The Daily COVID-19 Literature Surveillance Summary

September 23, 2020

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COVID-19 Daily Literature Surveillance

COVID19LST

Bringing you real time, distilled information for guiding best practices during the COVID-19 pandemic

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

EXECUTIVE SUMMARY

Climate

- An expert opinion from individuals affiliated with University of North Carolina and Boston University schools of medicine expose socioeconomic disparities and health inequities in US populations, with higher COVID-19 mortality present among Black, Latinx, and Indigenous populations when compared to Whites. They recommend new policies that include a monthly universal food income to all US households, unemployment insurance reform, and community development investment policies. Such policies may promote improvement of health inequity among Americans.

Epidemiology

- To assess environmental prevalence of SARS-CoV-2, microbiologists collected and analyzed 57 samples from 13 households, 9 public venues, and the wastewater sewage system of Horcajo de los Montes village in Spain (883 inhabitants). They found 12% of samples from clothing, fridge and oven handles, doors knobs, keyboards, and other items were SARS-CoV-2 positive via RT-PCR. Although 6% of villagers had COVID-19, most known cases had resolved prior to sample collection, suggesting there may be a significant incidence and persistence of SARS-CoV-2 in the environment even after recovery within the population.

- Physicians from Brigham and Women's Hospital in Boston, Massachusetts extracted data from the Premier Healthcare Database to explore outcomes and clinical profiles of 3,222 young adults (ages 18-34) hospitalized with COVID-19 and found 21% of patients required intensive care, 10% required mechanical ventilation, and 2.7% died. Also, there was increased risk of adverse outcomes in patients with morbid obesity, hypertension, or diabetes. Authors suggest young adults hospitalized for COVID-19 may experience significant adverse outcomes, emphasizing the importance of prevention among this age group.

- A case study conducted in Nice, France involved a 63 year-old female presenting with asthenia, fever, dry cough, and headache with chest CT showing evidence of COVID-19 pneumonia. Day 26 following onset, during the non-inflammatory timeline of infection, she noticed lower limb purpura without PT, aPTT, fibrinogen abnormalities, and consistent with immune thrombocytopenia, which resolved following IVIg therapy. This case indicates physicians need to be cautious of bleeding, thrombosis, and septic risks in COVID-19 patients and should consider IVIg therapy as a reasonable treatment for ITP.

Management

- A cohort-control study conducted by pathologists at University Women's Hospital Basel in Switzerland investigated 5 COVID-19 positive pregnant women (three mildly symptomatic and two asymptomatic) and 10 controls for the potential of vertical transmission of SARS-CoV-2. All 5 mothers and 2/5 fetuses has malperfusion, including 1 fetus having small thrombi. One patient, who was the only one symptomatic at childbirth, had placental pathological findings of lymphohistiocytic villitis and intervillositis, as well as viral RNA present in both the placenta and umbilical cord. The authors concluded that SARS-CoV2 infection displays potential for increased risk of fetal malperfusion through an increased coagulative state and and may result in placental infection.

Adjusting Practice During COVID-19

- A review of studies by surgeons in India assessed the efficacy of chest computed tomography (CT) as a preoperative COVID-19 diagnostic tool for patients undergoing elective surgeries and found early studies indicated chest CT as an effective screening tool, but further evaluation of subsequent studies showed low predictive value and potentially unnecessary surgery delay. Authors suggest chest CT is not practical in settings where RT-PCR is readily available, recommending its use only for symptomatic patients with high post-operative complication risk or pulmonary sequelae after COVID-19.

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CLIMATE

DISPARITIES

COVID-19 AND HEALTH EQUITY - TIME TO THINK BIG

Berkowitz SA, Cené CW, Chatterjee A.. N Engl J Med. 2020 Sep 17;383(12):e76. doi: 10.1056/NEJMp2021209. Epub 2020 Jul 22.
Level of Evidence: Other - Expert Opinion

BLUF

An expert opinion from individuals affiliated with University of North Carolina and Boston University schools of medicine expose socioeconomic disparities and health inequities in US populations, with higher COVID-19 mortality present among Black, Latinx, and Indigenous populations when compared to Whites. They recommend new policies that include a monthly universal food income to all US households, unemployment insurance reform, and community development investment policies. Such policies may promote improvement of health inequity among Americans.

