## Evidence Search Service Results of your search request

**Incidence of septicaemia in Covid patients**

Thank you for requesting this evidence search. We hope you find the results useful. If you would like to discuss the findings or require an additional search, please contact: Alison McLaren[alisonmclaren1@nhs.net](mailto:alisonmclaren1@nhs.net)

Please acknowledge this work in any resulting paper or presentation as: *Evidence search: Incidence of septicaemia in Covid patients* Alison McLaren. (4 March 2021). East Surrey Hospital, UK: Surrey and Sussex Library and Knowledge Services.

## Search Notes

UpToDate and BMJ best Practice were searched as were NICE, the Cochrane Library and various databases. Two pre-print publications have been included from MedRxiV although these have not been peer reviewed.

These papers explore and discuss the links between septicaemia and viral sepsis in patients with COVID-19 in those admitted to ICU.

## Contents

[A. National and International Guidance](#Content1)

Society of Critical Care Medicine

[Surviving Sepsis Campaign Guidelines on the Management of Adults With Coronavirus Disease 2019 (COVID-19) in the ICU: First Update](#Research862008)

[B. Synopses or Summaries](#Content2)

BMJ Best Practice

[Coronavirus disease 2019 (COVID-19)](#Research861899)

UpToDate

[Coronavirus disease 2019 (COVID-19): Clinical features](#Research861900)

[C. Systematic Reviews](#Content3)

MedRxiv

[COVID-19 as cause of viral sepsis: A Systematic Review and Meta-Analysis](#Research862034)

[D. Original Research](#Content5)

1. [Acute covid-19 and multisystem inflammatory syndrome in children](#Research862010)
2. [Acute respiratory distress syndrome during the COVID-19 pandemic: not only SARS-CoV-2.](#Research861999)
3. [COVID-19 increased the risk of ICU-acquired bloodstream infections: a case-cohort study from the multicentric OUTCOMEREA network.](#Research862001)
4. [Parallels in Sepsis and COVID-19 Conditions: Implications for Managing Severe COVID-19.](#Research862000)
5. [Pathophysiological Clues to How the Emergent SARS-CoV-2 Can Potentially Increase the Susceptibility to Neurodegeneration](#Research861883)
6. [Potential roles of mitochondrial cofactors in the adjuvant mitigation of proinflammatory acute infections, as in the case of sepsis and COVID-19 pneumonia.](#Research862002)
7. [Prophylactic or therapeutic doses of heparins for COVID-19 infection? A retrospective study](#Research861882)
8. [Resolution of Disseminated Intravascular Coagulation in a Patient with COVID-19 and Associated Sepsis-Induced Neutropenia.](#Research862003)
9. [Unexpectedly High Frequency of Enterococcal Bloodstream Infections in Coronavirus Disease 2019 Patients Admitted to an Italian ICU: An Observational Study.](#Research862004)
10. [An alternate venous access in covid-19 patients needing dialysis](#Research862025)
11. [Biclonal gammopathay in a case of severe COVID-19.](#Research861886)
12. [BobaHk COVID-19: ocobeHHocT TokHoBoo poCOVID-19 biobank: features of the cytokine profile](#Research861881)
13. [Coronavirus (Covid-19) sepsis: revisiting mitochondrial dysfunction in pathogenesis, aging, inflammation, and mortality.](#Research862006)
14. [Identification and Analysis of Shared Risk Factors in Sepsis and High Mortality Risk COVID-19 Patients](#Research862031)
15. [Immune Response and COVID-19: A mirror image of Sepsis.](#Research862050)
16. [Mesenchymal stromal cells for sepsis and septic shock: Lessons for treatment of COVID-19.](#Research862005)
17. [PIN117 Identification of Patients with COVID-19 Infection Prior to the New COVID-19 Diagnostic Code - a Premier Database Analysis](#Research861885)
18. [Respiratory viral sepsis: epidemiology, pathophysiology, diagnosis and treatment.](#Research862049)
19. [SARS-CoV-2 and Viral Sepsis: Immune Dysfunction and Implications in Kidney Failure.](#Research862048)
20. [SARS-CoV-2 and viral sepsis: observations and hypotheses.](#Research862007)
21. [Scoring cytokine storm by the levels of MCP-3 and IL-8 accurately distinguished COVID-19 patients with high mortality](#Research861884)

### [E. Search History](#SearchHistory)

## A. National and International Guidance

#### Society of Critical Care Medicine

**Surviving Sepsis Campaign Guidelines on the Management of Adults With Coronavirus Disease 2019 (COVID-19) in the ICU: First Update** (2021)

Waleed Alhazzan et al

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=6d9f81eeaa17423af745537f4518c8b4)

BACKGROUND: The coronavirus disease 2019 pandemic continues to affect millions worldwide. Given the rapidly growing evidence base, we implemented a living guideline model to provide guidance on the management of patients with severe or critical coronavirus disease 2019 in the ICU. METHODS: The Surviving Sepsis Campaign Coronavirus Disease 2019 panel has expanded to include 43 experts from 14 countries; all panel members completed an electronic conflict-of-interest disclosure form. In this update, the panel addressed nine questions relevant to managing severe or critical co-ronavirus disease 2019 in the ICU. We used the World Health Organization’s definition of severe and critical coronavirus disease 2019. The systematic reviews team searched the literature for relevant evidence, aiming to identify systematic reviews and clinical trials. When appropriate, we performed a random-effects meta-analysis to summarize treatment effects. We assessed the quality of the evidence using the Grading of Recommendations, Assessment, Development, and Evaluation approach, then used the evidence-to-decision framework to generate recommendations based on the balance between ben-efit and harm, resource and cost implications, equity, and feasibility. RESULTS: The Surviving Sepsis Campaign Coronavirus Diease 2019 panel issued nine statements (three new and six updated) related to ICU patients with severe or critical coronavirus disease 2019. For severe or critical coro-navirus disease 2019, the panel strongly recommends using systemic corti-costeroids and venous thromboprophylaxis but strongly recommends against using hydroxychloroquine. In addition, the panel suggests using dexamethasone (compared with other corticosteroids) and suggests against using convalescent plasma and therapeutic anticoagulation outside clinical trials. The Surviving Sepsis Campaign Coronavirus Diease 2019 panel suggests using remdesivir in nonventilated patients with severe coronavirus disease 2019 and suggests against starting remdesivir in patients with critical coronavirus di-sease 2019 outside clinical trials. Because of insufficient evidence, the panel did not issue a recommendation on the use of awake prone positioning. CONCLUSION: The Surviving Sepsis Campaign Coronavirus Diease 2019 panel issued several recommendations to guide healthcare professionals caring for adults with critical or severe coronavirus disease 2019 in the ICU. Based on a living guideline model the recommendations will be updated as new evidence becomes available.

