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## Covid effects on lymphoid organs, spleen and bone marrow

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

## A. Original Research

1. **Alveolar macrophage dysfunction and cytokine storm in the pathogenesis of two severe COVID-19 patients**  
   Wang C. EBioMedicine 2020;57:102833.

BACKGROUND: The novel coronavirus pneumonia COVID-19 caused by SARS-CoV-2 infection could lead to a series of clinical symptoms and severe illnesses, including acute respiratory distress syndrome (ARDS) and fatal organ failure. We report the fundamental pathological investigation in the lungs and other organs of fatal cases for the mechanistic understanding of severe COVID-19 and the development of specific therapy in these cases.

1. **BCG vaccine and COVID-19: implications for infection prophylaxis and cancer immunotherapy**  
   Koti M. Journal for Immunotherapy of Cancer 2020;8:07.

The COVID-19 pandemic has killed over 400 000 people globally. Ecological evidence indicates that countries with national universal BCG vaccination programs for tuberculosis (TB) prevention have a much lower incidence of severe COVID-19 and mortality compared with those that do not have such programs. BCG is a century old vaccine used for TB prevention via infant/childhood vaccination in lowto middle-income countries with high infection prevalence rate and is known to reduce all-cause neonatal mortality. BCG remains the standard immunotherapy treatment for patients with high-risk non-muscle invasive bladder cancer globally for more than 44 years. Several trials are, therefore, investigating BCG as a prophylactic against COVID-19 in healthcare workers and the elderly. In this commentary, we discuss the potential mechanisms that may underlie BCG associated heterologous protection with a focus on tertiary lymphoid structure (TLS) organogenesis. Given the significance of TLSs in mucosal immunity, their association with positive prognosis and response to immune checkpoint blockade with a critical role of Type I interferon (IFN-1) in inducing these, we also discuss potentiating TLS formation as a promising approach to enhance anti-tumor immunity. We propose that lessons learned from BCG immunotherapy success could be applied to not only augment such microbe-based therapeutics but also lead to similar adjunctive IFN-1 activating approaches to improve response to immune checkpoint blockade therapy in cancer.

1. **Bone Marrow Transplant Society of Australia and New Zealand COVID-19 consensus position statement**  
   Hamad N. Internal Medicine Journal 2020;50:774-775.

1. **Correction: The challenge of COVID-19 and hematopoietic cell transplantation: EBMT recommendations for management of hematopoietic cell transplant recipients, their donors, and patients undergoing CAR T-cell therapy (Bone Marrow Transplantation, (2020), 10.1038/s41409-020-0919-0)**  
   Ljungman P. Bone Marrow Transplantation. 2020;:No page numbers.

The original HTML and PDF versions of this article were updated shortly after publication to correct author Bregje Verhoeven's name and affiliation. Bregje Verhoeven was incorrectly associated with Willem-Alexander Children's Hospital, Department of Pediatrics, Leiden University Medical Center, Leiden, The Netherlands. The correct affiliation is Foundation Hematon, Utrecht, The Netherlands. This has now been corrected in both the PDF and HTML versions of the article. Copyright © 2020, The Author(s).

1. **Covid-19 containment measures adopted in bone marrow transplantation service**  
   Rodrigues J. A. P. Revista Brasileira de Enfermagem 2020;73 Suppl 2:e20200476.

OBJECTIVE: To describe the experience of nursing, in adopting containment measures, in the care of patients undergoing hematopoietic stem cell transplantation to avoid COVID-19.

1. **COVID-19 in bone marrow transplant recipients: reflecting on a single centre experience**  
   Kanellopoulos A. British Journal of Haematology 2020;190:e67-e70.

1. **Delayed-phase thrombocytopenia in patients with coronavirus disease 2019 (COVID-19)**  
   Chen W. British Journal of Haematology 2020;190:179-184.

Coronavirus disease 2019 (COVID-19) can affect the haematopoietic system. Thrombocytopenia at admission was prevalent, while late-phase or delayed-phase thrombocytopenia (occurred 14 days after symptom onset) is rare. This retrospective, single-centre study screened 450 COVID-19 patients and enrolled 271 patients at the Union Hospital, Wuhan, China, from January 25 to March 9, 2020. COVID-19-associated delayed-phase thrombocytopenia occurred in 11.8% of enrolling patients. The delayed-phase thrombocytopenia in COVID-19 is prone to develop in elderly patients or patients with low lymphocyte count on admission. The delayed-phase thrombocytopenia is significantly associated with increased length of hospital stay and higher mortality rate. Delayed-phase nadir platelet counts demonstrated a significantly negative correlation with B cell percentages. We also provided and described bone marrow aspiration pathology of three patients with delayed-phase thrombocytopenia, showing impaired maturation of megakaryocytes. We speculated that immune-mediated platelet destruction might account for the delayed-phase thrombocytopenia in a group of patients. In addition, clinicians need to pay attention to the delayed-phase thrombocytopenia especially at 3-4 weeks after symptom onset.

1. **Effect of hydroxychloroquine on COVID-19 prevention in cancer patients undergoing treatment: a structured summary of a study protocol for a randomised controlled trial**  
   Allahyari A. Trials [Electronic Resource] 2020;21:575.

OBJECTIVES: In this study, we investigate the effect of hydroxychloroquine on the prevention of Novel Coronavirus Disease (COVID-19) in cancer patients being treated. TRIAL DESIGN: This is a multi-centre, two-arm, parallel-group, triple-blind, phase 2-3 randomised controlled trial.

1. **Exosomes Derived from Bone Marrow Mesenchymal Stem Cells as Treatment for Severe COVID-19**  
   Sengupta V. Stem Cells & Development 2020;29:747-754.

This prospective nonrandomized open-label cohort study addresses the safety and efficacy of exosomes (ExoFlo TM) derived from allogeneic bone marrow mesenchymal stem cells as treatment for severe COVID-19. During April 2020, ExoFlo was provided to 24 SARS-CoV-2 polymerase chain reaction-positive patients at a single hospital center, all of whom met criteria for severe COVID-19 as well as moderate-to-severe acute respiratory distress syndrome. Patients received a single 15 mL intravenous dose of ExoFlo and were evaluated for both safety and efficacy from days 1 to 14 post-treatment. All safety endpoints were met with no adverse events observed within 72 h of ExoFlo administration. A survival rate of 83% was observed. In total, 17 of 24 (71%) patients recovered, 3 of 24 (13%) patients remained critically ill though stable, and 4 of 24 (16%) patients expired for reasons unrelated to the treatment. Overall, after one treatment, patients' clinical status and oxygenation improved with an average pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO<sub>2</sub>/FiO<sub>2</sub>) increase of 192% (P < 0.001). Laboratory values revealed significant improvements in absolute neutrophil count [mean reduction 32% (P value <0.001)] and lymphopenia with average CD3<sup>+</sup>, CD4<sup>+</sup>, and CD8<sup>+</sup> lymphocyte counts increasing by 46% (P < 0.05), 45% (P < 0.05), and 46% (P < 0.001), respectively. Likewise, acute phase reactants declined, with mean C-reactive protein, ferritin, and D-dimer reduction of 77% (P < 0.001), 43% (P < 0.001), and 42% (P < 0.05), respectively. In conclusion, owing to its safety profile, capacity to restore oxygenation, downregulate cytokine storm, and reconstitute immunity, ExoFlo is a promising therapeutic candidate for severe COVID-19. Future randomized controlled trials (RCTs) are needed to determine ExoFlo therapeutic potential.

1. **First case of persistent pancytopenia associated with SARS-CoV-2 bone marrow infiltration in an immunocompromised patient**  
   Issa N. Annals of Oncology 2020;29:29.

1. **Granulocyte-colony stimulating factor in COVID-19: Is it stimulating more than just the bone marrow?**  
   Nawar T. American Journal of Hematology 2020;95:E210-E213.

1. **Gut Microbiota and Liver Interaction through Immune System Cross-Talk: A Comprehensive Review at the Time of the SARS-CoV-2 Pandemic**  
   Scarpellini E. Journal of Clinical Medicine 2020;9:03.

BACKGROUND AND AIMS: The gut microbiota is a complex ecosystem containing bacteria, viruses, fungi, yeasts and other single-celled organisms. It is involved in the development and maintenance of both innate and systemic immunity of the body. Emerging evidence has shown its role in liver diseases through the immune system cross-talk. We review herein literature data regarding the triangular interaction between gut microbiota, immune system and liver in health and disease.

