (28%)	Sarilumab	NR	12% vs 12%	NR	9% vs 8%, $p = 0.85$
12	Monica Mehta *et al.* [42]	USA	Single center, Retrospective	33/74	54.6	M: 25 (76%) F: 8 (24%)	Pulmonary disease 22%	Tocilizumab	NR	30% vs 23%, $p = 0.193$	30% vs 14%, $p = 0.69$	NR
13	Ramiro *et al.* [43]	Netherlands	Prospective control study	86/86	67 ±12	M: 68 (79%) F: 18 (21%)	HTN: 19 (22%) DM: 9 (11%) COPD: 10 (12%)	Tocilizumab	100%	9% vs 8%, $p = 0.780$	NR	16% vs 47.6%, $p = 0.0004$
14	Amer *et al.* [44]	Multinational	Prospective multicenter	121/406	60.6 ±13.8	M: 87 (72%) F: 44 (28%)	NR	Tocilizumab vs Dexamethasone	NR	29.7% vs 23.9%, $p = 0.46$	29.7% vs 23.9%, $p = 0.46$	NR

Table 1. Continued.

	Reference study	Country	Study type	No. of patients (Treatment arm /Control)	Age (mean ± SD)	Gender	Common comorbidities	Study drug	Concomitant use of systemic steroids	Rates of any infections (Treatment arm vs Control)	Rates of Bacterial pneumonia	Mortality
15	Della-Torre *et al.* [45]	Italy	Prospective single center	28/28	56 (IQR: 49–60)	M: 24 (85%) F: 4 (15%)	DM: 3 (11%) HTN: 6 (21%)	Sarilumab	NR	21% vs 18%, $p = 0.99$	NR	7% vs 18%, $p = 0.42$
16	Campochiaro *et al.* [46]	Italy	Retrospective single center	32/33	64 (IQR: 53–75)	M: 29 (91%) F: 3 (9%)	DM: 4 (12%) HTN: 12 (37)	Tocilizumab	NR	13% vs 12%, $p = 0.99$	NR	16% vs 33%, $p = 0.15$
17	Sinha *et al.* [47]	USA	Prospective, Single center	255	59 (IQR: 47–70)	M: 161 (63%) F: 94 (37%)	DM: 79 (31%) HTN: 125 (49) Obesity: 135 (52)	Sarilumab or Tocilizumab	NR	13.3%	NR	10.9%
18	Lewis *et al.* [48]	USA	Retrospective, Multi center	497/497	60.2	M: 352 (70.8%) F: 145 (29.2%)	NR	Tocilizumab	51.7%	34.4% vs 10.7%, $p < 0.001$	25.9% vs 5.8%	29.2% vs 42.4%, $p = 0.001$
19	Morena *et al.* [26]	Italy	Prospective, Single centre	51	60 (IQR: 50–70)	M: 40 (79%) F: 11 (21%)	DM: 6 (12) HTN: 15 (30)	Tocilizumab	NR	27%	NR	27%
20	Nasa *et al.* [49]	India	Multicentre, Reterospective	22/63	51	M: 22 (100%)	DM: 13 (59%) HTN: 16 (72%)	Tocilizumab	NR	9%	NR	9%
21	Rosas *et al.* [50]	Spain	Reterospective study	43/17	67 ±14	M: 32 (74%) F: 11 (26%)	Charleson comorbidity index: 3.41	Tocilizumab and Baricitinib	82%	21% vs 25.9%	NR	20%
22	Roumier *et al.* [51]	France	Prospective, Single centre	49/47	57.8 ±11.5	M: 40 (82%) F: 9 (18%)	DM: 12 (24%) HTN: 9 (18%)	Tocilizumab	NR	22% vs. 38%, $p = 0.089$	8% vs 26%, $p = 0.022$	10.2% vs 12.8%, $p = 0.69$
23	Strohbehn *et al.* [52]	USA	Phase II open label	32/41	69 (IQR: 41–73)	M: 16 (50%) F: 16 (50%)	NR	Tocilizumab	NR	15.6%	16%	NR
24	Toniati *et al.* [53]	Italy	Prospective, single center	100	62	M: 88 (88%) F: 12 (12%)	DM: 17 (17%) HTN: 46 (46%)	Tocilizumab	100%	2%	NR	20%
25	Biran *et al.* [54]	USA	Retrospective, Multicenter	210	62 (IQR: 53–71)	M: 155 (74%) F: 55 (26%)	DM: 77 (37%) HTN: 122 (58%)	Tocilizumab	46%	17% vs 13%	12% vs 7%	49%
26	Canziani *et al.* [55]	Italy	Retrospective, Multicenter	64/64	63±12	M: 47 (73%) F: 16 (27%)	HTN: 33 (52%)	Tocilizumab	48%	27% vs 38%, $p = 0.185$	NR	27% vs 38%
27	Eimer *et al.* [56]	Sweden	Retrospective single center	22/22	56 (IQR: 49–64)	M: 21 (96%) F: 1 (4%)	DM: 4 (18.2%) HTN: 8 (37%)	Tocilizumab	13%	18.2% vs 27.3%, $p = 0.72$	23% vs 36.4%, $p = 0.51$	23% vs 32%, $p = 0.73$
28	Fisher *et al.* [57]	USA	Reterospective Single center	45/70	56.2	M: 29 (65%) F: 16 (35%)	NR	Tocilizumab	73%	29% vs 26%, $p = 0.71$	NR	29% vs 40%, $p = 0.23$
29	Guaraldi *et al.* [58]	Italy	Reterospective, Multicenter	179/365	64 (IQR: 54–72)	M: 127 (71%) F: 52 (29%)	NR	Tocilizumab	NR	13% vs 4%, $p < 0.0001$	NR	20% vs 7%, $p < 0.0001$

