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REVIEW ARTICLE

A Rapid Systematic Review of U.S. Food and Drug Administration-Authorized COVID-19 Treatments

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Background. The coronavirus disease 2019 (COVID-19) pandemic era saw numerous treatments authorized for emergency use by the United States (US) Food and Drug Administration (FDA). The purpose of the review was to determine if convalescent plasma, antivirals, or monoclonal antibodies are associated with serious adverse events (SAEs) and, if so, which specific populations are at risk.

Methods. PubMed, ClinicalTrials.gov, and the FDA submission database were searched through December 2023, and the Infectious Diseases Society of America guidelines, international COVID Network Meta-analysis database, and systematic reviews were reference mined to identify controlled studies with at least 1 US site. Reviewers abstracted study characteristics, number of patients experiencing each type of SAE, and methods of adverse event collection and reporting.

Results. Fifty-four studies met inclusion criteria, including 31 randomized controlled trials. We found insufficient evidence of association of any SAE with antivirals and spike protein receptor-binding antibodies. In patients hospitalized with COVID-19, the monoclonal antibody tocilizumab, an interleukin 6 inhibitor, may be associated with elevated risk of neutropenia (moderate certainty) and infection (limited certainty). Convalescent plasma may be associated with thrombotic events (limited certainty) as well as bleeding events and infection in patients with hematologic cancers (moderate certainty). Inclusion of studies without a US site could potentially change the findings.

Conclusions. Severe COVID-19 infection may have serious consequences, especially in hospitalized patients with comorbidities. These consequences may be confused with toxicities of the interventions. Based on our analysis, approved treatments for COVID-19 should be prescribed as clinically indicated, although continued vigilance is warranted to identify rare and potentially significant toxicities that may arise in clinical practice.

Clinical Trials Registration. PROSPERO (CRD42023467821).

Keywords. adverse events; convalescent plasma; COVID-19; spike protein receptor-binding antibodies; tocilizumab.

The coronavirus disease 2019 (COVID-19) pandemic era saw numerous treatments authorized for emergency use by the United States (US) Food and Drug Administration (FDA). The objective of this expedited review was to assess potential serious harms associated with COVID-19 treatments. The review was requested by the Health Resources and Services Administration (HRSA) Countermeasures Injury Compensation Program (CICP) to aid in developing a Countermeasures Injury Table, guiding benefits eligibility determinations for covered injuries or deaths. Commissioned by the Agency for Healthcare Research and Quality (AHRQ) and executed by an evidence-based practice center, the review employed abbreviated methods to assess evidence regarding treatments specified by HRSA: antivirals (remdesivir, nirmatrelvir and ritonavir in combination, and molnupiravir), monoclonal antibodies (bamlanivimab and etesevimab in combination, bebtelovimab, casirivimab and imdevimab in combination, sotrovimab, tixagevimab and cilgavimab in combination, and tocilizumab), and convalescent plasma.

METHODS

In December 2023, we searched PubMed, ClinicalTrials.gov, and the FDA submission database from January 2020 onward

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and the Cochrane Database of Systematic Reviews from January 2022 onward. We reference mined the Infectious Diseases Society of America guidelines, the international COVID Network Meta-Analysis database, and systematic reviews from 2022 and 2023. Full search terms are available in Supplementary Table 1.

We characterized serious adverse events (SAEs) using the definition of "serious injury" by US statute 42 Code of Federal Regulations 110.3(z): "Physical biochemical alterations leading to physical changes and serious functional abnormalities at the cellular or tissue level in any bodily function may, in certain circumstances, be considered serious injuries. As a general matter, only injuries that warranted hospitalization (whether or not the person was actually hospitalized) or injuries that led to a significant loss of function or disability (whether or not hospitalization was warranted) will be considered serious injuries" [1].

Eligible studies were required to have a placebo, untreated, or usual care comparison group. Having a comparison group that did not receive the intervention provides important information about the background rate of adverse events (AEs) in its absence. Numerous serious medical problems occur in patients hospitalized with COVID-19, given patients' advanced age, multiple preexisting medical conditions, and the natural sequalae of COVID-19 infection. This rate is essential for understanding what would be expected to occur naturally in the absence of any intervention. Thus, no case reports, case series, or uncontrolled surveillance studies were included. Head-to-head comparisons of medications were also excluded.

Per HRSA, the review was limited to studies that included at least 1 US site or territory where populations are permitted to submit a CICP claim.

Most studies used the Common Terminology Criteria for Adverse Events levels to classify AEs. The severity categories range from 1 to 5; we abstracted those at level 3, defined as "severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling" or higher. Researchers abstracted exact events as stated except pulmonary embolism and deep vein thrombosis, which were grouped as thrombotic events, and arterial or venous bleeding, grouped as bleeding events; we grouped all serious infections including sepsis, per prior work conducted for AHRQ [2]. For applicability, we abstracted data for the dosage authorized by the FDA when available. AE data were converted to rates for intervention and comparison groups; rates were used to compute risk ratios (RRs) to estimate effects. The Haldane-Anscombe correction was used to calculate RRs when there were zero events in 1 arm [3]. Reviewers worked individually; data were checked by the project leader.