EPIDEMIOLOGY

DETECTION OF ENVIRONMENTAL SARS-COV-2 RNA IN A HIGH PREVALENCE SETTING IN SPAIN

Fernández-de-Mera IG, Rodríguez Del-Río FJ, Fuente J, Pérez-Sancho M, Hervás D, Moreno I, Domínguez M, Domínguez L, Gortázar C.. Transbound Emerg Dis. 2020 Sep 7. doi: 10.1111/tbed.13817. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

To assess environmental prevalence of SARS-CoV-2, microbiologists collected and analyzed 57 samples on May 13 and June 5, 2020 from 13 households, 9 public venues, and the wastewater sewage system of Horcajo de los Montes village in Spain (883 inhabitants). They found 12% of samples from clothing, fridge and oven handles, doors knobs, keyboards, and other items were SARS-CoV-2 positive via RT-PCR. Although 6% of villagers had COVID-19, most known cases had resolved prior to sample collection, suggesting there may be a significant incidence and persistence of SARS-CoV-2 in the environment even after recovery within the population.

ABSTRACT

Since March 2020, Spain (along with many other countries) has been severely affected by the ongoing coronavirus disease 19 (COVID-19) pandemic caused by the rapid spread of a new virus (severe acute respiratory syndrome coronavirus 2; SARS-CoV-2). As part of global efforts to improve disease surveillance, we investigated how readily SARS-CoV-2 RNA could be detected in environmental samples collected from an isolated rural community in Spain with a high COVID-19 prevalence (6% of the population of 883 inhabitants). The first diagnosis of COVID-19-compatible symptoms in the village was recorded on March 3, 2020 and the last known active case resolved on June 5, 2020. By May 15, two months after strict movement constraints were imposed ("lockdown") the cumulative number of symptomatic cases had increased to 53. Of those cases, 22 (41%) had been tested and confirmed by RT-PCR. On May 13 and June 5, samples were collected from high-use surfaces and clothes in the homes of 13 confirmed cases, from surfaces in nine public service sites (e.g. supermarket and petrol station), and from the wastewater of the village sewage system. SARS-CoV-2 RNA was detected in 7 of 57 (12%) samples, including three households and three public sites. While there is not yet sufficient evidence to recommend environmental surveillance as a standard approach for COVID-19 epidemiology, environmental surveillance research may contribute to advance knowledge about COVID-19 by further elucidating virus shedding dynamics and environmental contamination, including the potential identification of animal reservoirs.

SYMPTOMS AND CLINICAL PRESENTATION

ADULTS

CLINICAL OUTCOMES IN YOUNG US ADULTS HOSPITALIZED WITH COVID-19

Cunningham JW, Vaduganathan M, Claggett BL, Jering KS, Bhatt AS, Rosenthal N, Solomon SD.. JAMA Intern Med. 2020 Sep 9. doi: 10.1001/jamainternmed.2020.5313. Online ahead of print.
Level of Evidence: 1 - Local and current random sample surveys (or censuses)

BLUF

Physicians from Brigham and Women's Hospital in Boston, Massachusetts extracted data from the Premier Healthcare Database to explore outcomes and clinical profiles of 3,222 young adults (ages 18-34) hospitalized between April 1st, 2020 and June 30th, 2020 with COVID-19 (Table 1) and found 21% of patients required intensive care, 10% required mechanical ventilation, and 2.7% died. Also, there was increased risk of adverse outcomes in patients with morbid obesity, hypertension, or diabetes (Figure 1). Authors suggest young adults hospitalized for COVID-19 may experience significant adverse outcomes, emphasizing the importance of prevention among this age group.