Table 1. Continued.

	Reference study	Country	Study type	No. of patients (Treatment arm /Control)	Age (mean ± SD)	Gender	Common comorbidities	Study drug	Concomitant use of systemic steroids	Rates of any infections (Treatment arm vs Control)	Rates of Bacterial pneumonia	Mortality
30	Gupta *et al*. [59]	USA	Retrospective Multicenter	433	58 (IQR: 48–65)	M: 299 (69%) F: 134 (31%)	DM: 165 (38.1%) HT: 234 (54%)	Tocilizumab	19%	32.3% vs 31.1%	26% vs 21%	29% vs 41%
31	Hill *et al*. [60]	USA	Retrospective, single cener	43/45	57.2 ±13.5	M: 30 (70%) F: 13 (30%)	DM: 16 (36%)	Tocilizumab	NR	21% vs 16%	21% vs 11%	20.9% vs 33.3%
32	Kewan *et al*. [61]	USA	Reteropsective single center	28/23	62 (IQR: 53–71)	M: 20 (71%) F: 8 (29%)	DM: 11 (39%) HTN: 19 (68%)	Tocilizumab	71%	18% vs 22%, $p = 0.74$	NR	11% vs 9%
33	Kimmig *et al*. [62]	USA	Reterospective single center	54/57	64.5 ± 13.6	M: 37 (68%) F: 17 (32%)	Charleson comorbidity index: 3.59 ± 3.82	Tocilizumab	24%	48.1% vs 28.1%, $p = 0.029$	33.3% vs 15.8%	35.2% vs 19.3%, $p = 0.020$
34	Pettit *et al*. [63]	USA	Reterospective single center	74/74	66 ± 13.7	M: 43 (58%) F: 31 (42%)	DM: 24 (32%) HTN: 41 (55%)	Tocilizumab	NR	23% vs 8%, $p = 0.013$	9.5% vs 6.8%, $p = 0.76$	39% vs 23%, $p = 0.03$
35	Rodriguez-Bano *et al*. [64]	Spain	Retrospective Multicenter	88/344	66 (IQR: 56–72)	M: 40 (73%) F: 24 (27%)	DM: 15 (17%) HTN: 30 (34.1)	Tocilizumab	18%	12.5% vs 10.3%, $p = 0.57$	NR	2.3% vs 11.9%, $p = 0.004$
36	Rossotti *et al*. [65]	Italy	Reterospective single center	74/148	59 (IQR: 51–70)	M: 61 (82%) F: 13 (18%)	NR	Tocilizumab	NR	32.4%	NR	NR
37	Somers *et al*. [66]	USA	Singlecenter	78/76	55 ± 14.9	M: 53 (68%) F: 25 (32%)	HTN: 50 (64%) Solid organ transplant 7 (9%)	Tocilizumab	30%	54% vs 26%, $p < 0.001$	45% vs 20%, $p < 0.001$	22% vs 15%, $p = 0.42$