We assessed risk of bias with respect to AEs using 2 domains: whether collection was passive (ie, whether outpatients contacted researchers if they experienced an event rather than the researchers actively contacting each patient and asking about a predetermined list of events); and whether the authors reported the proportion of patients experiencing each event (eg, rather than the total number of events because a patient could experience an event more than once, in which case the proportion of patients would lead to an underestimate of the number of events). As our project did not assess efficacy or comparative effectiveness of COVID-19 treatments, we did not include items that measure bias affecting efficacy or effectiveness outcomes, per prior AHRQ projects focused on intervention harms [4].

We summarized the RRs for each intervention and each event. Where possible, we summarized RRs for specific populations such as those hospitalized with specific COVID-19 symptoms, pregnant women, and those with preexisting medical conditions. Meta-analysis was not considered appropriate given the small number of trials reporting rare events; instead, we estimated effect sizes for each individual study.

We used a tool specific to adverse effects of vaccines to assess certainty of evidence [5] and differentiated the following levels:

- High: 2 or more studies with negligible methodological limitations that are consistent in terms of the direction of the effect provide high confidence.
- Moderate: 1 study with negligible methodological limitations, or a collection of studies generally consistent in terms of the direction of the effect, that provides moderate confidence.
- Limited: 1 study or a collection of studies lacking precision or consistency that provides limited, or low, confidence.
- Insufficient: No epidemiologic studies of sufficient quality.

RESULTS

After full text review of 320 publicly available documents, 54 studies published in 66 publications met eligibility criteria [6–71]. A literature flow diagram is available in Supplementary Figure 1. The primary reasons for exclusion were lack of US study locations (n = 70) and lack of reporting of AEs in studies of efficacy or effectiveness (n = 33). The number of included studies per intervention ranged from 1 (tixagevimab and cilgavimab) to 15 (convalescent plasma).

Thirty-one randomized controlled trials and 23 controlled observational studies met inclusion criteria. Fifteen studies compared an intervention to no treatment, 26 were placebo-controlled trials, and 12 studies compared an intervention to usual care. One observational study compared patients who received hydroxychloroquine with a group who received hydroxychloroquine plus tocilizumab [28]. Interventions were administered in an outpatient setting in 23 studies; the remainder involved patients hospitalized with COVID-19.

It was uncommon for studies to report the exact timing of AEs; researchers usually provided a table listing all SAEs that occurred within a specific number of days from administration. Most clinical trials, via ClinicalTrials.gov, provided a table that used MedDRA (Medical Dictionary for Regulatory Activities definitions) [72] terms for AEs and standard definitions of severity according to the Common Terminology Criteria for Adverse Events [73].

As displayed in the results tables, most studies (n = 37) had low overall risk of bias regarding the collection and reporting of AEs. Because manufacturers sought Emergency Use Authorization from the FDA, clinical trials carefully monitored and reported AEs, adhering to expected standards. Twelve studies were rated as moderate or unclear risk of bias; most were observational studies with unclear timing or data collection procedures. These were primarily conducted in hospitals where patients presumably were monitored regularly, but we did not make assumptions when this was not stated and classified AE collection in these cases as unclear. Five observational studies had high risk of bias; they focused on efficacy or effectiveness and included only a statement that certain AEs (eg, transfusion-related acute lung injury and transfusion-associated circulatory overload) did not occur. Below we discuss findings of statistical and clinical significance.

Insufficient evidence was found to establish an association between any antiviral treatment for COVID-19 (remdesivir, nirmatrelvir and ritonavir combination, and molnupiravir) and any SAE. There were no statistically significant differences between medication and comparison group for any SAE in any study. Detailed data are provided in Supplementary Tables 2–4.

Similarly, there was insufficient evidence of association between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein receptor-binding antibodies (bamlanivimab/etesevimab, bebtelovimab, sotrovimab, casirivimab/imdevimab, tixagevimab/cilgavimab) and any SAE. Notably, the few statistically significant differences observed all favored a reduced risk for patients receiving antibody treatment. Information is presented in Supplementary Tables 5–9.

As displayed in Table 1, 4 controlled trials [17, 51, 52, 58] and 8 observational studies [10, 20, 23, 25, 28, 29, 47, 50] of tocilizumab reported SAEs. All studies involved hospitalized patients; reporting periods ranged from 5 to 90 days. Risk of bias was low in 5 studies; the rest had a moderate or unclear risk of bias.