## B. Synopses or Summaries

#### BMJ Best Practice

**Coronavirus disease 2019 (COVID-19)** (2021)

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=3fc324570ab0f2bd033fe1042154ace9)

Complications: Early reports suggest that COVID-19 patients treated in the intensive care unit can present with post-intensive care syndrome, a spectrum of psychiatric, cognitive, and/or physical disability (e.g., muscleweakness, cognitive dysfunction, insomnia, depression, anxiety, post-traumatic stress disorder, delirium,encephalopathy) that affects survivors of critical illness, and persists after the patient has been discharged from the intensive care unit. Weakness affects 33% of patients who receive mechanical ventilation, 50% of patients with sepsis, and <50% of patients who remain in the intensive care unit for more than 1week.

#### UpToDate

**Coronavirus disease 2019 (COVID-19): Clinical features** (2021)

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=07002d60ce3e4b42fea48b1ee90fe670)

Inflammatory complications – Some patients with severe COVID-19 have laboratory evidence of an exuberant inflammatory response, with persistent fevers, elevated inflammatory markers (eg, D-dimer, ferritin), and elevated proinflammatory cytokines; these laboratory abnormalities have been associated with critical and fatal illnesses [25,139,140]. Although these features had been likened to cytokine release syndrome (eg, in response to T cell immunotherapy), the levels of proinflammatory cytokines in COVID-19 are substantially lower than those seen with cytokine release syndrome as well as with sepsis...

## C. Systematic Reviews

#### MedRxiv

**COVID-19 as cause of viral sepsis: A Systematic Review and Meta-Analysis** (2020)

Karakike E. et al

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=0107fd04e261c722c01e5dc2a43a7ac5)

***This is a preprint which has not been peer reviewed***. Importance COVID-19 is a heterogenous disease most frequently causing respiratory tract infection but in its severe forms, respiratory failure and multiple organ dysfunction syndrome may occur, resembling sepsis. The prevalence of viral sepsis among COVID-19 patients is still unclear. Objective We aimed to describe this in a systematic review. Data sources MEDLINE(PubMed), Cochrane and Google Scholar databases were searched for studies reporting on patients hospitalized with confirmed COVID-19, diagnosed with sepsis or infection-related organ dysfunctions or receiving organ replacement therapy. Study selection Eligible were full-text English articles of randomized and non-randomized clinical trials and observational studies reporting on patients with confirmed COVID-19, who are diagnosed with sepsis or have infection-related organ dysfunctions. Systematic reviews, editorials, conference abstracts, animal studies, case reports, articles neither in English nor full-text, and studies with fewer than 30 participants were excluded. Data extraction and synthesis All eligible studies were included in a narrative synthesis of results and after reviewing all included studies a meta-analysis was conducted. Separate sensitivity analyses were conducted per adult vs pediatric populations and per Intensive Care Unit (ICU) vs non-ICU populations. Main outcomes and measures Primary endpoint was the prevalence of sepsis using Sepsis-3 criteria among patients with COVID-19 and among secondary, new onset of infection-related organ dysfunction. Outcomes were expressed as proportions with respective 95% confidence interval (CI). Results Of 1,903 articles, 104 were analyzed. The prevalence of sepsis in COVID-19 was 39.9% (95% CI, 35.9-44.1; I2, 99%). In sensitivity analysis, sepsis was present in 25.1% (95% CI, 21.8-28.9; I2 99%) of adult patients hospitalized in non-Intensive-Care-Unit (ICU) wards (40 studies) and in 83.8 (95% CI, 78.1-88.2; I2,91%) of adult patients hospitalized in the ICU (31 studies). Sepsis in children hospitalized with COVID-19 was as high as 7.8% (95% CI, 0.4-64.9; I2, 97%). Acute Respiratory Distress Syndrome was the most common organ dysfunction in adult patients in non-ICU (27.6; 95% CI, 21.6-34.5; I2, 99%) and ICU (88.3%; 95% CI, 79.7-93.5; I2, 97%) Conclusions and relevance Despite the high heterogeneity in reported results, sepsis frequently complicates COVID-19 among hospitalized patients and is significantly higher among those in the ICU. PROSPERO registration number: CRD42020202018. No funding.

## D. Original Research

1. **Acute covid-19 and multisystem inflammatory syndrome in children**  
   Rubens JH et al The BMJ 2021;:-.

What you need to know: Children with acute covid-19 can present with non-specific symptoms. Exclude covid-19 in children with fever and respiratory tract symptoms or loss of taste or smell, especially if there is possible exposure to others with the virus -- Consider multisystem inflammatory syndrome (MIS-C) in children presenting with fever and abdominal symptoms—particularly if they develop conjunctivitis or rash—and refer to a paediatric emergency department for evaluation -- MIS-C can have overlapping symptomatology with disease processes that require prompt treatment, such as sepsis, toxic shock syndrome, myocarditis, and meningitis. Therefore, consider initiation of empiric antibiotics and necessary evaluations if the patient develops cardiovascular or respiratory compromise, evidence of acute abdomen, or meningismus -- Simple prevention measures, including mask wearing, hand hygiene, and social distancing remain crucial to prevent the spread of SARS-CoV-2 in children and adults

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=4ac2905694a8eede9be3efe0ec12b0b7)

1. **Acute respiratory distress syndrome during the COVID-19 pandemic: not only SARS-CoV-2.**  
   Meyer Sauteur P. M New microbes and new infections 2021;40:100836.