SD, Standard Deviation; RCT, Randomized Control Trial; DM, Diabetes Mellitus; HTN, Hypertension; M, Male; F, Female; NR, Not Reported.

line databases for "COVID-19", "tocilizumab", "sarilumab", "tofacitinib", and "baricitinib". Additionally, we examined the bibliography of the selected articles for further potential studies. Studies published in English, including adults with COVID-19 who received either IL-6 inhibitors or Janus Kinase inhibitors (JAK), were eligible to be included in this narrative review. We included only studies that reported details of nosocomial infection and the pertinent microbiological data. Additional information regarding the prevalence of nosocomial infection including ventilator-associated pneumonia (VAP), central line-associated bloodstream infections (CLABSI), catheter-associated urinary tract infections (CAUTI), length of hospital stay, intensive care admission rates, and mortality rates was collected. All the studies published before January 2022 were included. Articles that did not have patient details, conference papers, expert opinions, letters, articles not published in English, and studies not reporting nosocomial infections were excluded. All the articles were reviewed by 2 independent clinicians (CR and GN) and findings were confirmed by AL.

As of January 2022, a total of 828 papers were identified by literature search (Fig. 1). Among these, 40 fulfilled the eligibility criteria for our study. Out of these, 37 studies investigated IL-6 inhibitors and 3 studies analyzed the role of JAK inhibitors as a potential therapy in COVID-19 patients. There were significant differences in the study design, data collection, and measured outcomes among the studies which made the comparison of the data difficult.

6. Nosocomial Infections in COVID-19 Patients Receiving IL-6 Inhibitors

6.1 Study Characteristics

Among the 37 studies that reported nosocomial infections in hospitalized COVID-19 patients treated with IL-6 inhibitors, 18 studies were prospective in design, 18 were retrospective and 1 was a phase II trial evaluating tocilizumab dosage (Table 1, Ref. [26,31–66]). Out of 18 prospective studies, 11 were randomized control trials, 5 were prospective studies with a control arm, and the remaining 3 studies were without a control arm. 16 out of 18 retrospective studies had a control arm. Studies were published from all over the world with the majority from North American and European nations. Most of the included studies were from the United States with 13 studies followed by Italy with 8 studies, Spain with 2 studies, India with 2 studies, France with 2 studies, Sweden with 1 study, Brazil with 1 study, Egypt with 1 study, Belgium with 1 study, and the Netherlands with 1 study, respectively. There were 5 multinational studies. EMPACTA and COVACTA study groups reported the highest recruitment of ethnic minority groups at 40% and 29%, respectively [31,32]. The diagnosis of COVID-19 was uniformly established with a reverse transcription-polymerase chain reaction. Of the 38 studies that reported the use of IL-6 inhibitor, 34 studies investigated Tocilizumab, and 4 studies evaluated Sarilumab. A single dose of 400 mg or 8 mg/kg intravenous was the most reported regimen of Tocilizumab. 20 out of 34 studies suggested that the second dose of Tocilizumab may be administered based on clinical judgment. In terms of Sarilumab, two dosing regimens 200 mg and 400 mg were investigated. The patients with active bacterial, tuberculosis, fungal and viral infections were uniformly excluded across all the studies. Hydroxychloroquine, antivirals, azithromycin, steroids, or anticoagulants were the most reported regimen in the standard of care treatment. A total of 8325 patients were reported in the 38 studies, including 4560 patients in the tocilizumab group, 360 patients in the sarilumab group, and 3405 in the control group. All the subjects in the intervention group also received standard treatment for COVID-19 in addition to IL-6 inhibitors. The mean age of patients who received IL-6 inhibitors was 61.1 years with male preponderance reported in all the 38 studies. The most common comorbidities reported across all the studies were arterial hypertension (21% to 72%), diabetes mellitus (11% to 36%), and obesity with BMI greater than 30 (21% to 52%) which varied according to the country of study.