In 1 trial with low risk of bias [29], a significantly increased risk of infection in critically ill patients was observed (RR, 1.72 [95% confidence interval {CI}, 1.04–2.83]). Another large randomized controlled trial with low risk of bias administered tocilizumab after COVID-19 patients started organ support in the intensive care unit [17]. Patients on extracorporeal membrane oxygenation (ECMO) or intravenous infusion of a vasopressor or inotrope for cardiovascular support were included. Other studies included patients on ECMO but did not stratify AE results for that group. Within 90 days, the risk of infection was elevated (RR, 3.42 [95% CI, 0.14–83.57]) but not statistically significant based on only 1 of 353 intervention patients and none of 402 usual care patients experiencing infection. Tocilizumab patients had significantly reduced risk in 1 study [58], while 8 other studies had statistically insignificant results in conflicting directions. Certainty of evidence for the association of tocilizumab with serious infection was rated as limited.

Patients on tocilizumab demonstrated a significantly higher risk of neutropenia (RR, 11.20 [95% CI, 1.54–81.67]) within 28 days in 1 low-bias trial involving 243 patients [58]; 1 tocilizumab patient experienced grade 4 neutropenia (severe, absolute neutrophil count [ANC] <500 cells/μL, very high risk of life-threatening infection) and 21 experienced grade 3 neutropenia (moderate, ANC 500–999 cells/μL). Only 1 placebo patient had neutropenia (grade 3). A trial exclusively focused on patients with COVID-19–related pneumonia [51] reported neutropenia occurring in 4 of 295 patients in the tocilizumab arm, with no occurrences in the placebo arm within 60 days of administration. Although not statistically significant (RR, 4.38 [95% CI, .24–80.77]), investigators noted this potential risk in the submission for FDA approval. A small observational study reported no cases [23]. Certainty of evidence for the association of tocilizumab with neutropenia was rated as moderate.

We identified 15 controlled studies of convalescent plasma reporting SAEs [6, 7, 9, 11, 13, 24, 30, 33, 36, 39, 40, 53, 55, 60, 62] with timing ranging from 14 to 90 days (Table 2). Regarding AE collection and reporting, 9 had low risk of bias, 3 had moderate/unclear risk of bias, and 3 had high risk of bias. One trial reported no significant difference in the risk for all-cause mortality but did not report specific AEs [9]. Only 1 study reported significantly increased risk of SAEs; this study of hematological cancer patients with moderate/unclear risk of bias [62] showed increased risk of bleeding (RR, 1.96 [95% CI, 1.14–3.36]) and infection (RR, 1.79 [95% CI, 1.41–2.26]). Certainty of evidence was rated as moderate that the administration of convalescent plasma specifically to patients with hematologic cancers is associated with an elevated risk of serious bleeding events and infection. In the same study, congestive heart failure was diagnosed in 10 of the 143 patients who received plasma and <5 of the 143 matched patients who received usual care; unfortunately, the RR was not calculable because the authors did not report patient numbers when <5 patients experienced an AE. Certainty of evidence was rated as limited due to lack of reporting of the exact number of patients experiencing the event in the comparison group.

Two studies reported cerebrovascular accident cases in the intervention group but not the control group [36, 40]; risk was elevated 2- to 5-fold but was not statistically significant. Another trial reported decreased risk that was not statistically significant [7]. Risk of bias was low in these trials. Certainty of evidence for cerebrovascular accident is insufficient due to