1. **Haemophagocytosis in bone marrow aspirates in patients with COVID-19**  
   Debliquis A. British Journal of Haematology 2020;190:e70-e73.

1. **Hemophagocytic lymphohistiocytosis in SARS-CoV-2 infection**  
   Dewaele K. Blood 2020;135:2323.

1. **Higher plasma levels of Chemokine CCL19 are associated with poor SARS-CoV-2 acute respiratory distress syndrome (ARDS) outcomes**  
   Balnis J. MedRxiv : the Preprint Server for Health Sciences 2020;22:22.

COVID19 pandemic has so far caused over three hundred thousand deaths worldwide, primarily due to complications from SARS-CoV-2-associated acute respiratory distress syndrome (ARDS). While an ARDS-driven hyperinflammatory phenotype is associated with higher mortality in non-COVID patients, there is little information on how cytokines and chemokines expressions correlate with clinical outcomes in COVID19 patients. We prospectively enrolled a cohort of 41 patients with acute respiratory distress syndrome on mechanical ventilation. Patients blood was obtained at enrollment and outcome measures were liberation from mechanical ventilation and hospital-free days. We determined the expression levels of 44 circulating cytokines/chemokines and found 13 of them associated with worse outcomes. After correcting for multiple comparisons/false discovery rate, only one chemokine (CCL19) remained significantly associated with outcomes (p=0.009). Although not described in association with COVID19, this chemokine was previously found elevated in an animal model of SARS-CoV. Moreover, CCL19 seems to be relevant for bronchus-associated lymphoid tissue (BALT) maintenance and for lung immunity to influenza virus. While this finding requires corroboration, CCL19 determination could facilitate early identification COVID19-ARDS patients at higher risk of death and be novel target for immunotherapy in this setting.

1. **Histopathology and Ultrastructural Findings of Fatal COVID-19 Infections**  
   Bradley Benjamin T. medRxiv 2020;:2020.04.17.20058545.

Background SARS-CoV-2 is the cause of an ongoing pandemic with a projected 100,000 to 240,000 U.S. deaths. To date, documentation of histopathologic features in fatal cases of COVID-19 has been limited due to small sample size and incomplete organ sampling. Methods Post-mortem examinations were performed on 12 fatal COVID-19 cases in Washington State during February-March 2020. Clinical and laboratory data were reviewed. Tissue examination of all major organs was performed by light microscopy and electron microscopy. The presence of viral RNA in sampled tissues was tested by RT-PCR. Results All 12 patients were older with significant preexisting comorbidities. The major pulmonary finding was diffuse alveolar damage in the acute and/or organizing phases with virus identified in type I and II pneumocytes by electron microscopy. The kidney demonstrated viral particles in the tubular epithelium, endothelium, and podocytes without significant inflammation. Viral particles were also observed in the trachea and large intestines. SARS-CoV-2 RNA was detected in the cardiac tissue of a patient with lymphocytic myocarditis. RT-PCR also detected viral RNA in the subcarinal lymph nodes, liver, spleen, and large intestines. Conclusion SARS-CoV-2 represents the third novel coronavirus to cause widespread human disease since 2002. Similar to SARS and MERS, the primary pathology was diffuse alveolar damage with virus located in the pneumocytes. However, other major organs including the heart and kidneys may be susceptible to viral replication and damage leading to increased mortality in those with disseminated disease. Understanding the pathology of SARS-CoV-2 will be essential to design effective therapies.Competing Interest StatementThe authors have declared no competing interest.Funding StatementThis work was not supported by any institution or grant.Author DeclarationsAll relevant ethical guidelines have been followed; any necessary IRB and/or ethics committee approvals have been obtained and details of the IRB/oversight body are included in the manuscript.YesAll necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.YesI understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance).Yes I have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable.YesAll data will be made available by request to the corresponding author.

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=64e0cfdb2b0fe03ba3b5f0eb8aacad29)

1. **Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series**  
   Bradley B. T. Lancet 2020;396:320-332.

BACKGROUND: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of an ongoing pandemic, with increasing deaths worldwide. To date, documentation of the histopathological features in fatal cases of the disease caused by SARS-CoV-2 (COVID-19) has been scarce due to sparse autopsy performance and incomplete organ sampling. We aimed to provide a clinicopathological report of severe COVID-19 cases by documenting histopathological changes and evidence of SARS-CoV-2 tissue tropism.

1. **How to manage lymphoid malignancies during novel 2019 coronavirus (CoVid-19) outbreak: a Brazilian task force recommendation**  
   Perini G. F. Hematology Transfusion & Cell Therapy 2020;42:103-110.

The novel Coronavirus (CoVid-19) outbreak is now consider a world pandemic, affecting more than 1,300,000 people worldwide. Cancer patients are in risk for severe disease, including a higher risk of intensive care unit (ICU) admission, need for invasive ventilation or death. Management of patients with lymphoid malignancies can be challenging during the outbreak, due to need of multiple hospital visits and admissions, immunosuppression and need for chemotherapy, radiotherapy and stem cell transplantation. In this article, we will focus on the practical management of patients with lymphoid malignancies during the COVID-19 pandemic, focusing on minimizing the risk for patients.

1. **Impact of COVID-19 pandemic on bone marrow transplantation in Morocco**  
   Ahnach M. The Pan African medical journal 2020;35:5.

1. **Incidence of thrombosis and hemorrhage in hospitalized cancer patients with COVID-19**  
   Patell R. Journal of Thrombosis & Haemostasis 2020;21:21.

BACKGROUND: Coronavirus disease-2019 (COVID-19) is a recognized prothrombotic state. Patients hospitalized with active cancer are predisposed to thrombosis but whether active cancer further amplifies thrombotic risk with COVID-19 is not known.

1. **Local bone marrow renin-angiotensin system and covid-19**  
   Ciftciler R. UHOD - Uluslararasi Hematoloji-Onkoloji Dergisi 2020;30:113-124.

For the first time on December 31, 2019, 27 cases of pneumonia of unknown etiology were detected in Wuhan City, Hubei province, China. The factor that caused this clinic was called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). In the following days, WHO officially named the disease caused by the new coronavirus as Coronavirus Disease 2019 (COVID-19). Patients infected with SARS-CoV-2 mostly applied to health centers with symptoms of dry cough, shortness of breath and fever. some patients have developed death-causing complications such as organ failure, septic shock, pulmonary edema, severe pneumonia, and Acute Respiratory Distress Syndrome (ARDS). SARS-CoV-2 infects patients by binding human Angiotensin Converting Enzyme 2 (ACE 2), causing to severe pneumonia and high mortality. Circulating RAS and local paracrin-autocrin-intracrin tissue-based RAS participate in numerous pathobiological events. Pro-inflammatory, pro-fibrotic, and pro-thrombotic consequences associated with local RAS activation have been detected at cellular and molecular level. Regenerative progenitor cell therapy in response to RAS-modulating pharmacotherapy in context of endothelial cell damage and regeneration emerged as an auxiliary therapy to improve regeneration of the vascular endothelium. The aim of this article is to evaluate the relationship between circulating and local angiotensin systems and COVID-19. Copyright © 2020, UHOD - Uluslararasi Hematoloji Onkoloji Dergisi. All rights reserved.

1. **Managing the front-line treatment for diffuse large B-cell lymphoma and high-grade B-cell lymphoma during the COVID-19 outbreak**  
   de la Cruz-Benito B. British Journal of Haematology 2020;06:06.

The COVID-19 pandemic has dramatically challenged care for cancer patients, especially those with active treatment that represent a vulnerable population for SARS-CoV-2 infection. Aggressive lymphoid neoplasms, such as diffuse large B-cell lymphoma and high-grade B-cell lymphoma, need to be treated without delay in order to get the best disease outcome. Because of that, our clinical practice was changed so as to minimize risk of SARS-CoV-2 infection while continuing haematological treatment. In this report, we analyse the management of front-line therapy in 18 patients during COVID-19 outbreak, as well as the results of the implemented measures in their outcome.

1. **Morphoproteomics and Etiopathogenic Features of Pulmonary COVID-19 with Therapeutic Implications: A Case Study**  
   Brown R. E. Annals of Clinical & Laboratory Science 2020;50:308-313.

OBJECTIVE: The COVID-19 pandemic has challenged the world economically and medically. Understanding and defining the biology of this specific coronavirus infection may lead to targeted therapies to lessen its virulence and expand the host resistance. This study's objective was to apply morphoproteomics to pulmonary lung sections from a forensic autopsy of an untreated COVID-19 victim, so that we may better define its biology from the perspective of its interaction with the host and provide options for therapeutic targets.