A previously healthy 30-year-old woman developed severe ARDS at the beginning of the COVID-19 pandemic. SARS-CoV-2 infection was suspected, but testing was negative. Mycoplasma pneumoniae was detected by PCR in bronchoalveolar lavage fluid and blood. This case illustrates that M. pneumoniae infection can progress to septicemia and ARDS with severe respiratory failure in young healthy adults. Copyright © 2020 The Author(s).

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1. **COVID-19 increased the risk of ICU-acquired bloodstream infections: a case-cohort study from the multicentric OUTCOMEREA network.**  
   Buetti Niccolo Intensive care medicine 2021;47(2):180-187.

PURPOSE: The primary objective of this study was to investigate the risk of ICU bloodstream infection (BSI) in critically ill COVID-19 patients compared to non-COVID-19 patients. Subsequently, we performed secondary analyses in order to explain the observed results., METHODS: We conducted a matched case-cohort study, based on prospectively collected data from a large ICU cohort in France. Critically ill COVID-19 patients were matched with similar non-COVID-19 patients. ICU-BSI was defined by an infection onset occurring > 48 h after ICU admission. We estimated the effect of COVID-19 on the probability to develop an ICU-BSI using proportional subdistribution hazards models., RESULTS: We identified 321 COVID-19 patients and 1029 eligible controls in 6 ICUs. Finally, 235 COVID-19 patients were matched with 235 non-COVID-19 patients. We observed 43 ICU-BSIs, 35 (14.9%) in the COVID-19 group and 8 (3.4%) in the non-COVID-19 group (p <= 0.0001), respectively. ICU-BSIs of COVID-19 patients were more frequently of unknown source (47.4%). COVID-19 patients had an increased probability to develop ICU-BSI, especially after 7 days of ICU admission. Using proportional subdistribution hazards models, COVID-19 increased the daily risk to develop ICU-BSI (sHR 4.50, 95% CI 1.82-11.16, p = 0.0012). Among COVID-19 patients (n = 235), a significantly increased risk for ICU-BSI was detected in patients who received tocilizumab or anakinra (sHR 3.20, 95% CI 1.31-7.81, p = 0.011) but not corticosteroids., CONCLUSIONS: Using prospectively collected multicentric data, we showed that the ICU-BSI risk was higher for COVID-19 than non-COVID-19 critically ill patients after seven days of ICU stay. Clinicians should be particularly careful on late ICU-BSIs in COVID-19 patients. Tocilizumab or anakinra may increase the ICU-BSI risk.

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=fc0120704e01846ba0f7d13db15280b3)

1. **Parallels in Sepsis and COVID-19 Conditions: Implications for Managing Severe COVID-19.**  
   Olwal Charles Ochieng' Frontiers in immunology 2021;12:602848.

Sepsis is a life-threatening systemic illness attributed to a dysregulated host response to infection. Sepsis is a global burden killing ~11 million persons annually. In December 2019, a novel pneumonia condition termed coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged and has resulted in more than 1,535,982 deaths globally as of 8th December 2020. These two conditions share many pathophysiological and clinical features. Notably, both sepsis and COVID-19 patients experience consumptive thrombocytopenia, haemolytic anaemia, vascular microthrombosis, multi-organ dysfunction syndrome, coagulopathy, septic shock, respiratory failure, fever, leukopenia, hypotension, leukocytosis, high cytokine production and high predisposition to opportunistic infections. Considering the parallels in the immunopathogenesis and pathophysiological manifestations of sepsis and COVID-19, it is highly likely that sepsis care, which has a well-established history in most health systems, could inform on COVID-19 management. In view of this, the present perspective compares the immunopathogenesis and pathophysiology of COVID-19 and non-SARS-CoV-2 induced sepsis, and lessons from sepsis that can be applicable to COVID-19 management. Copyright © 2021 Olwal, Nganyewo, Tapela, Djomkam Zune, Owoicho, Bediako and Duodu.

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=d0689cf69fb3e7f3f85203c0d0b304d9)

1. **Pathophysiological Clues to How the Emergent SARS-CoV-2 Can Potentially Increase the Susceptibility to Neurodegeneration**  
   Dolatshahi M. Molecular Neurobiology 2021;:No page numbers.

Along with emergence of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in late 2019, a myriad of neurologic symptoms, associated with structural brain changes, were reported. In this paper, we provide evidence to critically discuss the claim that the survived patients could possibly be at increased risk for neurodegenerative diseases via various mechanisms. This virus can directly invade the brain through olfactory bulb, retrograde axonal transport from peripheral nerve endings, or via hematogenous or lymphatic routes. Infection of the neurons along with peripheral leukocytes activation results in pro-inflammatory cytokine increment, rendering the brain to neurodegenerative changes. Also, occupation of the angiotensin-converting enzyme 2 (ACE-2) with the virus may lead to a decline in ACE-2 activity, which acts as a neuroprotective factor. Furthermore, acute respiratory distress syndrome (ARDS) and septicemia induce hypoxemia and hypoperfusion, which are locally exacerbated due to the hypercoagulable state and micro-thrombosis in brain vessels, leading to oxidative stress and neurodegeneration. Common risk factors for COVID-19 and neurodegenerative diseases, such as metabolic risk factors, genetic predispositions, and even gut microbiota dysbiosis, can contribute to higher occurrence of neurodegenerative diseases in COVID-19 survivors. However, it should be considered that severity of the infection, the extent of neurologic symptoms, and the persistence of viral infection consequences are major determinants of this association. Importantly, whether this pandemic will increase the overall incidence of neurodegeneration is not clear, as a high percentage of patients with severe form of COVID-19 might probably not survive enough to develop neurodegenerative diseases

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=8596113bc5068b413f2829f37eb2ade5)

1. **Potential roles of mitochondrial cofactors in the adjuvant mitigation of proinflammatory acute infections, as in the case of sepsis and COVID-19 pneumonia.**  
   Pagano Giovanni Inflammation research : official journal of the European Histamine Research Society ... [et al.] 2021;70(2):159-170.