Table 1. Serious Adverse Events in Studies of Tocilizumab

Serious Adverse Event	Study ID	Days	Intervention, no./ No.	Control, no./ No.	Study Name	Dose	Risk Ratio (95% CI)	Risk of Bias
Acute kidney injury	Kewan, 2020 [28]	10	15/28	13/23	Tocilizumab for Severe COVID-19	400 mg	0.95 (.58–1.56)	Low
	Rajendram, 2021 [47]	28	18/82	27/82	Tocilizumab in Critical COVID	4–8 mg/kg	0.67 (.40–1.11)	Moderate/ Unclear
	Rojas-Marte, 2020 [50]	While hospitalized	22/96	13/97	Severe COVID-19 and Tocilizumab: A Case-Controlled Study	8 mg/kg	1.71 (.92–3.19)	Moderate/ Unclear
	Rosas, 2021 [51]	60	10/294	4/295	COVACTA	8 mg/kg	1.22 (.39–3.81)	Moderate/ Unclear
	Salama, 2021 [52]	60	1/250	3/127	EMPACTA	8 mg/kg	0.17 (.02–1.61)	Low
ALT increase	Salama, 2021 [52]	60	2/250	0/127	EMPACTA	8 mg/kg	2.55 (.12–52.72)	Low
	Stone, 2020 [58]	28	8/161	4/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg/kg	1.02 (.32–3.28)	Low
Allergic reaction (not anaphylaxis)	Stone, 2020 [58]	28	0/161	1/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg/kg	0.17 (.01–4.15)	Low
Anaphylaxis	Rosas, 2021 [51]	28	0/295	1/143	COVACTA	8 mg/kg	0.16 (.01–3.96)	Moderate/ Unclear
AST increase	Rosas, 2021 [51]	60	1/295	0/143	COVACTA	8 mg/kg	1.46 (.06–35.60)	Moderate/ Unclear
	Stone, 2020 [58]	28	6/161	3/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg/kg	1.02 (.26–3.97)	Low
Bleeding	Gordon, 2021 [17]	90	5/353	4/402	REMAP-CAP	8 mg/kg	1.42 (.39–5.26)	Low
	Rosas, 2021 [51]	60	9/294	4/143	COVACTA	8 mg/kg	1.09 (.34–3.49)	Moderate/ Unclear
	Salama, 2021 [52]	60	0/250	1/127	EMPACTA	8 mg/kg	0.17 (.01–4.14)	Low
	Stone, 2020 [58]	28	0/161	1/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg/kg	0.17 (.01–4.15)	Low
Cardiac arrythmia	Gupta, 2021 [20]	14	63/433	602/3491	Early Tocilizumab for Severe COVID	NR	0.84 (.66–1.07)	Low
	Rosas, 2021 [51]	60	3/295	1/143	COVACTA	8 mg/kg	1.45 (.15–13.86)	Moderate/ Unclear
	Salama, 2021 [52]	60	1/250	1/127	EMPACTA	8 mg/kg	0.51 (.03–8.06)	Low
	Stone, 2020 [58]	28	0/161	1/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg/kg	0.17 (.01–4.15)	Low
Cerebrovascular accident	Hill, 2021 [23]	14	0/43	0/45	Tocilizumab in Hospitalized Patients With COVID	400 mg	1.05 (.02–51.55)	Moderate/ Unclear
	Rosas, 2021 [51]	60	1/295	1/143	COVACTA	8 mg/kg	0.48 (.03–7.69)	Moderate/ Unclear
	Stone, 2020 [58]	28	2/161	0/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg/kg	2.56 (.12–52.75)	Low
Hypertension	Rosas, 2021 [51]	60	1/295	1/143	COVACTA	8 mg/kg	0.48 (.03–7.69)	Moderate/ Unclear
	Salama, 2021 [52]	60	0/250	1/127	EMPACTA	8 mg/kg	0.17 (.01–4.14)	Low
	Stone, 2020 [58]	28	0/161	1/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg/kg	0.17 (.01–4.15)	Low

Table 1. Continued

Serious Adverse Event	Study ID	Days	Intervention, no./ No.	Control, no./ No.	Study Name	Dose	Risk Ratio (95% CI)	Risk of Bias
Hypotension	Rosas, 2021 [51]	60	1/295	1/143	COVACTA	8 mg/kg	0.48 (.03–7.69)	Moderate/ Unclear
	Salama, 2021 [52]	60	0/250	1/127	EMPACTA	8 mg/kg	0.17 (.01–4.14)	Low
	Stone, 2020 [58]	28	3/161	2/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg/kg	0.76 (.13–4.48)	Low
Infection including sepsis	Biran, 2020 [10]	22	18/210	33/420	Tocilizumab for COVID-19 in the Intensive Care Unit	400 mg	1.09 (.63–1.89)	Low
	Gordon, 2021 [17]	90	1/353	0/402	REMAP-CAP	8 mg/kg	3.42 (.14–83.57)	Low
	Gupta, 2021 [20]	14	140/433	1085/3491	Early Tocilizumab for Severe COVID	NR	1.04 (.90–1.20)	Low
	Hill, 2021 [23]	14	13/43	9/45	Tocilizumab in Hospitalized Patients With COVID	400 mg	1.51 (.72–3.17)	Moderate/ Unclear
	Kewan, 2020 [28]	10	5/28	5/23	Tocilizumab for Severe COVID-19	400 mg	0.82 (.27–2.49)	Low
	Kimmig, 2020 [29]	5	26/54	16/57	Increased Secondary Infections in Critically Ill COVID-19 Patients	400 mg	1.72 (1.04–2.83)[a]	Low
	Rajendram, 2021 [47]	28	21/82	21/82	Tocilizumab in Critical COVID	4–8 mg/kg	1.00 (.59–1.68)	Moderate/ Unclear
	Rojas-Marte, 2020 [50]	While hospitalized	12/96	23/97	Severe COVID-19 and Tocilizumab: A Case-Controlled Study	8 mg/kg	0.53 (.28–1.00)	Moderate/ Unclear
	Rosas, 2021 [51]	60	90/295	55/143	COVACTA	8 mg/kg	0.79 (.61–1.04)	Moderate/ Unclear
	Salama, 2021 [52]	60	13/250	8/127	EMPACTA	8 mg/kg	0.83 (.35–1.94)	Low
	Stone, 2020 [58]	28	13/161	14/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg/kg	0.47 (.23–.96)[a]	Low
Myocardial infarction	Hill, 2021 [23]	14	0/43	0/45	Tocilizumab in Hospitalized Patients With COVID	400 mg	1.05 (.02–51.55)	Moderate/ Unclear
	Rosas, 2021 [51]	60	1/295	0/143	COVACTA	8 mg/kg	1.46 (.06–35.60)	Moderate/ Unclear
	Salama, 2021 [52]	60	0/250	1/127	EMPACTA	8 mg/kg	0.17 (.01–4.14)	Low
	Stone, 2020 [58]	28	0/161	1/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg/kg	0.17 (.01–4.15)	Low
Neutropenia	Hill, 2021 [23]	14	0/43	0/45	Tocilizumab in Hospitalized Patients With COVID	400 mg	1.05 (.02–51.55)	Moderate/ Unclear
	Rosas, 2021 [51]	60	4/295	0/143	COVACTA	8 mg/kg	4.38 (.24–80.77)	Moderate/ Unclear
	Stone, 2020 [58]	28	22/161	1/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg/kg	11.20 (1.54–81.67)[a]	Low
Seizure	Rosas, 2021 [51]	60	1/295	1/143	COVACTA	8 mg/kg	0.48 (.03–7.69)	Moderate/ Unclear
	Stone, 2020 [58]	28	0/161	1/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg/kg	0.17 (.01–4.15)	Low
Transfusion-related lung injury	Rosas, 2021 [51]	60	0/295	1/143	COVACTA	8 mg/kg	0.16 (.01–3.96)	Moderate/ Unclear
Thrombotic event	Gupta, 2021 [20]	14	46/433	342/3491	Early Tocilizumab for Severe COVID	NR	1.08 (.81–1.45)	Low