1. **Multi-organ Proteomic Landscape of COVID-19 Autopsies**  
   Nie Xiu medRxiv 2020;:2020.08.16.20176065.

The molecular pathology of multi-organ injuries in COVID-19 patients remains unclear, preventing effective therapeutics development. Here, we report an in-depth multi-organ proteomic landscape of COVID-19 patient autopsy samples. By integrative analysis of proteomes of seven organs, namely lung, spleen, liver, heart, kidney, thyroid and testis, we characterized 11,394 proteins, in which 5336 were perturbed in COVID-19 patients compared to controls. Our data showed that CTSL, rather than ACE2, was significantly upregulated in the lung from COVID-19 patients. Dysregulation of protein translation, glucose metabolism, fatty acid metabolism was detected in multiple organs. Our data suggested upon SARS-CoV-2 infection, hyperinflammation might be triggered which in turn induces damage of gas exchange barrier in the lung, leading to hypoxia, angiogenesis, coagulation and fibrosis in the lung, kidney, spleen, liver, heart and thyroid. Evidence for testicular injuries included reduced Leydig cells, suppressed cholesterol biosynthesis and sperm mobility. In summary, this study depicts the multi-organ proteomic landscape of COVID-19 autopsies, and uncovered dysregulated proteins and biological processes, offering novel therapeutic clues.Competing Interest StatementThe authors have declared no competing interest.Funding StatementThis work is supported by grants from Tencent Foundation (2020), National Natural Science Foundation of China (81972492, 21904107, 81672086, 81773022), Zhejiang Provincial Natural Science Foundation for Distinguished Young Scholars (LR19C050001), the Key Special Project of Ministry of Science and Technology, China (No.2020YFC0845700), the Fundamental Research Funds for the Central Universities (No.2020kfyXGYJ101), and Hangzhou Agriculture and Society Advancement Program (20190101A04).Author DeclarationsI confirm all relevant ethical guidelines have been followed, and any necessary IRB and/or ethics committee approvals have been obtained.YesThe details of the IRB/oversight body that provided approval or exemption for the research described are given below:This study was approved by the Medical Ethics Committee of Union Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology (No.2020-0043-1) and Medical Ethical Committee of Westlake University (No.20200329GTN001).All necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.YesI understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance).Yes I have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable.YesThe proteomics data is deposited in ProteomeXchange Consortium (https://www.iprox.org/). Project ID: IPX0002393000. The data will be publicly available upon publication in a journal.

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=486b9917847615aca0423e75a9194baf)

1. **Multisystemic Infarctions in COVID-19: Focus on the Spleen**  
   Santos Leite Pessoa M. European Journal of Case Reports in Internal Medicine 2020;7:001747.

The literature suggests that COVID-19 provokes arterial and venous thrombotic events, although the mechanism is still unknown. In this study, we describe patients with confirmed coronavirus infection associated with multisystemic infarction, focusing on splenic infarction. More data are required to elucidate how COVID-19 and thrombotic disease interact and so that preventive and early diagnosis strategies can be developed. LEARNING POINTS: Thrombotic disease as a complication of COVID-19 must be suspected by clinicians, and recognized and monitored by radiologists.Thrombosis is often the initial manifestation of SARS-CoV-2, hence the importance of early diagnosis to avoid complications and reduce morbidity and mortality.

1. **Pan-cancer analysis of transmembrane protease serine 2 and cathepsin L that mediate cellular SARS-CoV-2 infection leading to COVID-19**  
   Katopodis P. International Journal of Oncology 2020;57:533-539.

Severe acute respiratory syndrome (SARS) coronavirus-2 (SARS-CoV2) is the cause of a new disease (COVID-19) which has evolved into a pandemic during the first half of 2020. Older age, male sex and certain underlying diseases, including cancer, appear to significantly increase the risk for severe COVID-19. SARS-CoV-2 infection of host cells is facilitated by the angiotensin-converting enzyme 2 (ACE-2), and by transmembrane protease serine 2 (TMPRSS2) and other host cell proteases such as cathepsin L (CTSL). With the exception of ACE-2, a systematic analysis of these two other SARS-CoV2 infection mediators in malignancies is lacking. Here, we analysed genetic alteration, RNA expression, and DNA methylation of TMPRSS2 and CTSL across a wide spectrum of tumors and controls. TMPRSS2 was overexpressed in cervical squamous cell carcinoma and endocervical adenocarcinoma, colon adenocarcinoma, prostate adenocarcinoma (PRAD), rectum adenocarcinoma (READ), uterine corpus endometrial carcinoma and uterine carcinosarcoma, with PRAD and READ exhibiting the highest expression of all cancers. CTSL was upregulated in lymphoid neoplasm diffuse large B-cell lymphoma, oesophageal carcinoma, glioblastoma multiforme, head and neck squamous cell carcinoma, lower grade glioma, pancreatic adenocarcinoma, skin cutaneous melanoma, stomach adenocarcinoma, and thymoma. Hypo-methylation of both genes was evident in most cases where they have been highly upregulated. We have expanded on our observations by including data relating to mutations and copy number alterations at pan-cancer level. The novel hypotheses that are stemming out of these data need to be further investigated and validated in large clinical studies.

1. **Pathophysiology of SARS-CoV-2: targeting of endothelial cells renders a complex disease with thrombotic microangiopathy and aberrant immune response. The Mount Sinai COVID-19 autopsy experience**  
   Bryce Clare medRxiv 2020;:2020.05.18.20099960.

BACKGROUND Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and its associated clinical syndrome COVID-19 are causing overwhelming morbidity and mortality around the globe, disproportionately affecting New York City. A comprehensive, integrative autopsy series that advances the mechanistic discussion surrounding this disease process is still lacking. METHODS Autopsies were performed at the Mount Sinai Hospital on 67 COVID-19 positive patients and data from the clinical records were obtained from the Mount Sinai Data Warehouse. The experimental design included a comprehensive microscopic examination carried out by a team of expert pathologists, along with transmission electron microscopy, immunohistochemistry, RNA in situ hybridization, as well as immunology and serology assays. RESULTS Laboratory results of our COVID-19 cohort show elevated inflammatory markers, abnormal coagulation values, and elevated cytokines IL-6, IL-8 and TNFα. Autopsies revealed large pulmonary emboli in four cases. We report microthrombi in multiple organ systems including the brain, as well as conspicuous hemophagocytosis and a secondary hemophagocytic lymphohistiocytosis-like syndrome in many of our patients. We provide electron microscopic, immunofluorescent and immunohistochemical evidence of the presence of the virus and the ACE2 receptor in our samples. CONCLUSIONS We report a comprehensive autopsy series of 67 COVID-19 positive patients revealing that this disease, so far conceptualized as a primarily respiratory viral illness, also causes endothelial dysfunction, a hypercoagulable state, and an imbalance of both the innate and adaptive immune responses. Novel findings reported here include an endothelial phenotype of ACE2 in selected organs, which correlates with clotting abnormalities and thrombotic microangiopathy, addressing the prominent coagulopathy and neuropsychiatric symptoms. Another original observation is that of macrophage activation syndrome, with hemophagocytosis and a hemophagocytic lymphohistiocytosis-like disorder, underlying the microangiopathy and excessive cytokine release. We discuss the involvement of critical regulatory pathways.Competing Interest StatementThe authors have declared no competing interest.Funding StatementThis study was supported by the Department of Pathology, Molecular and Cell-Based Medicine at the Icahn School of Medicine at Mount Sinai.Author DeclarationsI confirm all relevant ethical guidelines have been followed, and any necessary IRB and/or ethics committee approvals have been obtained.YesAll necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.YesI understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance).Yes I have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable.Yesall data available are included in figures and tables. For any additional information feel free to contact the senior author.

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1. **Potential impact of SARS-CoV-2 infection on the thymus**  
   Lins M. P. Canadian Journal of Microbiology 2020;:1-6.

Understanding the pathogenesis of certain viral agents is essential for developing new treatments and obtaining a clinical cure. With the onset of the new coronavirus (SARS-CoV-2) pandemic in the beginning of 2020, a rush to conduct studies and develop drugs has led to the publication of articles that seek to address knowledge gaps and contribute to the global scientific research community. There are still no reports on the infectivity or repercussions of SARS-CoV-2 infection on the central lymphoid organ, the thymus, nor on thymocytes or thymic epithelial cells. In this brief review, we present a hypothesis about lymphopenia observed in SARS patients and the probable pathological changes that the thymus may undergo due to this new virus.