BACKGROUND: The mitochondrial cofactors alpha-lipoic acid (ALA), coenzyme Q10 (CoQ10) and carnitine (CARN) play distinct and complementary roles in mitochondrial functioning, along with strong antioxidant actions. Also termed mitochondrial nutrients (MNs), these cofactors have demonstrated specific protective actions in a number of chronic disorders, as assessed in a well-established body of literature., METHODS: Using PubMed, the authors searched for articles containing information on the utilization of MNs in inflammatory disorders as assessed from in vitro and animal studies, and in clinical trials, in terms of exerting anti-inflammatory actions., RESULTS: The retrieved literature provided evidence relating acute pathologic conditions, such as sepsis and pneumonia, with a number of redox endpoints of biological and clinical relevance. Among these findings, both ALA and CARN were effective in counteracting inflammation-associated redox biomarkers, while CoQ10 showed decreased levels in proinflammatory conditions. MN-associated antioxidant actions were applied in a number of acute disorders, mostly using one MN. The body of literature assessing the safety and the complementary roles of MNs taken together suggests an adjuvant role of MN combinations in counteracting oxidative stress in sepsis and other acute disorders, including COVID-19-associated pneumonia., CONCLUSIONS: The present state of art in the use of individual MNs in acute disorders suggests planning adjuvant therapy trials utilizing MN combinations aimed at counteracting proinflammatory conditions, as in the case of pneumonia and the COVID-19 pandemic.

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=5c3ab1a61a615d4d341e86d2e484ac86)

1. **Prophylactic or therapeutic doses of heparins for COVID-19 infection? A retrospective study**  
   Bolzetta F. Aging - Clinical and Experimental Research 2021;33(1):213-217.

Background: Coronavirus disease 19 (COVID-19) is a global outbreak. COVID-19 patients seem to have relevant coagulative abnormalities, even if they are not typical of disseminated intravascular coagulopathy (DIC) of the kind seen in septicaemia. Therefore, anticoagulant therapy with heparins is increasing in interest for a clinical approach to these patients, particularly if older. Studies comparing if prophylactic doses are more effective than therapeutic ones are still missing. Method(s): Data were collected in the Geriatric Section of the Dolo Hospital, ULSS 3 "Serenissima", Venice from 31st March to 01st May 2020. Heparins (calciparin, fondaparinux, enoxaparine) were divided into prophylactic or therapeutic doses. People previously treated with oral anticoagulants were removed. Vital status was assessed using administrative data. Cox's regression analysis, adjusted for potential confounders, was used for assessing the strength of the association between heparins and mortality. The data were reported as hazard ratio (HR) with 95% confidence intervals (CIs). Result(s): 81 older people (mean age 84.1 years; females = 61.9%) were included. No significant differences in terms of demographic and clinical characteristics emerged between people treated with prophylactic or therapeutic doses, including age, gender, X-rays findings or severity of disease. Therapeutic doses were not associated to a better survival rate (HR 1.06; 95% CI 0.47-2.60; p = 0.89), even after adjusting for 15 confounders related to mortality (HR 0.89; 95% CI 0.30-2.71; p = 0.84). Conclusion(s): Our paper indicates that in older people affected by COVID-19 there is no justification for using therapeutic doses instead of prophylactic ones, having a similar impact on mortality risk.

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=cb895ba8087ab666b8411b337cc1eba3)

1. **Resolution of Disseminated Intravascular Coagulation in a Patient with COVID-19 and Associated Sepsis-Induced Neutropenia.**  
   Di Micco Pierpaolo Medicina (Kaunas, Lithuania) 2021;57(2):No page numbers.

COVID-19 has been associated with a hypercoagulable state and thrombotic events. Venous thromboembolism has been the most commonly reported type of thrombosis but also arterial thrombosis and disseminated intravascular coagulation in inpatients have been described frequently in several clinical experiences. Patients with COVID-19, because of its tendency to induce leucopenia and overlapping of bacterial infection, may experience sudden disseminated intravascular coagulation (DIC), as in the case that we report here. However, early diagnosis and treatment may be associated with positive resolution of these severe complications.

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=9804bb253c7a1d928297175aea1c65e8)

1. **Unexpectedly High Frequency of Enterococcal Bloodstream Infections in Coronavirus Disease 2019 Patients Admitted to an Italian ICU: An Observational Study.**  
   Bonazzetti Cecilia Critical care medicine 2021;49(1):e31-e40.

OBJECTIVES: We aimed to assess the frequency of ICU-acquired bloodstream infections in coronavirus disease 2019 patients., DESIGN: Retrospective observational study., SETTING: The emergency expansion of an ICU from eight general beds to 30 coronavirus disease 2019 beds., PARTICIPANTS: Patients with coronavirus disease 2019 admitted to the ICU of Luigi Sacco Hospital (Milan, Italy) for greater than or equal to 48 hours between February 21, 2020, and April 30, 2020., INTERVENTIONS: None., MEASUREMENTS AND MAIN RESULTS: The frequency of bloodstream infections per 1,000 days of ICU stay was calculated in 89 coronavirus disease 2019 patients, and the cumulative probability of bloodstream infection was estimated using death and ICU discharge as competing events. Sixty patients (67.4%) experienced at least one of the 93 recorded episodes of bloodstream infection, a frequency of 87 per 1,000 days of ICU stay (95% CI, 67-112). The patients who experienced a bloodstream infection had a higher Sequential Organ Failure Assessment score upon ICU admission (9.5; interquartile range, 8-12 vs 8, interquartile range, 5-10; p = 0.042), a longer median ICU stay (15 d; interquartile range, 11-23 vs 8, interquartile range, 5-12; p < 0.001), and more frequently required invasive mechanical ventilation (98.3% vs 82.8%; p = 0.013) than those who did not. The median time from ICU admission to the first bloodstream infection episode was 10 days. Gram-positive bacteria accounted for 74 episodes (79.6%), with Enterococcus species being the most prevalent (53 episodes, 55.8%). Thirty-two isolates (27.3%) showed multidrug resistance., CONCLUSIONS: Coronavirus disease 2019 seemed to increase the frequency of bloodstream infections (particularly Enterococcus-related bloodstream infection) after ICU admission. This may have been due to enteric involvement in patients with severe coronavirus disease 2019 and/or limitations in controlling the patient-to-patient transmission of infectious agents in extremely challenging circumstances. Copyright © 2020 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=81bb58a268a22cf84b6c64b1255d432d)

1. **An alternate venous access in covid-19 patients needing dialysis**  
   Muthukumar A. Indian Journal of Critical Care Medicine 2020;24(9):888-889.