Table 1. Continued

Serious Adverse Event	Study ID	Days	Intervention, no./No.	Control, no./No.	Study Name	Dose	Risk Ratio (95% CI)	Risk of Bias
	Hill, 2021 [23]	14	5/43	2/45	Tocilizumab in Hospitalized Patients With COVID	400 mg	2.62 (.54–12.77)	Moderate/ Unclear
	Kewan, 2020 [28]	10	3/28	2/23	Tocilizumab for Severe COVID-19	400 mg	1.23 (.22–6.76)	Low
	Rosas, 2021 [51]	60	1/295	1/143	COVACTA	8 mg/kg	0.48 (.03–7.69)	Moderate/ Unclear
	Stone, 2020 [58]	28	4/161	5/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg/kg	0.41 (.11–1.48)	Low

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; COVID-19, coronavirus disease 2019; NR, Not Reported.

[a] $P < .05$.

Table 2. Serious Adverse Events in Studies of Convalescent Plasma

Serious Adverse Event	Study ID	Days	Intervention, no./No.	Control, no./No.	Study Name	Dose	Risk Ratio (95% CI)	Risk of Bias
Acute kidney injury	Begin, 2021 [7]	30	12/614	7/307	CONCOR-1	500 mL	0.86 (.34–2.16)	Low
	Korley, 2021 [30]	30	1/257	0/254	SIREN-C3PO	200 mL	2.97 (.12–72.45)	Low
	Ortigoza, 2022 [40]	90	16/468	19/473	CONTAIN	250 mL	0.85 (.44–1.63)	Low
	Self, 2022 [55]	90	2/495	10/479	Pass It On	500 mL	4.84 (.23–100.53)	Low
	Thompson, 2021 [62]	30	37/143	222/823	Convalescent Plasma and Hematologic Cancers	Not reported	0.96 (.71–1.29)	Moderate/ Unclear
ALT increase	Ortigoza, 2022 [40]	90	5/468	3/473	CONTAIN	250 mL	1.68 (.40–7.01)	Low
Anaphylaxis	Korley, 2021 [30]	30	1/257	0/254	SIREN-C3PO	200 mL	2.97 (.12–72.45)	Low
Allergic reaction (not anaphylaxis)	Salazar, 2021 [53]	60	1/351	0/594	High-Titer Convalescent Plasma for Severe COVID-19	300 mL	5.07 (.21–124.14)	High
Bleeding	Bar, 2021 [6]	60	1/40	0/39	PennCCP2	2 units	2.93 (.12–69.74)	Moderate/ Unclear
	Begin, 2021 [7]	30	8/614	1/307	CONCOR-1	500 mL	4.00 (.50–31.84)	Low
	Misset, 2023 [36]	28	9/237	14/238	Convalescent Plasma for COVID-19 Induced ARDS in Mechanically Ventilated Patients	400–500 mL	0.65 (.28–1.46)	Low
	Ortigoza, 2022 [40]	90	35/468	41/473	CONTAIN	250 mL	0.86 (.56–1.33)	Low
	Thompson, 2021 [62]	30	16/143	47/823	Convalescent Plasma and Hematologic Cancers	Not reported	1.96 (1.14–3.36)[a]	Moderate/ Unclear