Characteristic	No. (%) Full case series (N = 3222)	No death or ventilation (n = 2879)	Death or ventilation (n = 343)	*P* value
Age, mean (SD), y	28.3 (4.4)	28.3 (4.4)	28.3 (4.5)	.90
Men	1849 (57.6)	1626 (56.7)	223 (65.0)	.003
Race/ethnicity				
White non-Hispanic	536 (16.6)	479 (16.6)	57 (16.6)	
White Hispanic	350 (10.9)	324 (11.3)	26 (7.6)	
Black non-Hispanic	748 (23.2)	675 (23.4)	73 (21.3)	.14
Black Hispanic	14 (0.4)	13 (0.5)	1 (0.3)	
Other/unknown	1574 (48.9)	1388 (48.2)	186 (54.2)	
Black and/or Hispanic	1838 (57.0)	1669 (58.0)	169 (49.3)	.002
Discharge month				
April 2020	1680 (52.1)	1495 (51.9)	185 (53.9)	
May 2020	1063 (33.0)	936 (32.5)	127 (37.0)	.004
June 2020	479 (14.9)	448 (15.6)	31 (9.0)	
Region				
Northeast	1298 (40.3)	1161 (40.4)	137 (39.9)	
South	1130 (35.1)	1032 (35.9)	98 (28.6)	.002
Midwest	558 (17.3)	488 (17.0)	70 (20.4)	
West	233 (7.2)	195 (6.8)	38 (11.1)	
Any obesity, BMI ≥ 30	1187 (36.8)	1007 (35.0)	180 (52.5)	<.001
Morbid obesity, BMI ≥ 40	789 (24.5)	649 (22.5)	140 (40.8)	<.001
Asthma	545 (16.9)	495 (17.2)	50 (14.6)	.22
Hypertension	519 (16.1)	412 (14.3)	107 (31.2)	<.001
Smoking	513 (15.9)	472 (16.4)	41 (12.0)	.03
Diabetes	588 (18.2)	494 (17.2)	94 (27.4)	<.001

Table 1. Baseline characteristics of young adults age 18 to 34 years with COVID-19.

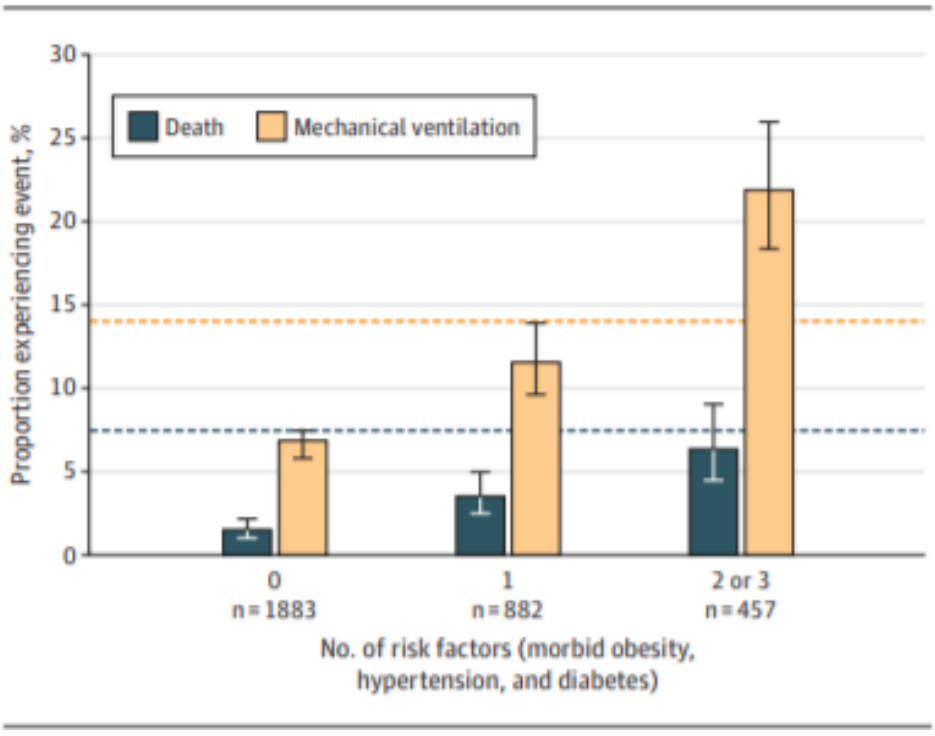

Figure 1. Death and mechanical ventilation in young adults with and without morbid obesity, hypertension, and diabetes.