1. **Potential neurological impact of coronaviruses: implications for the novel SARS-CoV-2**  
   Iroegbu J. D. Neurological Sciences 2020;41:1329-1337.

Coronaviruses (CoV) are viruses widely known to cause severe respiratory distress due to the prominent clinical symptoms presented. These symptoms, which include fever and dry cough, are frequently found in individuals with CoV infection. Neurological manifestations of CoV have often been neglected; however, recent studies have reported neurological consequences of CoV infection. Here, we review these literatures and discuss the neurologic impact of CoV while highlighting potential implications of the novel SARS-CoV-2 in the nervous system. We also discuss the possible routes by which these viruses invade the nervous system and the mechanism by which they may induce neurological damage.

1. **Prostaglandin D2 as a mediator of lymphopenia and a therapeutic target in COVID-19 disease**  
   Gupta A. Medical Hypotheses 2020;143:110122.

A characteristic feature of COVID-19 disease is lymphopenia. Lymphopenia occurs early in the clinical course and is a predictor of disease severity and outcomes. The mechanism of lymphopenia in COVID-19 is uncertain. It has been variously attributed to the release of inflammatory cytokines including IL-6 and TNF-alpha; direct infection of the lymphocytes by the virus; and rapid sequestration of lymphocytes in the tissues. Additionally, we postulate that prostaglandin D<sub>2</sub> (PGD<sub>2</sub>) is a key meditator of lymphopenia in COVID-19. First, SARS-CoV infection is known to stimulate the production of PGD<sub>2</sub> in the airways, which inhibits the host dendritic cell response via the DP<sub>1</sub> receptor signaling. Second, PGD<sub>2</sub> is known to upregulate monocytic myeloid-derived suppressor cells (MDSC) via the DP<sub>2</sub> receptor signaling in group 2 innate lymphoid cells (ILC2). We propose targeting PGD<sub>2</sub>/DP<sub>2</sub> signaling using a receptor antagonist such as ramatroban as an immunotherapy for immune dysfunction and lymphopenia in COVID-19 disease.

1. **Re: "Exosomes Derived from Bone Marrow Mesenchymal Stem Cells as Treatment for Severe COVID-19" by Sengupta et al**  
   Lim S. K. Stem Cells & Development 2020;29:877-878.

1. **Regulation of Immunity-Related Genes by Infectious Bronchitis Virus Challenge in Spleen of Laying Chickens**  
   Khan S. Viral Immunology 2020;33:413-420.

Understanding of host pathogen interactions is important in planning strategies for effective control of the pathogen. The present study investigated the regulation of genes involved in the activation of splenic immune system in mature laying chickens challenged with T strain of infectious bronchitis virus (IBV). Among all the genes studied, the relative expression levels of Fas cell surface death receptor (FAS), interleukin 7 (IL7), IL18, proteasome subunit alpha 3 (PSMA3), major histocompatibility complex, class II (MHCII), interferon alpha (IFNalpha), immunoglobulin A (IgA), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappaB) were significantly (p < 0.05) upregulated, while Toll-like receptor 7 (TLR7) and TLR5 were significantly downregulated in the challenge compared with the control group. Genes such as vascular cell adhesion molecule 1 (VCAM1), FK506-binding protein 1B (FKBP1B), transforming growth factor-beta 3 (TGFB3), NLR family pyrin domain containing 3 (NLRP3), TYRO3 protein tyrosine kinase (TYRO3), TNF receptor-associated factor 3 (TRAF3), C-X-C motif chemokine receptor 4 (CXCR4), macrophage inflammatory protein-3 (MIP3A), TLR2-1, TLR3, and TLR21 were not altered in mRNA expression levels between the challenge and control groups. In conclusion, the splenic immune response to IBV infection involved the regulation of cytokines, TLRs and NF-kappaB. Copyright © 2020, Mary Ann Liebert, Inc., publishers.

1. **Response to Lim et al. re: "Exosomes Derived from Bone Marrow Mesenchymal Stem Cells as Treatment for Severe COVID-19"**  
   Sengupta V. Stem Cells & Development 2020;29:879-881.

1. **SARS-CoV-2 Infection Associated Hemophagocytic Lymphohistiocytosis: An autopsy series with clinical and laboratory correlation**  
   Prilutskiy Andrey medRxiv 2020;:2020.05.07.20094888.

Background: A subset of COVID-19 patients exhibit clinical features of cytokine storm. However, clinicopathologic features diagnostic of hemophagocytic lymphohistiocytosis (HLH) have not been reported. Pathologic studies to date have largely focused on the pulmonary finding of diffuse alveolar damage (DAD). To this aim, we study the reticuloendothelial organs of four consecutive patients dying of COVID-19 and correlate with clinical and laboratory parameters to detect HLH. Methods: Autopsies restricted to chest and abdomen were performed on four patients who succumbed to COVID-19. Spleen, liver, and multiple pulmonary hilar/mediastinal lymph nodes were sampled in all cases. Bone marrow was obtained by rib squeeze in a subset of cases. Routine H&amp;amp;E staining as well as immunohistochemical staining for CD163 was performed to detect hemophagocytosis. Clinical and laboratory results from pre-mortem blood samples were used to calculate H-scores. Findings: All four cases demonstrated DAD within the lungs. Three of the four cases had histologic evidence of hemophagocytosis within pulmonary hilar/mediastinal lymph nodes. One case showed hemophagocytosis in the spleen but none showed hemophagocytosis in liver or bone marrow. Lymphophagocytosis was the predominant form of hemophagocytosis observed. One patient showed diagnostic features of HLH with an H-score of 217 while a second patient was likely HLH with a partial H-score of 145 due to missing triglyceride level. Both patients exhibited high fever and early onset rise in serum ferritin; however, neither bicytopenia, pancytopenia, nor hypofibrinogenemia were observed in either. The remaining two patients had H-scores of 131 and 96. Interpretation: This is the first report of SARS-CoV-2 associated HLH. Identification of HLH in a subset of patients with severe COVID-19 will inform clinical trials of therapeutic strategies.Competing Interest StatementThe authors have declared no competing interest.Funding StatementFunding was partially provided by the Boston University Mallory Pathology Associates, Inc. and Boston Medical Center.Author DeclarationsAll relevant ethical guidelines have been followed; any necessary IRB and/or ethics committee approvals have been obtained and details of the IRB/oversight body are included in the manuscript.YesAll necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.YesI understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance).Yes I have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable.YesAll data is collected by the authors

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1. **SARS-CoV2 entry and spread in the lymphatic drainage system of the brain**  
   Bostanciklioglu M. Brain, Behavior, & Immunity 2020;87:122-123.

1. **Standardized Testing Demonstrates Altered Odor Detection Sensitivity and Hedonics in Asymptomatic College Students as SARS-CoV-2 Emerged Locally**  
   Walsh-Messinger J. MedRxiv : the Preprint Server for Health Sciences 2020;19:19.

Background Anosmia is a recognized symptom of COVID-19, but the relationship of SARS-CoV-2 exposure with olfactory dysfunction remains enigmatic. This report adds unique data from healthy students tested as the virus emerged locally. Methods Psychometrically validated measures assessed odor detection, identification and hedonics in healthy university students. Data from asymptomatic students (N=22), tested as SARS-CoV-2 unknowingly emerged locally, were compared to students tested just prior to local virus transmission (N=25), and our normative sample (N=272) tested over the previous 4 years. Results The exposed cohort demonstrated significantly reduced odor detection sensitivity compared to the students in the prior group (P=.01; d=0.77; CI 0.17, 1.36), with a distribution skewed towards less detection sensitivity (P=.03). Categorically, the exposed group was significantly more likely to have hyposmia (OR=7.7; CI, 3.1, 19.4), particularly the subset assessed in the final week before campus closure (OR=13.6; CI, 3.4, 35.7). The exposed group also rated odors as less unpleasant (P<.001, CLES=0.77, CI, 0.51, 1.56) and showed a similarly skewed distribution (P=.005). The groups had similar odor identification performance. Conclusion Psychometric measures of odor detection sensitivity and hedonics may detect early SARS-CoV-2 exposure in asymptomatic and pre-symptomatic persons with normal odor identification. Viral detection by nasal associated lymphoid tissue is known to trigger systemic immune effects, but its activation may also reduce smell sensitivity and shift perception of the environment towards unpleasant, increasing the social isolation that may mitigate viral infection or transmission. Regular testing of odor detection and hedonics may have value for identifying regional viral exposure.