The current rapidly rising pandemic scenario due to the SARS COVID-19 infection is known to cause acute respiratory distress syndrome (ARDS) in severely ill patients. Meanwhile, many patients get to suffer multiple comorbidities like septicemia and acute kidney injury (AKI). Most of the critically ill mechanical ventilated patients are nowadays being given trials of prone ventilation for at least one-third duration of a day. These patients may require central venous catheter for various purposes such as fluid resuscitation, vasopressor administration, hemodialysis owing to the fact that many critically ill COVID-19 patients are going for AKI. Central venous access has a major role in accelerating the impending septicemia due to ARDS, by causing catheter-related blood stream infection, thereby having a synergistic effect in causing sepsis. By using the unconventional methods which are used to give venous access, apart from the regularly used traditional methods of Internal Jugular, subclavian as well as femoral sites, this impending septicemia can be prevented or at least be hampered. This in turn will have major impact in the overall critically ill COVID-19-positive patient's outcome and will have a reduced mortality.Copyright © The Author(s). 2020.

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1. **Biclonal gammopathay in a case of severe COVID-19.**  
   Vashistha Pooja Clinica chimica acta; international journal of clinical chemistry 2020;511:342-345.

COVID-19 is a disease caused by a coronavirus named as SARS-CoV-2. It has become pandemic due to its contagious nature. Majority of the patients are asymptomatic or having mild flu like symptoms. Few need hospitalisation due to severe acute respiratory infection (SARI). Co-morbidity like diabetes, hypertension, renal failure etc. are associated with severe COVID-19 that often causes death. There have been only two published case reports of monoclonal gammopathy of unknown significance (MGUS) in patients with COVID-19 disease. Cytokine storm is often observed in severe COVID-19 and various cytokines including IL-6 that activates plasma cells are increased in blood in this condition. Here we present a case of severe COVID-19 patient with bioclonal gammopathy. He was known diabetic and hypertensive on treatment. He developed SARI, cytokines storm and septicaemia, treated with antibiotics, enoxaparin, hydroxychloroquine, insulin, anti-hypertensives, put on ventilator, subsequently developed septicaemia, multi-organ failure and died. Two M-bands on serum capillary electrophoresis with presence IgG-κ on both the M-bands indicates a biclonal gammopathy of unknown significance in this patient. We conclude that like MGUS, early stage biclonal gammopathy, although rare, gets manifested with M-bands on plasma protein electrophoresis. It is probably due to high level of IL-6 associated with cytokine storm in severe COVID-19 that stimulate early stage dyscratic plasma cells. Such biclonal gammopathy might be a risk factor for severe COVID-19 and associated mortality.

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=357373b70d711d13b03cf65fa38283fe)

1. **BobaHk COVID-19: ocobeHHocT TokHoBoo poCOVID-19 biobank: features of the cytokine profile**  
   Sushentseva N.N. Cardiovascular Therapy and Prevention 2020;19(6):No page numbers.

Aim. Using a collection of samples from the biobank of City Hospital 40 of St. Petersburg, to study the cytokine profile in patients with coronavirus disease 2019 (COVID-19) and sepsis, in comparison with patients with abdominal inflammation and septicemia. Material and methods. The study included serum samples from 181 patients with sepsis and COVID-19 (127 patients with a diagnosis confirmed by polymerase chain reaction (PCR); 54 patients with a negative PCR test, but with a characteristic computed tomographic lung performance) and 47 patients with abdominal sepsis. The content of cytokines was determined using a multiplex immunofluorescence analysis based on the Luminex xMAP technology using the HCYTOMAG-60K panel - a soluble CD40 ligand (sCD40L), interleukin-1alpha (IL-1alpha), interleukin-1beta (IL-1beta), interleukin 6 (IL-6), interleukin 8 (IL-8), monocyte chemoattractant protein 1 (MCP-1), tumor necrosis factor alpha (TNFalpha), vascular endothelial growth factor (VEGF). Other laboratory parameters (C-reactive protein (CRP), ferritin, procalcitonin) were taken from patient records. Normality of distribution was assessed by the Shapiro-Wilk test. To compare groups, the Mann-Whitney test for independent samples, Wilcoxon test for dependent samples, and the Kruskal-Wallis test with Bonferroni correction for multiple comparisons were used. Results. In patients with sepsis and COVID-19 infection, no differences in the concentrations of cytokines, ferritin and CRP were found between the groups with detected and not detected virus by PCR test. Based on this, this group was considered homogeneous when studying the cytokine profile. It was shown that in patients with sepsis and COVID-19, significantly higher levels of sCD40L (p&lt;0,0001) and VEGF (p=0,037) and relatively low levels of CRP (p&lt;0,0001), IL-6 (p&lt;0,0001), IL-8 (p&lt;0,0001), TNFalpha (p&lt;0,00058). Conclusion. These results indicate that sepsis in patients with COVID-19 courses with less elevation in inflammatory cytokine than in abdominal sepsis. At the same time, a critically high level of sCD40L indicates the significant endothelial damage.<br/>Copyright &#xa9; 2020 Vserossiiskoe Obshchestvo Kardiologov. All rights reserved.

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1. **Coronavirus (Covid-19) sepsis: revisiting mitochondrial dysfunction in pathogenesis, aging, inflammation, and mortality.**  
   Shenoy Santosh Inflammation research : official journal of the European Histamine Research Society ... [et al.] 2020;69(11):1077-1085.