IMMUNE THROMBOCYTOPENIC PURPURA AFTER COVID-19 INFECTION

Levraut M, Ottavi M, Lechtman S, Mondain V, Jeandel PY.. Int J Lab Hematol. 2020 Sep 20. doi: 10.1111/ijlh.13346. Online ahead of print.
Level of Evidence: 5 - Case report

BLUF

A case study conducted in Nice, France involved a 63 year-old female presenting with asthenia, fever, dry cough, and headache with chest CT showing evidence of COVID-19 pneumonia. Day 26 following onset, during the non-inflammatory timeline of infection, she noticed lower limb purpura (Figure 1) without PT, aPTT, fibrinogen abnormalities, and consistent with immune thrombocytopenia, which resolved following IVIg therapy. This case indicates physicians need to be cautious of bleeding, thrombosis, and septic risks in COVID-19 patients and should consider IVIg therapy as a reasonable treatment for ITP.

SUMMARY

A 63 year-old female with a past medical history of autoimmune hypothyroidism and stroke presented to the ED with 7 days of fever, dry cough, headache, and fatigue. Despite having normal vital signs, physical exam revealed bilateral crackles of lung bases with corresponding CT imaging studies that showed bilateral and subpleural frosted glass beaches in lower lung bases consistent with COVID-19 pneumonia. Laboratory studies showed normal levels of platelets and hemoglobin, however did reveal lymphocytopenia. Her initial SARS-CoV-2 RT-PCR was negative, but her husband tested positive within 24 hours, which led to her starting prophylactic azithromycin 500 mg and hydroxychloroquine 600 mg daily. On Day 26, patient presented to the ED with lower limb purpura and severe thrombocytopenia and lymphopenia, which successfully resolved with IVIg. At this time, she tested positive for SARS-CoV-2 qualitative studies, despite having a negative RT-PCR test. She was discharged on day 33 following progressively increasing platelet counts.

FIGURES

FIGURE 1 A, Chest CT scan showing bilateral and subpleural frosted glass beaches evocative of COVID-19 pneumonia. B, Lower limb purpura and bruises [Colour figure can be viewed at wileyonlinelibrary.com]

T CELL RESPONSES AND THERAPIES AGAINST SARS-COV-2 INFECTION

Toor SM, Saleh R, Sasidharan Nair V, Taha RZ, Elkord E.. Immunology. 2020 Sep 15. doi: 10.1111/imm.13262. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

Biomedical researchers from Qatar present a review article highlighting the current understanding of how T cells initially respond to the SARS-CoV-2 Spike (S) protein (Figures 1 & 2) and the mechanisms of excess innate and dysregulated adaptive immunity resulting in tissue damage, in addition to explaining the latest therapeutic approaches (Table 1) aimed at: T cell responses, its cytokines, vaccines inducing T cells, Th1 responses, reverting T cell exhaustion, and clinical trials assessing safety and efficacy of new drugs. The researchers emphasize that further studies on SARS-CoV-2 reconstruction can aid in understanding viral targets, immune responses, and potential therapeutic objectives.

SUMMARY

Innate and adaptive immunity play a vital role in eliciting antiviral immune response against SARS-CoV-2 (Figures 1 & 2).
- Dendritic cells and macrophages constituting the innate immunity can phagocytose the virus-infected cells and initiate an adaptive immune response.
- CD4+ T cells stimulate B cells for the production of IgM antibodies as an early antiviral immune response followed later by IgG.
- CD8+ T cells expressing granzyme and FAS ligand with cytotoxic activity eliminate virus-infected cells.
- ACE2 receptor expression on the lung alveolar cells reduces IFN expression and adaptive immune cells infiltrate leading to pulmonary edema.
- Excessive innate immunity and impaired adaptive immune response lead to tissue damage.
- Previous studies have shown that COVID-19 patients exhibit a similar percentage of naive, memory central, and effector CD4+ T cells, in addition to lower naive and central memory CD8+cells when compared to healthy controls.
- "Grifoni et al highlight 100% CD4+T cells and 70% CD8+T cells have SARS-CoV-2 spike protein-specific responses in recovered patients."
- Pathophysiology: ARDS is the main primary complication of COVID-19, and endothelitis leads to the progression of ARDS. Cardiovascular and neurological complications, venous thromboembolism, disseminated intravascular coagulation, and septic shock contribute to secondary complications of COVID-19 disease.
- Excessive pro-inflammatory cytokines and chemokines lead to cytokine storms. TNF alpha, IL-6, and IL-1 beta released by innate immune cells is the major cause of hyperinflammatory state in COVID-19. TNF-alpha and IL-6 levels were inversely related to T cell count in patients with severe disease. This suggests IL-6 blockers tocilizumab, sarilumab, and IL-1 beta blockers may have therapeutic benefits in treating the disease.