1. **Synthesis of N,N'-bis(1,5-dimethyl-2-phenyl-1,2-dihydro-3-oxopyrazol-4-yl) sebacamide that ameliorate osteoarthritis symptoms and improve bone marrow matrix structure and cartilage alterations induced by monoiodoacetate in the rat model: "Suggested potent anti-inflammatory agent against COVID-19"**  
   Refat M. S. Human & Experimental Toxicology 2020;:960327120945779.

To assess the chondroprotective effect and influence of N,N'-bis(1,5-dimethyl-2-phenyl-1,2-dihydro-3-oxopyrazol-4-yl) sebacamide (dpdo) that was synthesized through the reaction of phenazone with sebacoyl chloride and screened for its biological activity especially as anti-arthritic and anti-inflammatory agent in a monoiodoacetate (MA)-induced experimental osteoarthritis (OA) model. Thirty male albino rats weighing "190-200 g" were divided randomly into three groups (10 each): control, MA-induced OA, and MA-induced OA + dpdo. In MA-induced OA rat, the tumor necrosis factor alpha, interleukin 6, C-reactive protein, rheumatoid factors, reactive oxygen species, as well as all the mitochondrial markers such as mitochondria membrane potential, swelling mitochondria, cytochrome c oxidase (complex IV), and serum oxidative/antioxidant status (malondialdehyde level and activities of myeloperoxidase and xanthine oxidase) are elevated. Also, the activity of succinate dehydrogenase (complex II), levels of ATP, the level of glutathione (GSH), and thiol were markedly diminished in the MA-induced OA group compared to the normal control rats. These findings showed that mitochondrial function is associated with OA pathophysiological alterations and high gene expressions of (IL-6, TNF-a, and IL-1b) and suggests a promising use of dpdo as potential ameliorative agents in the animal model of OA and could act as anti-inflammatory agent in case of severe infection with COVID-19. It is clearly appeared in improving the bone cortex and bone marrow in the treated group with the novel compound in histological and transmission electron microscopic sections which is a very important issue today in fighting severe infections that have significant effects on the blood indices and declining of blood corpuscles like COVID-19, in addition to declining the genotoxicity and inflammation induced by MA in male rats. The novel synthesized compound was highly effective in improving all the above mentioned parameters.

1. **Telomeres and COVID-19**  
   Aviv A. FASEB Journal 2020;34:7247-7252.

The medical, public health, and scientific communities are grappling with monumental imperatives to contain COVID-19, develop effective vaccines, identify efficacious treatments for the infection and its complications, and find biomarkers that detect patients at risk of severe disease. The focus of this communication is on a potential biomarker, short telomere length (TL), that might serve to identify patients more likely to die from the SARS-CoV-2 infection, regardless of age. The common thread linking these patients is lymphopenia, which largely reflects a decline in the numbers of CD4/CD8 T cells but not B cells. These findings are consistent with data that lymphocyte TL dynamics impose a limit on T-cell proliferation. They suggest that T-cell lymphopoiesis might stall in individuals with short TL who are infected with SARS-CoV-2.

1. **The Novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Directly Decimates Human Spleens and Lymph Nodes**  
   chen yongwen medRxiv 2020;:2020.03.27.20045427.

While lymphocytopenia is a common characteristic of patients infected by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the mechanisms responsible for this depletion are unclear. Through careful inspection of the spleens and lymph nodes (LNs) from six cases with postmortem examinations, we observed that SARS-CoV-2 could directly infect secondary lymphoid organs to induce cell death. Immunohistochemistry demonstrated ACE2 (angiotensin-converting enzyme 2), the potential receptor of SARS-CoV-2, expresses on tissue-resident CD169+ macrophages in spleens and LNs. Immunofluorescent staining confirmed that viral nucleocaspid protein (NP) can be found in ACE2+ cells, CD169+ macrophages, but not in CD3+ T cells or B220+ B cells in spleens and LNs. SARS-CoV-2 infection induces severe tissue damage including lymph follicle depletion, splenic nodule atrophy, histiocyte hyperplasia and lymphocyte reductions. Moreover, in situ TUNEL staining illustrated that viral infection leads to severe lymphocyte apoptosis, which might be mediated by viral antigens inducing Fas upregulation. Furthermore, SARS-CoV-2 also triggers macrophages to produce IL-6, a proinflammatory cytokine that directly promotes lymphocyte necrosis. Collectively, these results demonstrate that SARS-CoV-2 directly neutralizes human spleens and LNs through infecting tissue- resident CD169+ macrophages.Competing Interest StatementThe authors have declared no competing interest.Funding StatementThe funding agencies did not participate in study design, sample collection, data analysis, or manuscript writing.Author DeclarationsAll relevant ethical guidelines have been followed; any necessary IRB and/or ethics committee approvals have been obtained and details of the IRB/oversight body are included in the manuscript.YesAll necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.YesI understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance).Yes I have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable.YesFor protection of patients&#039; privacy, all data are only provided by authors with anonymous version.

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1. **The underpinning biology relating to multiple sclerosis disease modifying treatments during the COVID-19 pandemic**  
   Baker D. Multiple Sclerosis and Related Disorders 2020;43:102174.

BACKGROUND: SARS-CoV-2 viral infection causes COVID-19 that can result in severe acute respiratory distress syndrome (ARDS), which can cause significant mortality, leading to concern that immunosuppressive treatments for multiple sclerosis and other disorders have significant risks for both infection and ARDS.

1. **Therapeutic and Surgical Indications for Patients with Penile Cancer in the COVID-19 era**  
   Casco N. C. International Braz J Urol 2020;46:86-92.

PURPOSE: The aim of this work is to review and synthesize the existing evidence and recommendations regarding to the therapeutic and surgical indications as well as monitoring of patients with Penile Cancer in COVID-19 era and to propose an action protocol to facilitate decision-making. MATERIAL AND METHODS: A non-systematic review of the literature regarding the management of penile cancer during the COVID-19 pandemic was performed until April 30, 2020. We propose our recommendations based on this evidence.

1. **Unspecific post-mortem findings despite multiorgan viral spread in COVID-19 patients**  
   Remmelink M. Critical Care (London, England) 2020;24:495.

BACKGROUND: Post-mortem studies can provide important information for understanding new diseases and small autopsy case series have already reported different findings in COVID-19 patients.

1. **Upper airway gene expression differentiates COVID-19 from other acute respiratory illnesses and reveals suppression of innate immune responses by SARS-CoV-2**  
   Mick E. MedRxiv : the Preprint Server for Health Sciences 2020;19:19.

We studied the host transcriptional response to SARS-CoV-2 by performing metagenomic sequencing of upper airway samples in 238 patients with COVID-19, other viral or non-viral acute respiratory illnesses (ARIs). Compared to other viral ARIs, COVID-19 was characterized by a diminished innate immune response, with reduced expression of genes involved in toll-like receptor and interleukin signaling, chemokine binding, neutrophil degranulation and interactions with lymphoid cells. Patients with COVID-19 also exhibited significantly reduced proportions of neutrophils and macrophages, and increased proportions of goblet, dendritic and B-cells, compared to other viral ARIs. Using machine learning, we built 26-, 10- and 3-gene classifiers that differentiated COVID-19 from other acute respiratory illnesses with AUCs of 0.980, 0.950 and 0.871, respectively. Classifier performance was stable at low viral loads, suggesting utility in settings where direct detection of viral nucleic acid may be unsuccessful. Taken together, our results illuminate unique aspects of the host transcriptional response to SARS-CoV-2 in comparison to other respiratory viruses and demonstrate the feasibility of COVID-19 diagnostics based on patient gene expression.

1. **[Pathological changes of the spleen in ten patients with coronavirus disease 2019(COVID-19) by postmortem needle autopsy]**  
   Xu X. Chung-Hua Ping Li Hsueh Tsa Chih - Chinese Journal of Pathology 2020;49:576-582.

<b>Objective:</b> To study the pathological changes of the spleen in patients with COVID-19 and to analyze the relationship between the weakened immune system and splenic lesions.

1. **Broad Cross-Species Infection of Cultured Cells by Bat HKU2-Related Swine Acute Diarrhea Syndrome Coronavirus and Identification of Its Replication in Murine Dendritic Cells In Vivo Highlight Its Potential for Diverse Interspecies Transmission**  
   Yang Y. L. Journal of Virology 2019;93:15.