6.2 IL-6 Inhibition and Infection

The rates of nosocomial infection reported among the patients who received IL-6 inhibitors range from 1.7% to 54% depending on the severity of COVID-19 in study patients [34,66]. Most infections were bacterial with pneumonia being the most common manifestation followed by bloodstream infections [48,56,58,59,62,66]. Four retrospective studies reported a statistically significant higher rate of infections in the tocilizumab group compared to the control group [48,58,62,66]. Out of 11 randomized control trials, 9 trials reported similar rates of nosocomial infections among the tocilizumab-treated group and control group [31–34,36–38,40,41]. Interestingly, one double blinded randomized trial showed statistically significant higher infection rates in the control arm than the tocilizumab arm [35].

Lewis *et al.* [48] reported a higher prevalence of nosocomial infections in the tocilizumab group compared with propensity-matched controls in the retrospective analysis of 497 patients with an odds ratio of 4.18 (95% CI = 2.72–6.52, $p < 0.001$) [48]. A higher prevalence of bloodstream infections, pneumonia, and urinary tract infections was noted in the tocilizumab group. In comparison with matched controls, infections occurred later during the course among the tocilizumab group (median 10d; IQR, 5–15 vs 4d; IQR, 1–8). Of note, a higher proportion of tocilizumab-treated patients received steroids compared with matched controls (51.7% vs 25.2%) and the cumulative dose of corticosteroids was higher in the tocilizumab group (median methylprednisolone equivalents, 350 mg vs 125 mg). Despite a higher prevalence of nosocomial infections, the tocilizumab-treated group was associated with

Table 2. Study demographics and rates of nosocomial infection in COVID-19 patients receiving JAK inhibitors.

	Reference study	Country	Study type	Study drug	No. of patients (Tx/Control)	Age (mean ± SD)	Gender	Common comorbidities	Rates of nosocomial infections (Tx vs Control)	Concomitant use of systemic steroids	Mortality
1	COV-BARRIER Vincent Marconi *et al*. [74]	Asia, Europe, North America, South America	Double blinded RCT	Baricitinib vs Placebo	764/761	57.8 (±14.3)	M: 490 (64%) F: 274 (36%)	HTN: 48% Obesity 33% DM: 29% Chronic Respiratory disease 4%	16% Treatment emergent infections in baricitinib vs 16 % placebo Details of infection, Serious infections (9%) vs 10%, Herpes simplex (<1%) vs 1%, Tuberculosis (<1%) vs 0, Opportunistic infections Candida Infection (<1%) vs 1%, Eye infection fundal, Fungal retinitis(<1%) Herpes Zoster (<1%) Listerosis 0, Oropharyngeal candidiasis 0, Pulmonary TB (<1%), Systemic candida (<1%)	80% vs 78%	8% vs 13%
2	ACCT-2 AC Kalil *et al*. [72]	United States, Singapore, South Korea, Mexico, Japan, Spain, the United Kingdom, and Denmark	Double blinded RCT	Baricitinib and remdesivir vs placebo and remdesivir	515/518	55 (±15.4)	M: 319 (61.9 %) F: 196 (38.1%)	Obesity: 295 (58%), HTN: 258 (51%) DM: 200 (40%)	6.6% vs 8.9% Details of infection Septic shock: 4 (0.8%) vs 8 (1.6%) Pneumonia: 12 (2.4%) vs 21 (4.1%) UTI: 5 (1%) vs 2 (0.4%) Bacteraemia: 2 (0.4%) vs 5 (1%) Fungaemia: 1 (0.2%) vs 0	21.2% vs 22%	4.6% vs 7.1%
3	STOP-COVID Guimaraes *et al*. [73]	Brazil	Double blinded RCT	Tofacitinib	144/145	55 ± 14	M: 94 (65%) F: 50 (35%)	HTN: 67 (46.5%) DM: 34 (23.6%)	3.5% vs 4.2% risk ratio 0.83 (95% CI 0.25 to 2.58), Pneumonia: 0.7% vs 1.4% , UTI: 0.7% VS 0%	79.2% vs 77.9%	2.8% vs 5.5%