Therapeutic strategies (Table 1):
- SARS-CoV-2 specific T cells isolated and expanded in vitro from convalescent donors may prove efficacious and beneficial for treating COVID-19 patients.
- Vaccine development should aim at inducing protective T cell and antibody immune responses against SARS-CoV-2 spike protein, with adenovirus type-5 (Ad5-nCoV) employed as the vector.
- Moderna has developed an mRNA-based vaccine coding S-protein of SARS-CoV-2 via liposomal delivery system, which is undergoing clinical trials to assess safety and efficacy.
- Since IL-7 promotes T cell trafficking to infectious sites and increases naive and memory T cells, clinical trials with recombinant IL-7 to restore lymphocyte count in COVID-19 patients is underway.
- Since IL-2 promote the proliferation of Treg and T effector cells, trials with recombinant IL-2 to restore normal T cell count is registered.
- Th17 responses via antibodies against IL-17, IL-17R, and JAK2 may have therapeutic benefits against cytokine storm.
- Therapeutics targeting PD-1 immune checkpoints (IC) in COVID-19 may induce sustained antiviral immune responses mediated by CD4+ and CD8+ Tcells which need to be further analyzed.
- A combination of anti PD-1 mAb with anti IL-6 and anti IL-1R mAb may prevent hyperinflammation since preclinical studies showed anti PD-1 mAb alone resulted in severe tissue damage.
- Late therapeutic interventions to revert T cell exhaustion and hyperinflammatory response have more beneficial effects than early interventions do, in preventing the pro-infalmmatory responses leading to insufficient immune responses.

ABSTRACT

Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2, a novel coronavirus strain. Some studies suggest that COVID-19 could be an immune-related disease, and failure of effective immune responses in initial stages of viral infection contribute to systemic inflammation and tissue damage, leading to worse disease outcomes. T cells can act as a double-edge sword with both pro- and anti-roles in the progression of COVID-19. Thus, better understanding of their roles in immune responses to SARS-CoV-2 infection is crucial. T cells primarily react to the spike protein on the coronavirus to initiate antiviral immunity; however, T cell responses can be suboptimal, dysfunctional or excessive in severe COVID-19 patients. This review focusses on the multi-faceted roles of T cells in COVID-19 pathogenesis and rationalizes their significance in eliciting appropriate antiviral immune responses in COVID-19 patients and unexposed individuals. In addition, we summarize the potential therapeutic approaches related to T cells to treat COVID19 patients. These include adoptive T cell therapies, vaccines activating T cell responses, recombinant cytokines, Th1 activators and Th17 blockers, and potential utilization of immune checkpoint inhibitors alone or in combination with anti-inflammatory drugs to improve antiviral T cell responses against SARS-CoV-2.

FIGURES

Therapeutic strategy	Drug/ inhibitor	Clinical trial number	Potential benefits	Ref.
Adoptive T cell transfer (SARS-CoV-2-reactive T cells)	-	NCT04351659 NCT04401410	Improved specific antiviral T cell responses against SARS-CoV-2	(9)
SARS-CoV-2-reactive T cell-derived IFN-γ exosomes		NCT04389385		
Viral vector-based vaccines mRNA-based and DNA-based vaccines	-	NCT04313127 NCT04398147 NCT04341389 NCT04276896 NCT04283461 NCT04336410	Improved specific antiviral T cell responses against SARS-CoV-2 and production of IFN-γ	(9, 101)
Recombinant IL-7	CYT107	NCT04407689 NCT04379076 NCT04426201	Restored T cell count and reverse lymphopenia Enhanced TCR repertoire diversity and generation of memory CD8+ T cells Improved trafficking of T cells to infection site	(9)
Low dose of recombinant IL-2	ILT101	NCT04357444	Expansion/activation of Tregs to control excessive inflammation Expansion of other T cell subsets, including effector cells	(9)
Th1 activators	IFN-β1b (Ziferon)	NCT04343768	Improved symptoms Activated Th1 response Viral clearance	(113)

Th17 blockers	Anti-IL17, IL17R and anti-IL-23	N/A	Ameliorated inflammation induced by cytokine storm	(114)
JAK2 inhibitor	Fedratinib	N/A		(114)
ICIs	Anti-PD-1 (pembrolizumab or nivolumab)	NCT04268537 NCT04333914 NCT04356508 NCT04413838	Reversal of T cell exhaustion Restored effector T cell function	(9, 120)

Table 1. Therapeutic Strategies to improve antiviral T cell responses and resolve systemic inflammation in COVID-19.