Table 2. Continued

Serious Adverse Event	Study ID	Days	Intervention, no./No.	Control, no./No.	Study Name	Dose	Risk Ratio (95% CI)	Risk of Bias
Cardiac arrythmia	Bar, 2021 [6]	60	1/40	0/39	PennCCP2	2 units	2.93 (.12–69.74)	Moderate/ Unclear
	Begin, 2021 [7]	30	0/614	3/307	CONCOR-1	500 mL	0.07 (.00–1.38)	Low
	Korley, 2021 [30]	30	1/257	1/254	SIREN-C3PO	200 mL	0.99 (.06–15.72)	Low
	Ortigoza, 2022 [40]	90	23/468	16/473	CONTAIN	250 mL	1.45 (.78–2.71)	Low
	Self, 2022 [55]	90	0/495	1/479	Pass It On	500 mL	0.32 (.01–7.90)	Low
	Thompson, 2021 [62]	30	5/143	27/823	Convalescent Plasma and Hematologic Cancers	Not reported	1.07 (.42–2.72)	Moderate/ Unclear
Cerebrovascular accident	Begin, 2021 [7]	30	0/614	2/307	CONCOR-1	500 mL	0.10 (.00–2.08)	Low
	Misset, 2023 [36]	28	1/237	0/238	Convalescent Plasma for COVID-19 Induced ARDS in Mechanically Ventilated Patients	400–500 mL	3.01 (.12–73.58)	Low
	Ortigoza, 2022 [40]	90	2/468	0/473	CONTAIN	250 mL	5.05 (.24–104.97)	Low
Fever	Begin, 2021 [7]	30	1/614	0/307	CONCOR-1	500 mL	1.50 (.06–36.77)	Low
	Chauhan, 2022 [13]	Unclear, varied	1/188	0/188	Convalescent Plasma for Hospitalized Patients	100–250 mL	3.00 (.12–73.18)	Moderate/ Unclear
Headache	Bar, 2021 [6]	60	1/40	0/39	PennCCP2	2 units	2.93 (.12–69.74)	Moderate/ Unclear
	Sullivan, 2022 [60]	90	0/592	1/589	CSSC-004	250 mL	0.33 (.01–8.12)	Low
Hypotension	Bar, 2021 [6]	60	0/40	2/39	PennCCP2	2 units	0.20 (.01–3.94)	Moderate/ Unclear
	Begin, 2021 [7]	30	8/614	0/307	CONCOR-1	500 mL	8.51 (.49–147.02)	Low
	Korley, 2021 [30]	30	1/257	0/254	SIREN-C3PO	200 mL	2.97 (.12–72.45)	Low
	Ortigoza, 2022 [40]	90	38/468	55/473	CONTAIN	250 mL	0.70 (.47–1.03)	Low
	Self, 2022 [55]	90	1/495	1/479	Pass It On	500 mL	0.97 (.06–15.43)	Low
	Sullivan, 2022 [60]	90	0/592	1/589	CSSC-004	250 mL	0.33 (.01–8.12)	Low
Hypertension	Sullivan, 2022 [60]	90	2/592	1/589	CSSC-004	250 mL	1.99 (.18–21.89)	Low
Infection including sepsis	Begin, 2021 [7]	30	20/614	10/307	CONCOR-1	500 mL	1.00 (.47–2.11)	Low
	Korley, 2021 [30]	30	32/257	40/254	SIREN-C3PO	200 mL	0.79 (.51–1.22)	Low
	Misset, 2023 [36]	28	24/237	21/238	Convalescent Plasma for COVID-19 Induced ARDS in Mechanically Ventilated Patients	400–500 mL	1.15 (.66–2.00)	Low
	O'Donnell, 2021 [39]	28	5/147	10/72	AAAS9924	200–250 mL	0.24 (.09–.69)[a]	Low
	Ortigoza, 2022 [40]	90	36/468	55/473	CONTAIN	250 mL	0.73 (.48–1.10)	Low
	Self, 2022 [55]	90	4/495	2/479	Pass It On	500 mL	1.94 (.36–10.52)	Low
	Sullivan, 2022 [60]	90	0/592	0/589	CSSC-004	250 mL	0.99 (.02–50.06)	Low
	Thompson, 2021 [62]	30	58/143	187/823	Convalescent Plasma and Hematologic Cancers	Not reported	1.79 (1.41–2.26)[a]	Moderate/ Unclear
Myocardial infarction	Begin, 2021 [7]	30	3/614	2/307	CONCOR-1	500 mL	0.75 (.13–4.46)	Low
	Ortigoza, 2022 [40]	90	61/468	70/473	CONTAIN	250 mL	0.88 (.64–1.21)	Low
	Self, 2022 [55]	90	1/495	1/479	Pass It On	500 mL	0.97 (.06–15.43)	Low
	Thompson, 2021 [62]	30	5/143	26/823	Convalescent Plasma and Hematologic Cancers	Not reported	1.11 (.43–2.83)	Moderate/ Unclear