SD, Standard Deviation; RCT, Randomized Control Trial; DM, Diabetes Mellitus; HTN, Hypertension; M, Male; F, Female; NR, Not Reported.

improved survival (HR = 0.24, 95% CI = 0.18–0.33, $p < 0.001$). Similar conclusions were drawn by Somers *et al*. [66] based on a single-center retrospective analysis of critically ill patients receiving tocilizumab within 24 hours of endotracheal intubation, wherein tocilizumab-treated patients developed higher rates of nosocomial infections than controls (54% vs 26%, $p < 0.001$). The results were driven primarily by an increase in ventilator-associated pneumonia (45% vs 20%, $p < 0.001$). This did not impact the patient mortality as the case fatality rates were similar between infected and uninfected tocilizumab-treated patients (22% vs 15%, $p = 0.42$). Staphylococcus aureus was identified as the predominant pathogen responsible for pneumonia in both groups [66].

Five studies reported the prevalence of fungal infection among tocilizumab-treated patients, which ranges from 1.35% to 6.9% [35,38,41,63,67]. The commonly reported invasive fungal infection was candidemia followed by pneumonia and sinusitis. Antinori *et al*. [67] reported 6.9% of candidemia in a retrospective analysis of 43 patients treated with tocilizumab wherein all the patients with candidemia received parenteral nutrition during hospitalization.

7. Discussion

7.1 IL-6 Inhibitors: Current Evidence in Treatment of COVID-19

The EMPACTA trial reported fewer patients on IL-6 blockade progressed to mechanical ventilation, but it did not translate to increased survival [31]. The RECOVERY trial showed an increased survival rate in tocilizumab-treated patients with respiratory failure and elevated C-Reactive Protein (CRP) levels above 75 mg/L [68,69]. The REMAP-CAP trial concluded an increased number of organ support-free days at day 21 with tocilizumab or sarilumab in patients who were ventilated or received cardiovascular organ support [70]. On July 6, 2021, based on a meta-analysis of 27 RCTs, the World Health Organization (WHO) rapid evidence appraisal for COVID-19 therapies (REACT) working group showed an association between administration of IL-6 inhibitors and reduced 28-day all-cause mortality, compared with the standard of care, in hospitalized patients with COVID-19 (pooled odds ratio = 0.86; 95% confidence interval 0.79–0.95) [71]. Based on the above evidence, the National Institutes of Health conditionally recommend tocilizumab or sarilumab in combination with steroids for intensive care unit (ICU) patients with rapidly progressing respiratory failure or high inflammatory markers.

7.2 Nosocomial Infections in COVID-19 Patients Receiving Janus Kinase (JAK) Inhibitors

Three double-blinded randomized control trials reported nosocomial infection in hospitalized COVID-19 patients treated with JAK inhibitors (baricitinib and tofacitinib) [39,72,73]. Of the 3 studies that reported the use of JAK inhibitor, 2 multinational studies investigated baricitinib, and 1 study from Brazil evaluated tofacitinib (Table 2, Ref. [71–73]). A total of 2847 patients were reported in the 3 trials, including 1279 patients in the baricitinib group, 144 patients in the tofacitinib group, and 1424 patients in the control group. All the subjects in the intervention group received standard treatment for COVID-19 in addition to JAK inhibitors. The mean age of patients who received JAK inhibitors was 55.9 years with male preponderance reported in all the 3 studies ranging from 61.9% to 65% of the study population. The investigated dose of baricitinib was 4 mg daily and tofacitinib was 10 mg daily for 14 days or until hospital discharge in patients with estimated glomerular filtration $\geq$60 mL/min/1.73 m^2.

The reported rates of nosocomial infections among the patients who received JAK inhibitors ranges from 3.5% to 16% [73,74]. Pneumonia was the most common reported infection in JAK inhibitors group [72,73]. Viral mediated respiratory epithelial cell damage and defective mucociliary clearance may have a role in the observation of pneumonia being commonly reported as a nosocomial infection regardless of the class of immunomodulators (IL-6 inhibitors or JAK inhibitors). These three trials with high quality evidence, reported similar rates of nosocomial infections between the patients treated with JAK inhibitors and the control group. Pertinent microbiological data including the pathogen and its susceptibility were not reported.