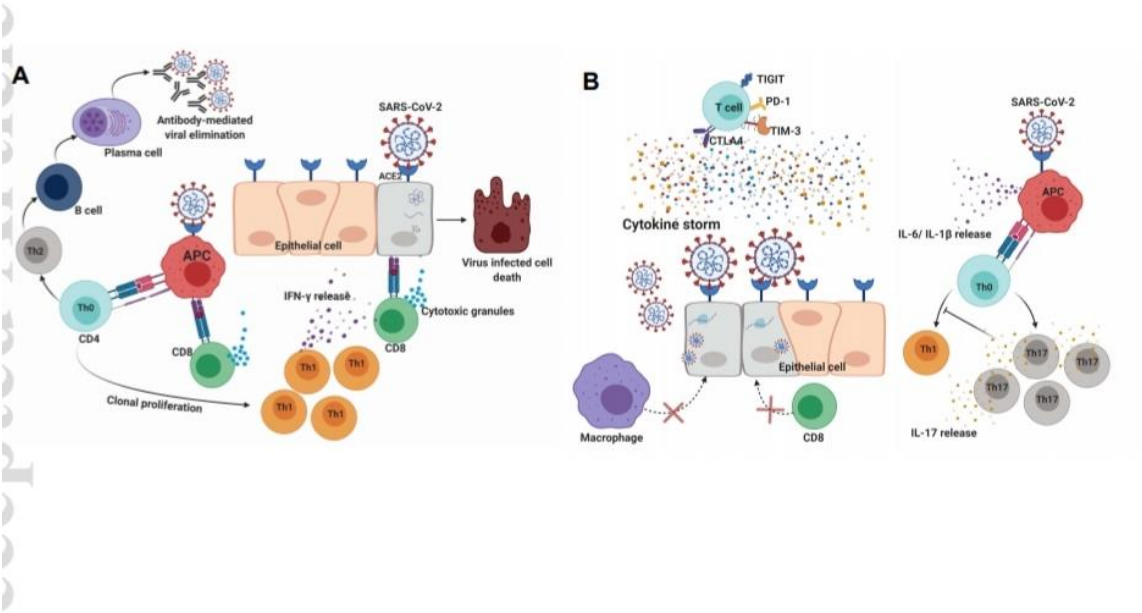

Figure 1. T cell responses against SARS-CoV-2. SARS-CoV-2 recognizes cells expressing ACE2 receptor including epithelial cells and macrophages. In normal immune environment, infected epithelial cells degrade viral particles and present them to cytotoxic CD8+ T cells (CTLs). CTLs detect viral protein through classical TCR-MHC I interaction, release cytotoxic granules, including granzyme B and perforin, and eliminate infected cells. Additionally, macrophages detect SARS-CoV-2 via ACE2 receptor and present the virus-derived peptides to CD4+ T cells (Th0) via TCR-MHC II interaction. Once exposed to antigen, Th0 cells polarize primarily towards Th1, leading to the release of IFN-γ to eliminate the virus, and Th2 to trigger humoral mediated immune responses and antibody secretion against SARS-CoV-2 virus (A). In incompetent immune environment, SARS-CoV-2 recognizes epithelial cells or macrophages via ACE2 receptor. Viral RNA will replicate by hijacking host transcriptional machinery. These viral progenies will infect multiple cells leading to tissue damage and further lethal complications. In these circumstances, CD4+ and CD8+ T cells fail to provide adequate cell/humoral-mediated immune responses to eliminate viral infected cells. On the other hand, Th0 cells are primed towards Th17 phenotype, resulting in the inhibition of Th1-mediated immune responses (B). In COVID-19, T cells exhausted and overexpress exhaustion markers including PD-1, CTLA-4, TIM-3 and TIGIT through unknown mechanisms, which eventually lead to lymphopenia. In severe COVID-19 cases, the production of cytokines, including IL-1β, IL-6, IL-2, IL-10 and TNFα, is increased leading to the generation of cytokine storm which induces further unfavorable outcomes (B).