Table 2. Continued

Serious Adverse Event	Study ID	Days	Intervention, no./No.	Control, no./No.	Study Name	Dose	Risk Ratio (95% CI)	Risk of Bias
Seizure	Korley, 2021 [30]	30	1/257	0/254	SIREN-C3PO	200 mL	2.97 (.12–72.45)	Low
Thrombotic event	Bar, 2021 [6]	60	2/40	1/39	PennCCP2	2 units	1.95 (.18–20.64)	Moderate/ Unclear
	Begin, 2021 [7]	30	4/614	2/307	CONCOR-1	500 mL	1.00 (.18–5.43)	Low
	Korley, 2021 [30]	30	3/257	2/254	SIREN-C3PO	200 mL	1.48 (.25–8.80)	Low
	Ortigoza, 2022 [40]	90	22/468	14/473	CONTAIN	250 mL	1.59 (.82–3.07)	Low
	Self, 2022 [55]	90	1/495	1/479	Pass It On	500 mL/h	0.97 (.06–15.43)	Low
	Sullivan, 2022 [60]	90	2/592	0/589	CSSC-004	250 mL	4.97 (.24–103.4)	Low
	Thompson, 2021 [62]	30	15/143	63/823	Convalescent Plasma and Hematologic Cancers	Not reported	1.37 (.80–2.34)	Moderate/ Unclear
Transfusion-associated lung injury	Begin, 2021 [7]	30	1/614	0/307	CONCOR-1	500 mL	1.50 (.06–36.77)	Low
	Briggs, 2021 [11]	14	0/132	0/132	Early vs Late Convalescent Plasma for Moderate to Severe COVID-19	200 mL	1.00 (.02–50.03)	High
	Chauhan, 2022 [13]	Unclear, varied	0/188	0/188	Convalescent Plasma for Hospitalized Patients	100–250 mL	1.00 (.02–50.14)	Moderate/ Unclear
	Liu, 2020 [33]	14	0/39	0/39	Convalescent Plasma for Severe COVID-19	Not reported	1.00 (.02–49.17)	High
	Ortigoza, 2022 [40]	90	0/468	0/473	CONTAIN	250 mL	1.01 (.02–50.83)	Low
	Self, 2022 [55]	Unclear	0/487	0/473	Pass It On	500 mL	0.97 (.02–48.85)	Low
Transfusion-associated circulatory overload	Briggs, 2021 [11]	14	0/132	0/132	Early vs Late Convalescent Plasma for Moderate to Severe COVID-19	200 mL	1.00 (.02–50.03)	High
	Chauhan, 2022 [13]	Unclear, varied	0/188	0/188	Convalescent Plasma for Hospitalized Patients	100–250 mL	1.00 (.02–50.14)	Moderate/ Unclear
	Liu, 2020 [33]	14	0/39	0/39	Convalescent Plasma for Severe COVID-19	Not reported	1.00 (.02–49.17)	High
	Ortigoza, 2022 [40]	90	0/468	0/473	CONTAIN	250 mL	1.01 (.02–50.83)	Low
	Salazar, 2021 [53]	60	1/351	0/594	High-Titer Plasma for Severe COVID-19	300 mL, titer 1:1350	5.07 (.21–124.14)	High
	Self, 2022 [55]	28	1/487	0/473	Pass It On	500 mL	2.91 (.12–71.35)	Low

Abbreviations: ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; CI, confidence interval; COVID-19, coronavirus disease 2019.

[a] $P < .05$.

ack of statistical significance, extremely wide CIs, and inconsistent findings.

Seven studies of convalescent plasma reported serious thrombotic events [6, 7, 30, 40, 55, 60, 62]; 5 of the these reported elevated risk (1 almost 5-fold [60]), but results were not statistically significant. Only 1 journal manuscript mentioned these events; Thompson et al [62] reported that rates of venous thrombosis (10.5% vs 8.4%) and arterial thrombotic events (3.5% vs 3.5%) were comparable in patients receiving convalescent plasma and propensity-matched controls. The other events were identified through online supplements, FDA filings, and ClinicalTrials.gov. Review of a supplement to another journal article [30] identified a death in a convalescent plasma patient with pulmonary embolism; this death was classified as not related to the study intervention. The other studies provided little or no detail on type or consequence of the events. Certainty of evidence is limited due to conflicting results, lack of statistical significance, and wide CIs.