Outbreaks of severe diarrhea in neonatal piglets in Guangdong, China, in 2017 resulted in the isolation and discovery of a novel swine enteric alphacoronavirus (SeACoV) derived from the species Rhinolophus bat coronavirus HKU2 (Y. Pan, X. Tian, P. Qin, B. Wang, et al., Vet Microbiol 211:15-21, 2017). SeACoV was later referred to as swine acute diarrhea syndrome CoV (SADS-CoV) by another group (P. Zhou, H. Fan, T. Lan, X.-L. Yang, et al., Nature 556:255-258, 2018). The present study was set up to investigate the potential species barriers of SADS-CoV in vitro and in vivo We first demonstrated that SADS-CoV possesses a broad species tropism and is able to infect cell lines from diverse species, including bats, mice, rats, gerbils, hamsters, pigs, chickens, nonhuman primates, and humans. Trypsin contributes to but is not essential for SADS-CoV propagation in vitro Furthermore, C57BL/6J mice were inoculated with the virus via oral or intraperitoneal routes. Although the mice exhibited only subclinical infection, they supported viral replication and prolonged infection in the spleen. SADS-CoV nonstructural proteins and double-stranded RNA were detected in splenocytes of the marginal zone on the edge of lymphatic follicles, indicating active replication of SADS-CoV in the mouse model. We identified that splenic dendritic cells (DCs) are the major targets of virus infection by immunofluorescence and flow cytometry approaches. Finally, we demonstrated that SADS-CoV does not utilize known CoV receptors for cellular entry. The ability of SADS-CoV to replicate in various cells lines from a broad range of species and the unexpected tropism for murine DCs provide important insights into the biology of this bat-origin CoV, highlighting its possible ability to cross interspecies barriers. <b>IMPORTANCE</b> Infections with bat-origin coronaviruses (CoVs) (severe acute respiratory syndrome CoV [SARS-CoV] and Middle East respiratory syndrome CoV [MERS-CoV]) have caused severe illness in humans after "host jump" events. Recently, a novel bat-HKU2-like CoV named swine acute diarrhea syndrome CoV (SADS-CoV) has emerged in southern China, causing lethal diarrhea in newborn piglets. It is important to assess the species barriers of SADS-CoV infection since the animal hosts (other than pigs and bats) and zoonotic potential are still unknown. An in vitro susceptibility study revealed a broad species tropism of SADS-CoV, including various rodent and human cell lines. We established a mouse model of SADS-CoV infection, identifying its active replication in splenic dendritic cells, which suggests that SADS-CoV has the potential to infect rodents. These findings highlight the potential cross-species transmissibility of SADS-CoV, although further surveillance in other animal populations is needed to fully understand the ecology of this bat-HKU2-origin CoV.

1. **Co-localization of Middle East respiratory syndrome coronavirus (MERS-CoV) and dipeptidyl peptidase-4 in the respiratory tract and lymphoid tissues of pigs and llamas**  
   Te N. Transboundary and Emerging Diseases 2019;66:831-841.

This study investigated the co-localization of the Middle East respiratory syndrome coronavirus (MERS-CoV) and its receptor dipeptidyl peptidase-4 (DPP4) by immunohistochemistry (IHC) across respiratory and lymphoid organs of experimentally MERS-CoV infected pigs and llamas. Also, scanning electron microscopy was performed to assess the ciliary integrity of respiratory epithelial cells in both species. In pigs, on day 2 post-inoculation (p.i.), DPP4-MERS-CoV co-localization was detected in medial turbinate epithelium. On day 4 p.i., the virus/receptor co-localized in frontal and medial turbinate epithelial cells in pigs, and epithelial cells distributed unevenly through the whole nasal cavity and in the cervical lymph node in llamas. MERS-CoV viral nucleocapsid was mainly detected in upper respiratory tract sites on days 2 and 4 p.i. in pigs and day 4 p.i. in llamas. No MERS-CoV was detected on day 24 p.i. in any tissue by IHC. While pigs showed severe ciliary loss in the nasal mucosa both on days 2 and 4 p.i. and moderate loss in the trachea on days 4 and 24 p.i., ciliation of respiratory organs in llamas was not significantly affected. Obtained data confirm the role of DPP4 for MERS-CoV entry in respiratory epithelial cells of llamas. Notably, several nasal epithelial cells in pigs were found to express viral antigen but not DPP4, suggesting the possible existence of other molecule/s facilitating virus entry or down regulation of DPP4 upon infection. Copyright © 2018 The Authors. Transboundary and Emerging Diseases published by Blackwell Verlag GmbH.

1. **Modeling [(18)F]-FDG lymphoid tissue kinetics to characterize nonhuman primate immune response to Middle East respiratory syndrome-coronavirus aerosol challenge**  
   Chefer S. EJNMMI Research 2015;5:65.

BACKGROUND: The pathogenesis and immune response to Middle East respiratory syndrome (MERS) caused by a recently discovered coronavirus, MERS-CoV, have not been fully characterized because a suitable animal model is currently not available. (18)F-Fluorodeoxyglucose ([(18)F]-FDG)-positron emission tomography/computed tomography (PET/CT) as a longitudinal noninvasive approach can be beneficial in providing biomarkers for host immune response. [(18)F]-FDG uptake is increased in activated immune cells in response to virus entry and can be localized by PET imaging. We used [(18)F]-FDG-PET/CT to investigate the host response developing in nonhuman primates after MERS-CoV exposure and applied kinetic modeling to monitor the influx rate constant (K i ) in responsive lymphoid tissue.

1. **Modeling [18F]-FDG lymphoid tissue kinetics to characterize nonhuman primate immune response to Middle East respiratory syndrome-coronavirus aerosol challenge**  
   Chefer S. EJNMMI Research 2015;5:1-11.

Background: The pathogenesis and immune response to Middle East respiratory syndrome (MERS) caused by a recently discovered coronavirus, MERS-CoV, have not been fully characterized because a suitable animal model is currently not available. <sup>18</sup>F-Fluorodeoxyglucose ([<sup>18</sup>F]-FDG)-positron emission tomography/computed tomography (PET/CT) as a longitudinal noninvasive approach can be beneficial in providing biomarkers for host immune response. [<sup>18</sup>F]-FDG uptake is increased in activated immune cells in response to virus entry and can be localized by PET imaging. We used [<sup>18</sup>F]-FDG-PET/CT to investigate the host response developing in nonhuman primates after MERS-CoV exposure and applied kinetic modeling to monitor the influx rate constant (K<inf>i</inf>) in responsive lymphoid tissue. Method(s): Multiple [<sup>18</sup>F]-FDG-PET and CT images were acquired on a PET/CT clinical scanner modified to operate in a biosafety level 4 environment prior to and up to 29 days after MERS-CoV aerosol exposure. Time activity curves of various lymphoid tissues were reconstructed to follow the [<sup>18</sup>F]-FDG uptake for approximately 60 min (3,600 s). Image-derived input function was used to calculate K<inf>i</inf> for lymphoid tissues by Patlak plot. Result(s): Two-way repeated measures analysis of variance revealed alterations in K<inf>i</inf> that was associated with the time point (p < 0.001) after virus exposure and the location of lymphoid tissue (p = 0.0004). As revealed by a statistically significant interaction (p < 0.0001) between these two factors, the pattern of K<inf>i</inf> changes over time differed between three locations but not between subjects. A distinguished pattern of statistically significant elevation in K<inf>i</inf> was observed in mediastinal lymph nodes (LNs) that correlated to K<inf>i</inf> changes in axillary LNs. Changes in LNs K<inf>i</inf> were concurrent with elevations of monocytes in peripheral blood. Conclusion(s): [<sup>18</sup>F]-FDG-PET is able to detect subtle changes in host immune response to contain a subclinical virus infection. Full quantitative analysis is the preferred approach rather than semiquantitative analysis using standardized uptake value for detection of the immune response to the virus. Copyright © 2015, Chefer et al.

1. **Severe Acute Respiratory Syndrome Coronavirus ORF7a Inhibits Bone Marrow Stromal Antigen 2 Virion Tethering through a Novel Mechanism of Glycosylation Interference**  
   Taylor J. K. Journal of Virology 2015;89:11820-33.