BACKGROUND: Decline in mitochondrial function occurs with aging and may increase mortality. We discuss mitochondrial contribution to Covid-19 sepsis, specifically the complex interaction of innate immune function, viral replication, hyper-inflammatory state, and HIF-alpha/Sirtuin pathways., METHODS: Articles from PubMed/Medline searches were reviewed using the combination of terms "SARS-CoV-2, Covid-19, sepsis, mitochondria, aging, and immunometabolism"., RESULTS: Evidence indicates that mitochondria in senescent cells may be dysfunctional and unable to keep up with hypermetabolic demands associated with Covid-19 sepsis. Mitochondrial proteins may serve as damage-associated molecular pattern (DAMP) activating innate immunity. Disruption in normal oxidative phosphorylation pathways contributes to elevated ROS which activates sepsis cascade through HIF-alpha/Sirtuin pathway. Viral-mitochondrial interaction may be necessary for replication and increased viral load. Hypoxia and hyper-inflammatory state contribute to increased mortality associated with Covid-19 sepsis., CONCLUSIONS: Aging is associated with worse outcomes in sepsis. Modulating Sirtuin activity is emerging as therapeutic agent in sepsis. HIF-alpha, levels of mitochondrial DNA, and other mitochondrial DAMP molecules may also serve as useful biomarker and need to be investigated. These mechanisms should be explored specifically for Covid-19-related sepsis. Understanding newly discovered regulatory mechanisms may lead to the development of novel diagnostic and therapeutic targets.

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1. **Identification and Analysis of Shared Risk Factors in Sepsis and High Mortality Risk COVID-19 Patients**  
   Sayoni Das et al MedRxiv 2020;:-.

***This is a preprint which has not been peer-reviewed***. Coronavirus disease 2019 (COVID-19) is a novel coronavirus strain disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease is highly transmissible and severe disease including viral sepsis has been reported in up to 16% of hospitalized cases. The admission characteristics associated with increased odds of hospital mortality among confirmed cases of COVID-19 include severe hypoxia, low platelet count, elevated bilirubin, hypoalbuminemia and reduced glomerular filtration rate. These symptoms correlate highly with severe sepsis cases. The diseases also share similar co-morbidity risks including dementia, type 2 diabetesmellitus, coronary heart disease, hypertension and chronic renal failure. Sepsis has been observed in up to 59% of hospitalized COVID-19 patients. It is highly desirable to identify risk factors and novel therapy/drug repurposing avenues for late-stage severe COVID-19 patients. This would enable better protection of at-risk populations and clinical stratification of COVID-19 patients according to their risk for developing life threatening disease. METHODS As there is currently insufficient data available for confirmed COVID-19 patients correlating their genomic profile, disease severity and outcome, co-morbidities and treatments as well as epidemiological risk factors (such as ethnicity, blood group, smoking, BMI etc.), a direct study of the impact of host genomics on disease severity and outcomes is not yet possible. We therefore ran a study on the UK Biobank sepsis cohort as a surrogate to identify sepsis associated signatures and genes, and correlated these with COVID-19 patients. Sepsis is itself a life-threatening inflammatory health condition with a mortality rate of approximately 20%. Like the initial studies forCOVID-19 patients, standard genome wide association studies (GWAS) have previously failed to identify more than a handful of genetic variants that predispose individuals to developing sepsis. RESULTS We used a combinatorial association approach to analyzea sepsis population derived from UK Biobank. We identified 70 sepsis risk-associated genes, which provide insights into the disease mechanisms underlying sepsis pathogenesis. Many of these targets can be grouped by common mechanisms of action such as endothelial cell dysfunction, PI3K/mTOR pathway signaling, immune response regulation, aberrant GABA and neurogenic signaling. CONCLUSION This study has identified 70 sepsis related genes, many of them for the first time, that can reasonably be considered to be potentially relevant to severe COVID-19 patients. We have further identified 59 drug repurposing candidates for 13 of these targets that canbe used for the development of novel therapeutic strategies toincrease the survival rate of patients who develop sepsis and potentially severe COVID-19.

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1. **Immune Response and COVID-19: A mirror image of Sepsis.**  
   López-Collazo E. International journal of biological sciences 2020;16(14):2479-2489.

The emergence of SARS-CoV-2 virus and its associated disease COVID-19 have triggered significant threats to public health, in addition to political and social changes. An important number of studies have reported the onset of symptoms compatible with pneumonia accompanied by coagulopathy and lymphocytopenia during COVID-19. Increased cytokine levels, the emergence of acute phase reactants, platelet activation and immune checkpoint expression are some of the biomarkers postulated in this context. As previously observed in prolonged sepsis, T-cell exhaustion due to SARS-CoV-2 and even their reduction in numbers due to apoptosis hinder the response to the infection. In this review, we synthesized the immune changes observed during COVID-19, the role of immune molecules as severity markers for patient stratification and their associated therapeutic options.

1. **Mesenchymal stromal cells for sepsis and septic shock: Lessons for treatment of COVID-19.**  
   Laroye Caroline Stem cells translational medicine 2020;9(12):1488-1494.

Sepsis is defined as life-threatening organ dysfunction caused by a deregulated immune host response to infection. The emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has highlighted this multifactorial and complex syndrome. The absence of specific treatment neither against SARS-CoV-2 nor against acute respiratory distress syndrome (ARDS), the most serious stage of this infection, has emphasized the need to find alternative treatments. Several therapeutics are currently being tested, including mesenchymal stromal cells. These cells, already used in preclinical models of ARDS, sepsis, and septic shock and also in a few clinical trials, appear well-tolerated and promising, but many questions remain unanswered. Copyright © 2020 The Authors. STEM CELLS Translational Medicine published by Wiley Periodicals LLC on behalf of AlphaMed Press.

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1. **PIN117 Identification of Patients with COVID-19 Infection Prior to the New COVID-19 Diagnostic Code - a Premier Database Analysis**  
   Holy C. Value in Health 2020;23:No page numbers.