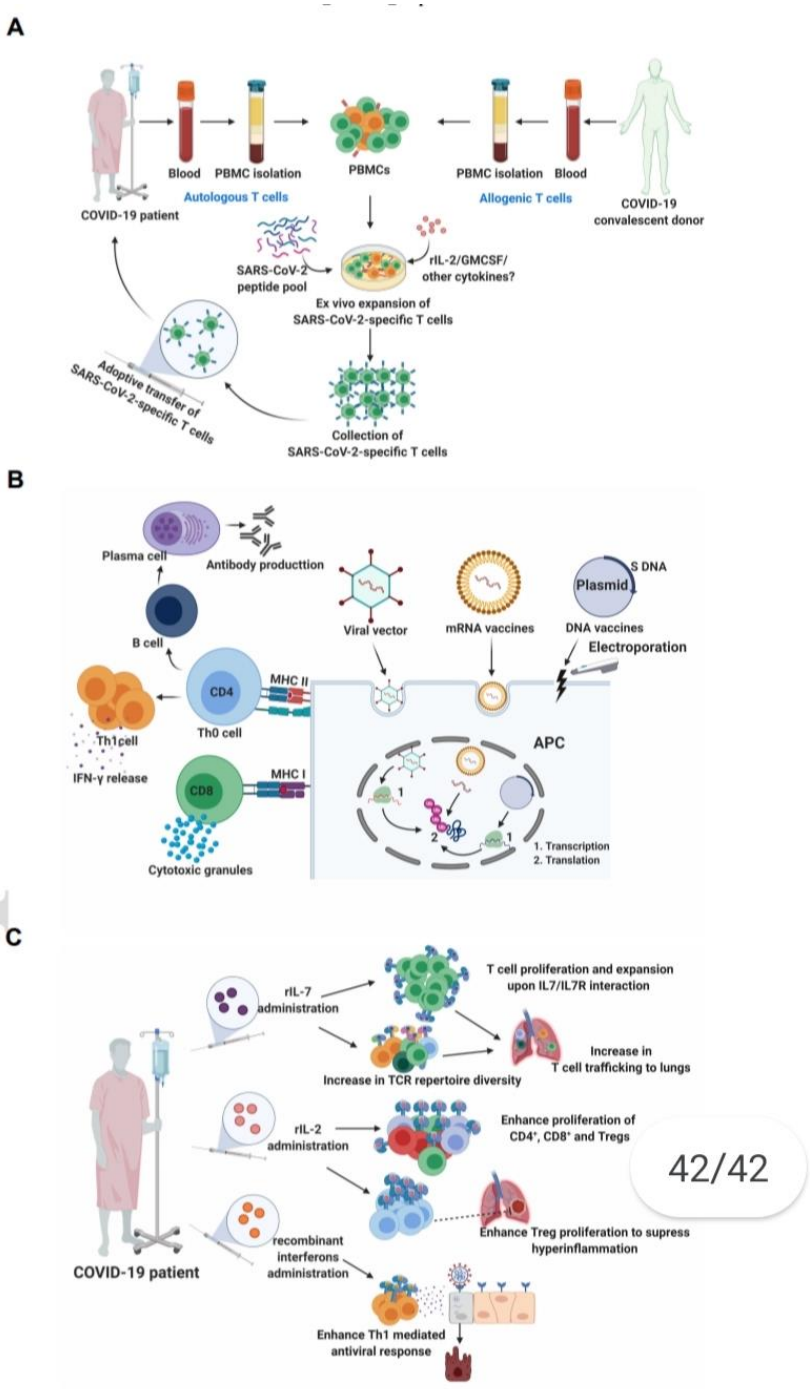

Figure 2. Therapeutic strategies to restore SARS-CoV-2-specific T cell immune responses. Autologous (from a COVID-19 patient) or allogeneic (from a recovered patient), peripheral blood mononuclear cells (PBMCs) can be cultured in the presence of SARS-CoV-2-derived peptides, IL2, GM-CSF or possibly other cytokines to enhance the function of antigen-presenting cells and enrich T cells and enhance the generation of activated viral-specific T cells, which can be infused back into a COVID-19 patient. This could restore effective antiviral T cell immunity, and result in beneficial clinical outcomes (A). The use of viral vector-based, mRNA-based or DNA-based vaccines expressing the S protein of SARS-CoV-2 can lead to the activation of virus-specific CD4+ and CD8+ T cells via antigen-presenting cells, followed by the activation of B cells and secretion of antibodies by plasma cells (B). In COVID-19 patients, the administration of recombinant IL-7 could enhance T cell receptor repertoire diversity, promote the capacity of T cell trafficking to the lungs and alleviate lymphopenia leading to enhanced antiviral immune response. Low dose recombinant IL-2 could control ARDS and excessive inflammation by expanding and activating Tregs, and possibly increase the level of effector CD4+ and CD8+ T cells as they express IL-2 receptor. Additionally, administration of interferons could also help in viral clearance and improving antiviral T cell responses (C).

PLACENTAL PATHOLOGY FINDINGS DURING AND AFTER SARS-COV-2 INFECTION: FEATURES OF VILLITIS AND MALPERFUSION