UNLABELLED: Severe acute respiratory syndrome (SARS) emerged in November 2002 as a case of atypical pneumonia in China, and the causative agent of SARS was identified to be a novel coronavirus, severe acute respiratory syndrome coronavirus (SARS-CoV). Bone marrow stromal antigen 2 (BST-2; also known as CD317 or tetherin) was initially identified to be a pre-B-cell growth promoter, but it also inhibits the release of virions of the retrovirus human immunodeficiency virus type 1 (HIV-1) by tethering budding virions to the host cell membrane. Further work has shown that BST-2 restricts the release of many other viruses, including the human coronavirus 229E (hCoV-229E), and the genomes of many of these viruses encode BST-2 antagonists to overcome BST-2 restriction. Given the previous studies on BST-2, we aimed to determine if BST-2 has the ability to restrict SARS-CoV and if the SARS-CoV genome encodes any proteins that modulate BST-2's antiviral function. Through an in vitro screen, we identified four potential BST-2 modulators encoded by the SARS-CoV genome: the papain-like protease (PLPro), nonstructural protein 1 (nsp1), ORF6, and ORF7a. As the function of ORF7a in SARS-CoV replication was previously unknown, we focused our study on ORF7a. We found that BST-2 does restrict SARS-CoV, but the loss of ORF7a leads to a much greater restriction, confirming the role of ORF7a as an inhibitor of BST-2. We further characterized the mechanism of BST-2 inhibition by ORF7a and found that ORF7a localization changes when BST-2 is overexpressed and ORF7a binds directly to BST-2. Finally, we also show that SARS-CoV ORF7a blocks the restriction activity of BST-2 by blocking the glycosylation of BST-2.

1. **Intranasal vaccination with recombinant receptor-binding domain of MERS-CoV spike protein induces much stronger local mucosal immune responses than subcutaneous immunization: Implication for designing novel mucosal MERS vaccines**  
   Ma C. Vaccine 2014;32:2100-8.

Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) was originally identified in Saudi Arabia in 2012. It has caused MERS outbreaks with high mortality in the Middle East and Europe, raising a serious concern about its pandemic potential. Therefore, development of effective vaccines is crucial for preventing its further spread and future pandemic. Our previous study has shown that subcutaneous (s.c.) vaccination of a recombinant protein containing receptor-binding domain (RBD) of MERS-CoV S fused with Fc of human IgG (RBD-Fc) induced strong systemic neutralizing antibody responses in vaccinated mice. Here, we compared local and systemic immune responses induced by RBD-Fc via intranasal (i.n.) and s.c. immunization pathways. We found that i.n. vaccination of MERS-CoV RBD-Fc induced systemic humoral immune responses comparable to those induced by s.c. vaccination, including neutralizing antibodies, but more robust systemic cellular immune responses and significantly higher local mucosal immune responses in mouse lungs. This study suggests the potential of developing MERS-CoV RBD protein into an effective and safe mucosal candidate vaccine for prevention of respiratory tract infections caused by MERS-CoV.

1. **Regulatory T cells selectively preserve immune privilege of self-antigens during viral central nervous system infection**  
   Cervantes-Barragan L. Journal of Immunology 2012;188:3678-85.

Regulatory T cells (Tregs) are important for the attenuation of immune reactions. During viral CNS infections, however, an indiscriminate maintenance of CNS immune privilege through Treg-mediated negative regulation could prevent autoimmune sequelae but impair the control of viral replication. We analyzed in this study the impact of Tregs on the development of acute viral encephalomyelitis, T cell-mediated antiviral protection, and prevention of CNS autoimmunity following intranasal infection with the gliatropic mouse hepatitis virus strain A59. To assess the contribution of Tregs in vivo, we specifically depleted CD4(+)Foxp3(+) T cells in a diphtheria toxin-dependent manner. We found that depletion of Tregs had no impact on viral distribution and clearance and did not significantly alter virus-specific CD4(+) and CD8(+) T cell responses. However, Treg depletion led to a more severe CNS inflammation associated with neuronal damage. Dissection of the underlying immunopathological mechanisms revealed the elaborate Treg-dependent regulation of self-reactive CD4(+) T cell proliferation within the CNS-draining lymph node and downtuning of CXCR3 expression on T cells. Taken together, these results suggest that Tregs preserve CNS immune privilege through selective control of CNS-specific Th cells while keeping protective antiviral immunity fully operative.

1. **Severe acute respiratory syndrome and venous thromboembolism in multiple organs**  
   Xiang-Hua Y. American Journal of Respiratory & Critical Care Medicine 2010;182:436-7.

1. **Intranasal vaccination of recombinant adeno-associated virus encoding receptor-binding domain of severe acute respiratory syndrome coronavirus (SARS-CoV) spike protein induces strong mucosal immune responses and provides long-term protection against SARS-CoV infection**  
   Du L. Journal of Immunology 2008;180:948-56.

We have previously reported that a subunit protein vaccine based on the receptor-binding domain (RBD) of severe acute respiratory syndrome coronavirus (SARS-CoV) spike protein and a recombinant adeno-associated virus (rAAV)-based RBD (RBD-rAAV) vaccine could induce highly potent neutralizing Ab responses in immunized animals. In this study, systemic, mucosal, and cellular immune responses and long-term protective immunity induced by RBD-rAAV were further characterized in a BALB/c mouse model, with comparison of the i.m. and intranasal (i.n.) routes of administration. Our results demonstrated that: 1) the i.n. vaccination induced a systemic humoral immune response of comparable strength and shorter duration than the i.m. vaccination, but the local humoral immune response was much stronger; 2) the i.n. vaccination elicited stronger systemic and local specific cytotoxic T cell responses than the i.m. vaccination, as evidenced by higher prevalence of IL-2 and/or IFN-gamma-producing CD3+/CD8+ T cells in both lungs and spleen; 3) the i.n. vaccination induced similar protection as the i.m. vaccination against SARS-CoV challenge in mice; 4) higher titers of mucosal IgA and serum-neutralizing Ab were associated with lower viral load and less pulmonary pathological damage, while no Ab-mediated disease enhancement effect was observed; and 5) the vaccination could provide long-term protection against SARS-CoV infection. Taken together, our findings suggest that RBD-rAAV can be further developed into a vaccine candidate for prevention of SARS and that i.n. vaccination may be the preferred route of administration due to its ability to induce SARS-CoV-specific systemic and mucosal immune responses and its better safety profile.

1. **The expression and antigenicity of a truncated spike-nucleocapsid fusion protein of severe acute respiratory syndrome-associated coronavirus**  
   Mu F. BMC Microbiology 2008;8:207.

BACKGROUND: In the absence of effective drugs, controlling SARS relies on the rapid identification of cases and appropriate management of the close contacts, or effective vaccines for SARS. Therefore, developing specific and sensitive laboratory tests for SARS as well as effective vaccines are necessary for national authorities.

1. **The spleen as a target in severe acute respiratory syndrome**  
   Zhan J. FASEB Journal 2006;20:2321-8.

It has been proposed that immune injury is the central mechanism of pathogenesis of the infectious disease, severe acute respiratory syndrome (SARS). To gain a better understanding of immune injury in the spleen, we investigated the number and distribution of various immune cell types in the spleens of SARS patients. We performed autopsies on six confirmed SARS cases, with six normal subjects as controls; spleen samples from these autopsies were examined with hematoxylin and eosin (H&E) sections, in situ hybridization for SARS virus genomic sequences, and immunohistochemistry with seven monoclonal antibodies to five cell types. The number and distribution of these cells were measured and analyzed using an image analysis system. SARS genomic sequences were detected in all SARS spleens. The SARS spleens all had severe damage to the white pulp and showed an alteration of the normal distribution of various cell types. Immunocytes in the red pulp were decreased by 68.0-90.7% except for CD68+ macrophages and human leukocyte antigen (HLA)-DR positive antigen-presenting cells (APC), which were decreased to a lesser degree. On average, CD68+ macrophages were increased in size by 2.21-fold. We hypothesize that the collapse of the splenic immune system plays a key role in the clinical outcome of these patients.

1. **Multiple organ infection and the pathogenesis of SARS**  
   Gu J. Journal of Experimental Medicine 2005;202:415-24.