Two studies showed highly elevated but not statistically significant risk of transfusion-associated circulatory overload based on only 1 person experiencing it; a study of high-titer plasma for severe COVID-19 [53] had high risk of bias, whereas the PassItOn trial [55] had low risk of bias. Certainty of evidence is insufficient due to risk of bias, lack of statistical significance, and extremely wide CIs.

DISCUSSION

We identified few associations between pharmaceutical interventions authorized for emergency use to treat COVID-19 and SAEs. The associations found included an increased risk of infection and serious bleeding events in 1 trial of patients with hematologic cancers who received convalescent plasma. Certainty of evidence was rated moderate. Both increased risk of infection and bleeding events might be expected given the patient population.

Although AEs previously reported as associated with convalescent plasma such as allergic reactions, transfusion-related acute lung injury, and transfusion-associated circulatory overload [74] were reported in controlled studies, there was insufficient evidence of increased risk compared to placebo infusion. Evidence of limited certainty from 7 studies suggested that convalescent plasma may be associated with serious thrombotic events among patients hospitalized for COVID-19, aligning with product labeling that identifies blood clotting as a potential AE.

We found no evidence of an association of SARS-CoV-2 antiviral treatment with SAEs. This is consistent with a prior network meta-analysis of antiviral agents for COVID-19 treatment that found no increased risk of AEs when compared with placebo [75].

While infusion-related reactions ranging from mild to severe are common among recipients of monoclonal antibodies [76], we found insufficient evidence of elevated risk of these reactions when compared with placebo infusions. The studies of SARS-CoV-2 spike protein receptor-binding antibodies (bamlanivimab/etesevimab, bebtelovimab, sotrovimab, casirivimab/imdevimab, tixagevimab/cilgavimab) showed no association with any SAE. We identified evidence of moderate certainty that tocilizumab, an interleukin 6 inhibitor, may be associated with elevated risk of neutropenia, a previously described adverse effect [77] noted on the product label. We also identified evidence of limited certainty that tocilizumab may be associated with an increased risk of infection, as described previously in patients with arthritis [78].

A serious limitation of this review is the inclusion requirement that studies have at least 1 US site. Inclusion of studies conducted in other regions could potentially change or strengthen the findings. The certainty of evidence for the findings described above could increase if additional studies showed elevated risk but could decrease if those studies showed no elevated risk. Studies from other regions might also report elevated risks for additional SAEs.

Due to the abbreviated timeline, we worked with published reviews and searched PubMed to identify studies, supplemented by trial registry searches and FDA submission. While it is not impossible that we missed studies, we believe that selection bias was avoided (no studies missed) given that Emergency Use Authorization for COVID-19 treatment required study submission to the FDA for review.

Most studies focused on efficacy of the intervention; many journal articles did not report AEs classified as serious if there was no significant difference with the control group rate. We identified these events through supplements, FDA filings, and ClinicalTrials.gov. Future manuscripts on COVID-19 treatments should report all SAEs, regardless of statistical significance.

Another limitation is that although most studies included patients with various conditions such as chronic obstructive pulmonary disease, obesity, cardiovascular disease, diabetes, chronic kidney disease, and cancer, few were limited to patients with a specific preexisting condition or reported AE data stratified by specific preexisting conditions. No studies reported AEs for specific age groups such as adolescents or older adults.

We limited to studies with a control group to detect elevated rates of events. Such studies are crucial in determining the true association of a side effect with the intervention being studied. Excluded uncontrolled studies may provide signals that should be investigated further, but controlled studies help establish whether observed AEs are directly caused by the treatment rather than being manifestations of the disease process, thus providing more accurate and reliable information for clinical decision-making. For example, a 2021 analysis of AE reports submitted to the FDA Adverse Event Reporting System found that bradycardia and cardiac arrest had disproportionately

higher reporting with remdesivir as a suspect drug compared with other medications [79]. The authors suggested reevaluation for possible drug-labeling changes. In contrast, we found no SAEs associated with remdesivir. By comparing an intervention against either a placebo or an alternative treatment, researchers can isolate the effects of the intervention from those that might naturally occur due to the underlying disease itself.

In sum, no associations between FDA-authorized COVID-19 treatments and increased risk of SAEs had high-certainty evidence. The lack of statistically significant association of most SAEs with treatments for COVID-19, when compared with no treatment, placebo, or usual care, suggests that adverse outcomes may be the result of COVID-19 itself. Severe COVID-19 infection may have serious consequences, especially in hospitalized patients with comorbidities [80].

These consequences may be confused with toxicities of the interventions. Based on our analysis, approved treatments for COVID-19 should be prescribed as clinically indicated, although continued vigilance is warranted to identify rare and potentially significant toxicities that may arise in clinical practice.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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