The COV-BARRIER trial showed a 38.2% relative reduction in 28-day all-cause mortality in the baricitinib group among hospitalized COVID-19 patients with $\geq$1 elevated inflammatory marker [39]. The ACCT-2 trial demonstrated that baricitinib used in combination with remdesivir accelerates the recovery time in COVID-19 patients especially in adults who were receiving high-flow oxygen or non-invasive ventilation [72]. Based on the above evidence, the NIH expert panel recommends baricitinib can be used in hospitalized COVID-19 patients with rapidly increasing oxygen requirements and systemic inflammation. Tofacitinib can be used in a scenario where baricitinib treatment is unavailable or not feasible [21]. There are no studies directly comparing JAK inhibitors and IL-6 inhibitors, leading to insufficient evidence to recommend either a drug or a class of drug over the other.

In this review, we summarized the nosocomial infections among the COVID-19 patients receiving immunomodulators (IL-6 inhibitors and JAK-2 inhibitors). Our review of the literature revealed many interesting findings. The reported rates of nosocomial infections among the COVID-19 patients treated with immunomodulators were similar to patients receiving standard of care for COVID-19 based on the randomized control trials with high quality of evidence. However, none of these studies were powered to assess the side effect profile of these medications. Phase IV studies to assess the long-term outcomes and population-

based data is necessary to comment on the potential risks associated with these agents. Most infections were bacterial with pneumonia being the most common manifestation followed by bloodstream infections. Out of the reported pathogens, staphylococcus aureus was identified as the predominant pathogen responsible (cause) for pneumonia. Nosocomial bacterial infections occurred later during the course of treatment among the patients receiving tocilizumab when compared to the control group, necessitating longer surveillance. Whether this is related to the long half-life of the tocilizumab (11 days) causing prolonged immunomodulation is a question worth asking. As most of the inflammatory response to infection and diagnostic clues (i.e., fever, high C-reactive protein) can be blunted following immunomodulatory treatment, a high index of suspicion with proactive surveillance should be necessitated for these patients. While similar rates of infection were observed between the treated patients and the control, larger randomized control with longer follow up are needed in this field to confirm this finding.

Implementation of strict infection control measures during the COVID-19 pandemic like hand washing, widespread use of personal protective equipment and limiting visitors is important to reduce nosocomial transmission of infection. The evolving evidence suggests that these infection control measures might have contributed to reduction in nosocomial transmission of Clostridium difficile, infections with multidrug resistant organisms and surgical site infections during COVID-19 pandemic [64,75–80]. König *et al*. [81] in their retrospective analysis of multicentric inpatient data from Germany reported that strict hygiene measures during the pandemic might have contributed to decreased rates of in-hospital mortality when compared to pre-pandemic era, after excluding COVID-19 cases.

8. Limitations

Our review provides comprehensive, up-to-date information in a timely manner about nosocomial infections among COVID-19 patients treated with immunomodulators by analyzing studies from different countries across the globe. However, this review also has important limitations. The nosocomial infections were possibly under- or over-represented, as there was a lack of consistent microbiological diagnostic methods. A specific testing method was not reported in half of all the studies. Further, distinguishing bacterial colonization from infection presents a challenge, particularly in the context of critically ill or rapidly progressing COVID-19 infection who may have clinical deterioration for various reasons [82–84]. With the evolving standard of care for COVID-19 infections, varying proportions of patients received steroids and antibiotics across all the studies which may skew our conclusions.

9. Conclusions

We conclude that the reported rate of nosocomial infections among the COVID-19 patients treated with immunomodulators were similar to patients who received standard of care for COVID-19 based on the 40 studies reviewed. As most of the inflammatory response to infection (i.e., fever, high C-reactive protein) can be blunted following immunomodulatory treatment, a high index of suspicion with proactive surveillance should be the standard of care for these patients. Implementation of strict inflection control measures is necessary to reduce the nosocomial transmission of infections.

Author Contributions

Manuscript draft—CR, GN, AKM, KJJ, AL; Conception of idea—CR, GN, AL; Data Accrual—CR, GN, AKM; Figures and Tables—CR, GN, KJJ; Critical review and revision of manuscript—CR, GN, AKM, KJJ, AL. All authors reviewer and approved the final version of the manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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