Objectives: A new diagnostic code was released in April 2020 for COVID-19 infection. Prior to that, database research used CDC-listed symptoms to identify COVID-19 cases. This study evaluates whether use of these symptoms can accurately identify patients with COVID-19, and at what time an increase in mortality was first observed using combinations of these symptoms. Method(s): Patients from the Premier Healthcare Database with an inpatient event during which patients deceased, with COVID-19 related symptoms and a DRG (diagnostic related group) of respiratory infection or sepsis and, from April 2020 onwards, a COVID-19 diagnosis, were identified, from September 2019 to most recent. Comorbidities and symptoms of COVID-19 and related treatments were used as model variables. Patients with and without COVID-19 diagnosis were matched using propensity score matching (model: logit, method: nearest neighbor, caliper: 0.1). Time of discharge was analyzed to evaluate changes in mortality in the matched cohorts. Result(s): Pre-match, 3,923 patients without (noDiag) and 4,903 patients with COVID-specific diagnosis codes (withDiag) were identified. In the noDiag group, there were 52.7% males and 11.8% African Americans (AA). In the withDiag group, there were 56.4% males and 21.1% AA. In the noDiag cohort, 71.2% patients had a DRG code of septicemia vs 52.9% in the withDiag group. After matching, there were 1,340 patients in each group, 60% males, 21.7% AA. In the NoDiag matched cohort, 59% death occurred in 2020, with a clear spike in March (30%). The remaining 41% were identified prior to 2020, as early as October 2020, suggesting potential contamination with mortality due to other causes. Conclusion(s): Due to the similarity of COVID-symptoms to those observed with other common respiratory diseases, and concurrent timing of COVID mortality with that of viral pneumonia, matching on symptoms and treatments identified patients prior to first US-reported case and therefore included patients with infections other than COVID-19.

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1. **Respiratory viral sepsis: epidemiology, pathophysiology, diagnosis and treatment.**  
   Gu X. European respiratory review : an official journal of the European Respiratory Society 2020;29(157):No page numbers.

According to the Third International Consensus Definition for Sepsis and Septic Shock, sepsis is a life-threatening organ dysfunction resulting from dysregulated host responses to infection. Epidemiological data about sepsis from the 2017 Global Burden of Diseases, Injuries and Risk Factor Study showed that the global burden of sepsis was greater than previously estimated. Bacteria have been shown to be the predominant pathogen of sepsis among patients with pathogens detected, while sepsis caused by viruses is underdiagnosed worldwide. The coronavirus disease that emerged in 2019 in China and now in many other countries has brought viral sepsis back into the vision of physicians and researchers worldwide. Although the current understanding of the pathophysiology of sepsis has improved, the differences between viral and bacterial sepsis at the level of pathophysiology are not well understood. Diagnosis methods that can broadly differentiate between bacterial and viral sepsis at the initial stage after the development of sepsis are limited. New treatments that can be applied at clinics for sepsis are scarce and this situation is not consistent with the growing understanding of pathophysiology. This review aims to give a brief summary of current knowledge of the epidemiology, pathophysiology, diagnosis and treatment of viral sepsis.

1. **SARS-CoV-2 and Viral Sepsis: Immune Dysfunction and Implications in Kidney Failure.**  
   Stasi A. Journal of clinical medicine 2020;9(12):No page numbers.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causal agent of coronavirus disease 2019 (COVID-19), first emerged in Wuhan, China. The clinical manifestations of patients infected with COVID-19 include fever, cough, and dyspnea, up to acute respiratory distress syndrome (ARDS) and acute cardiac injury. Thus, a lot of severe patients had to be admitted to intensive care units (ICU). The pathogenic mechanisms of SARS-CoV-2 infection are mediated by the binding of SARS-CoV-2 spikes to the human angiotensin-converting enzyme 2 (ACE-2) receptor. The overexpression of human ACE-2 is associated with the disease severity in SARS-CoV-2 infection, demonstrating that viral entry into cells is a pivotal step. Although the lung is the organ that is most commonly affected by SARS-CoV-2 infection, acute kidney injury (AKI), heart dysfunction and abdominal pain are the most commonly reported co-morbidities of COVID-19. The occurrence of AKI in COVID-19 patients might be explained by several mechanisms that include viral cytopathic effects in renal cells and the host hyperinflammatory response. In addition, kidney dysfunction could exacerbate the inflammatory response started in the lungs and might cause further renal impairment and multi-organ failure. Mounting recent evidence supports the involvement of cardiovascular complications and endothelial dysfunction in COVID-19 syndrome, in addition to respiratory disease. To date, there is no vaccine, and no specific antiviral medicine has been shown to be effective in preventing or treating COVID-19. The removal of pro-inflammatory cytokines and the shutdown of the cytokine storm could ameliorate the clinical outcome in severe COVID-19 cases. Therefore, several interventions that inhibit viral replication and the systemic inflammatory response could modulate the severity of the renal dysfunction and increase the probability of a favorable outcome.

1. **SARS-CoV-2 and viral sepsis: observations and hypotheses.**  
   Li Hui Lancet (London, England) 2020;395(10235):1517-1520.

Since the outbreak of coronavirus disease 2019 (COVID-19), clinicians have tried every effort to understand the disease, and a brief portrait of its clinical features have been identified. In clinical practice, we noticed that many severe or critically ill COVID-19 patients developed typical clinical manifestations of shock, including cold extremities and weak peripheral pulses, even in the absence of overt hypotension. Understanding the mechanism of viral sepsis in COVID-19 is warranted for exploring better clinical care for these patients. With evidence collected from autopsy studies on COVID-19 and basic science research on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and SARS-CoV, we have put forward several hypotheses about SARS-CoV-2 pathogenesis after multiple rounds of discussion among basic science researchers, pathologists, and clinicians working on COVID-19. We hypothesise that a process called viral sepsis is crucial to the disease mechanism of COVID-19. Although these ideas might be proven imperfect or even wrong later, we believe they can provide inputs and guide directions for basic research at this moment. Copyright © 2020 Elsevier Ltd. All rights reserved.

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1. **Scoring cytokine storm by the levels of MCP-3 and IL-8 accurately distinguished COVID-19 patients with high mortality**  
   Chen L. Signal Transduction and Targeted Therapy 2020;5(1):No page numbers.