After >8,000 infections and >700 deaths worldwide, the pathogenesis of the new infectious disease, severe acute respiratory syndrome (SARS), remains poorly understood. We investigated 18 autopsies of patients who had suspected SARS; 8 cases were confirmed as SARS. We evaluated white blood cells from 22 confirmed SARS patients at various stages of the disease. T lymphocyte counts in 65 confirmed and 35 misdiagnosed SARS cases also were analyzed retrospectively. SARS viral particles and genomic sequence were detected in a large number of circulating lymphocytes, monocytes, and lymphoid tissues, as well as in the epithelial cells of the respiratory tract, the mucosa of the intestine, the epithelium of the renal distal tubules, the neurons of the brain, and macrophages in different organs. SARS virus seemed to be capable of infecting multiple cell types in several organs; immune cells and pulmonary epithelium were identified as the main sites of injury. A comprehensive theory of pathogenesis is proposed for SARS with immune and lung damage as key features.

1. **Clinicopathology of severe acute respiratory syndrome: an autopsy case report**  
   Hsiao C. H. Journal of the Formosan Medical Association 2004;103:787-92.

In mid-April 2003, a major outbreak of severe acute respiratory syndrome (SARS) developed in Taiwan. During the outbreak, SARS-associated coronavirus (SARS-CoV) was documented in 346 patients and 73 of them died. Autopsy was performed in 9 of the suspected SARS patients who died during the outbreak, but SARS was the cause of death in only 1 of these patients. Here we report the histological features of this patient and their clinicopathological correlations. The patient, a 36-year-old Indonesian woman, was a caretaker working for a Taiwanese family. She stayed in Taipei Jen-Chi Hospital from April 10 to April 19 to take care of her elderly employer. She developed fever on April 21 and respiratory distress on April 25, and received ribavirin, intravenous immunoglobulin, and steroid. The respiratory distress persisted and worsened, and intubation was performed on April 27. The respiratory condition improved initially after mechanical ventilation, but subcutaneous emphysema and pneumomediastinum developed on May 1. Her condition deteriorated rapidly and she died on May 2, 11 days after the onset of fever. Autopsy was performed on the same day. Histologically, the lungs showed severe diffuse alveolar damage and bronchopneumonia, but no viral inclusion. The spleen and lymph nodes revealed lymphoid depletion and the liver showed microvesicular steatosis. No specific pathological change was seen in the gastrointestinal tract and kidneys. SARS-CoV genome was detected in the nasopharyngeal aspirate and the autopsy lung specimen.

1. **Identification of an HLA-A 0201-restricted CD8+ T-cell epitope SSp-1 of SARS-CoV spike protein**  
   Wang B. Blood 2004;104:200-6.

A novel coronavirus, severe acute respiratory syndrome (SARS)-associated coronavirus (SARS-CoV), has been identified as the causal agent of SARS. Spike (S) protein is a major structural glycoprotein of the SARS virus and a potential target for SARS-specific cell-mediated immune responses. A panel of S protein-derived peptides was tested for their binding affinity to HLA-A\*0201 molecules. Peptides with high affinity for HLA-A\*0201 were then assessed for their capacity to elicit specific immune responses mediated by cytotoxic T lymphocytes (CTLs) both in vivo, in HLA-A2.1/K(b) transgenic mice, and in vitro, from peripheral blood lymphocytes (PBLs) harvested from healthy HLA-A2.1(+) donors. SARS-CoV protein-derived peptide-1 (SSp-1 RLNEVAKNL), induced peptide-specific CTLs both in vivo (transgenic mice) and in vitro (human PBLs), which specifically released interferon-gamma (IFN-gamma) upon stimulation with SSp-1-pulsed autologous dendritic cells (DCs) or T2 cells. SSp-1-specific CTLs also lysed major histocompatibility complex (MHC)-matched tumor cell lines engineered to express S proteins. HLA-A\*0201-SSp-1 tetramer staining revealed the presence of significant populations of SSp-1-specific CTLs in SSp-1-induced CD8(+) T cells. We propose that the newly identified epitope SSp-1 will help in the characterization of virus control mechanisms and immunopathology in SARS-CoV infection, and may be relevant to the development of immunotherapeutic approaches for SARS.

1. **A clinicopathological study of three cases of severe acute respiratory syndrome (SARS)**  
   Lang Z. W. Pathology 2003;35:526-31.

AIMS: The severe acute respiratory syndrome (SARS) caused a large outbreak of atypical pneumonia in Beijing, China from early March 2003. We report the pathological features from three patients who died of SARS.

1. **Pathological study on severe acute respiratory syndrome**  
   Lang Z. Chinese Medical Journal 2003;116:976-80.

OBJECTIVE: To study the pathological characteristics of severe acute respiratory syndrome (SARS) and its relationship to clinical manifestation.

1. **The clinical pathology of severe acute respiratory syndrome (SARS): a report from China**  
   Ding Y. Journal of Pathology 2003;200:282-9.

In order to investigate the clinical pathology of severe acute respiratory syndrome (SARS), the autopsies of three patients who died from SARS in Nan Fang Hospital Guangdong, China were studied retrospectively. Routine haematoxylin and eosin (H&E) staining was used to study all of the tissues from the three cases. The lung tissue specimens were studied further with Macchiavello staining, viral inclusion body staining, reticulin staining, PAS staining, immunohistochemistry, ultrathin sectioning and staining, light microscopy, and transmission electron microscopy. The first symptom was hyperpyrexia in all three cases, followed by progressive dyspnoea and lung field shadowing. The pulmonary lesions included bilateral extensive consolidation, localized haemorrhage and necrosis, desquamative pulmonary alveolitis and bronchitis, proliferation and desquamation of alveolar epithelial cells, exudation of protein and monocytes, lymphocytes and plasma cells in alveoli, hyaline membrane formation, and viral inclusion bodies in alveolar epithelial cells. There was also massive necrosis of splenic lymphoid tissue and localized necrosis in lymph nodes. Systemic vasculitis included oedema, localized fibrinoid necrosis, and infiltration of monocytes, lymphocytes, and plasma cells into vessel walls in the heart, lung, liver, kidney, adrenal gland, and the stroma of striated muscles. Thrombosis was present in small veins. Systemic toxic changes included degeneration and necrosis of the parenchyma cells in the lung, liver, kidney, heart, and adrenal gland. Electron microscopy demonstrated clusters of viral particles, consistent with coronavirus, in lung tissue. SARS is a systemic disease that injures many organs. The lungs, immune organs, and systemic small vessels are the main targets of virus attack, so that extensive consolidation of the lung, diffuse alveolar damage with hyaline membrane formation, respiratory distress, and decreased immune function are the main causes of death.

1. **[Morphological study of severe acute respiratory syndrome (SARS)]**  
   Chen J. Chung-Hua Ping Li Hsueh Tsa Chih - Chinese Journal of Pathology 2003;32:516-20.

OBJECTIVE: Seven cases of autopsy from SARS patients are studied to investigate the pathogenesis and the pathologic changes of the major organs.

1. **[Pathological and ultramicrostructural changes of tissues in a patient with severe acute respiratory syndrome]**  
   Lai R. Q. Chung-Hua Ping Li Hsueh Tsa Chih - Chinese Journal of Pathology 2003;32:205-8.

OBJECTIVE: To study the morphological, ultramicrostructural and pathological changes of tissues from a patient with severe acute respiratory syndrome (SARS).

1. **Coronavirus pneumonia following autologous bone marrow transplantation for breast cancer**  
   Folz R. J. Chest 1999;115:901-5.

Infectious bronchitis virus, otherwise known as coronavirus, can cause mild upper respiratory tract illnesses in children and adults. Rarely has coronavirus been linked, either by serology or nasal wash, to pneumonia. We report a case of a young woman who, following treatment for stage IIIA breast cancer using a high-dose chemotherapy regimen followed by autologous bone marrow and stem cell transplantation, developed respiratory failure and was found to have coronavirus pneumonia as diagnosed by electron microscopy from BAL fluid. We propose that coronavirus should be considered in the differential diagnosis of acute respiratory failure in cancer patients who have undergone high-dose chemotherapy and autologous hematopoietic support.

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| --- | --- | --- | --- |
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| 5. |  | (("seafood market\*" or "food market\*") adj10 (Wuhan\* or Hubei\* or China\* or Chinese\* or Huanan\*)).ti,ab. | 80 |
| 6. |  | 1 or 2 or 3 or 4 or 5 | 64803 |
| 7. |  | exp Lymphatic System/ | 272781 |
| 8. |  | exp Spleen/ | 115655 |
| 9. |  | exp Bone Marrow/ | 67050 |
| 10. |  | lymphoid.ti. | 20871 |
| 11. |  | bone marrow.ti. | 68849 |
| 12. |  | spleen.ti. | 24105 |
| 13. |  | 7 or 8 or 9 or 10 or 11 or 12 | 390444 |
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