Letter: [...] Selected extract: The cytokine profiles in the ICU patients were further compared with those in patients with active bacterial septicemia (unpublished data generated by measuring electroluminescence) and patients with severe (grade 3–4) CRS due to anti-BCMA CAR-T cell therapy (Fig. 1a). In general, the cytokine responses to bacterial septicemia and CAR-T cells were much broader than those to SARS-CoV-2 infection. While profoundly elevated levels of IL-6 were consistently observed in COVID-19 ICU patients, bacterial sepsis, and CAR-T cell-induced CRS, increased levels of MCP-3 were found only in patients with COVID-19 or CAR-T cell-induced CRS but not in those with bacterial sepsis. [...]

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## Search History

Sources searched include BMJ Best Practice, Embase, Cinahl, Cochrane, Google Scholar, Medline, MedRxiv, NICE, PubMed, TRIP PRO, UpToDate

**Date range used** (5 years, 10 years):   
**Limits used** (gender, article/study type, etc.):   
**Search terms and notes** (full search strategy for database searches below): septicaemia, septicemia, sepsis, SARS-CoV2, COVID-19

Database(s): Embase 1974 to 2021 March 03   
Search Strategy:

|  |  |  |
| --- | --- | --- |
| **#** | **Searches** | **Results** |
| 1 | exp Coronavirus/ | 23255 |
| 2 | exp Coronavirus Infections/ | 24610 |
| 3 | (coronavirus\* or corona virus\* or OC43 or NL63 or 229E or HKU1 or HCoV\* or ncov\* or covid\* or sars-cov\* or sarscov\* or Sars-coronavirus\* or Severe Acute Respiratory Syndrome Coronavirus\*).mp. | 137377 |
| 4 | (or/1-3) and 20190101:20301231.(dc). | 116331 |
| 5 | 4 not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel\* or dromedar\* or equine or coronary or coronal or covidence\* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona\*).mp. | 72509 |
| 6 | ((pneumonia or covid\* or coronavirus\* or corona virus\* or ncov\* or 2019-ncov or sars\*).mp. or exp pneumonia/) and Wuhan.mp. | 4861 |
| 7 | (coronavirus disease 2019 or 2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or severe acute respiratory syndrome coronavirus 2 or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus\* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus\* or corona virus or Pandemi\*2)) or ((covid or covid19 or covid-19) and pandemic\*2) or (coronavirus\* and pneumonia)).mp. | 114118 |
| 8 | (coronavirus disease 2019 or severe acute respiratory syndrome coronavirus 2).sh,dj. | 94425 |
| 9 | ("630575119" or "630830186" or "630941329" or "631043694" or "631260659" or "631272428" or "631272880" or "631286076" or "631290163" or "631308782" or "631324397" or "631352500" or "631416440" or "631431802" or "631452886" or "631456079" or "631457551" or "631462438" or "631462876" or "631465538" or "631465685" or "631469310" or "2004499662" or "2004505338" or "2005280837" or "2005387675" or "2005408544" or "2005484987" or "2005549151").an. | 16 |
| 10 | (or/6-9) and 20191201:20301231.(dc). | 111021 |
| 11 | 5 or 10 | 112801 |
| 12 | exp septicemia/ or septicemia.mp. | 28693 |
| 13 | 11 and 12 | 20 |
| 14 | from 13 keep 9 | 1 |

|  | **Source** | **Criteria** | **Results** |
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| 1. | EMBASE | exp CORONAVIRUS/ | 23226 |
| 2. | EMBASE | (covid-19).ti,ab | 90012 |
| 3. | EMBASE | (coronavirus).ti,ab | 48142 |
| 4. | EMBASE | ("Corona virus").ti,ab | 1714 |
| 5. | EMBASE | (2019-nCoV).ti,ab | 1185 |
| 6. | EMBASE | (SARS-CoV).ti,ab | 31027 |
| 7. | EMBASE | (MERS-CoV).ti,ab | 2697 |
| 8. | EMBASE | ("Severe Acute Respiratory Syndrome").ti,ab | 16571 |
| 9. | EMBASE | ("Middle East Respiratory Syndrome").ti,ab | 2974 |
| 10. | EMBASE | (1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9) | 122144 |
| 11. | EMBASE | exp SEPTICEMIA/ | 19357 |
| 12. | EMBASE | (septic?emia).ti,ab | 22783 |
| 13. | EMBASE | (11 OR 12) | 31620 |
| 14. | EMBASE | (10 AND 13) | 37 |
| 15. | EMBASE | 14 [DT 2020-2021] [English language] | 20 |
| 16. | Medline | exp "SARS-COV-2"/ | 47608 |
| 17. | Medline | (covid-19).ti,ab | 90411 |
| 18. | Medline | (coronavirus).ti,ab | 48043 |
| 19. | Medline | ("Corona virus").ti,ab | 1396 |
| 20. | Medline | (2019-nCoV).ti,ab | 1108 |
| 21. | Medline | (SARS-CoV).ti,ab | 31360 |
| 22. | Medline | (MERS-CoV).ti,ab | 2489 |
| 23. | Medline | ("Severe Acute Respiratory Syndrome").ti,ab | 16491 |
| 24. | Medline | ("Middle East Respiratory Syndrome").ti,ab | 2753 |
| 25. | Medline | (16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24) | 117480 |
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| 27. | Medline | (25 AND 26) | 14 |
| 28. | Medline | 27 [DT 2020-2021] [Languages English] | 7 |
| 29. | CINAHL | exp "COVID-19"/ OR exp "MIDDLE EAST RESPIRATORY SYNDROME"/ OR exp "SEVERE ACUTE RESPIRATORY SYNDROME"/ | 15960 |
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| 31. | CINAHL | (coronavirus).ti,ab | 12532 |
| 32. | CINAHL | ("Corona virus").ti,ab | 286 |
| 33. | CINAHL | (2019-nCoV).ti,ab | 230 |
| 34. | CINAHL | (SARS-CoV).ti,ab | 327 |
| 35. | CINAHL | (MERS-CoV).ti,ab | 508 |
| 36. | CINAHL | ("Severe Acute Respiratory Syndrome").ti,ab | 3509 |
| 37. | CINAHL | ("Middle East Respiratory Syndrome").ti,ab | 784 |
| 38. | CINAHL | (29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37) | 41237 |
| 39. | CINAHL | (septic?emia).ti,ab | 1760 |
| 40. | CINAHL | (38 AND 39) | 1 |

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