Menter T, Mertz KD, Jiang S, Chen H, Monod C, Tzankov A, Waldvogel S, Schulzke SM, Hösli I, Bruder E.. Pathobiology. 2020 Sep 18:1-9. doi: 10.1159/000511324. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

A cohort-control study conducted by pathologists at University Women's Hospital Basel in Switzerland since March 2020 investigated 5 COVID-19 positive pregnant women (three mildly symptomatic and two asymptomatic) and 10 controls for the potential of vertical transmission of SARS-CoV-2. All 5 mothers and 2/5 fetuses has malperfusion, including 1 fetus having small thrombi. One patient, who was the only one symptomatic at childbirth, had placental pathological findings of lymphohistiocytic villitis and intervillositis (Figure 1), as well as viral RNA present in both the placenta and umbilical cord. The authors concluded that SARS-CoV2 infection displays potential for increased risk of fetal malperfusion through an increased coagulative state and and may result in placental infection.

FIGURES

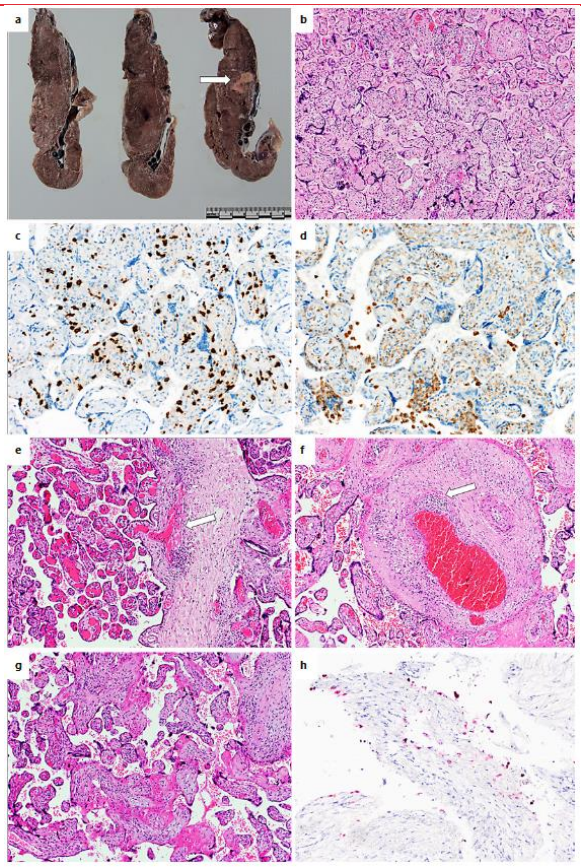

Figure 1. Findings of the placenta with manifest COVID-19. a Mac-roscopic image showing inhomogeneous and unusually con-densed placental parenchyma and an area of infarction (arrow). b Chronic villitis and intervillositis (haematoxylin and eosin [H&E], 40×). c, d Characterisation of the inflammatory infiltrate consisting primarily of cytotoxic T-cells expressing CD8 (c) and fewer macrophages expressing CD68 (d) (immunohistochemistry, 200×). e, f Lymphohistiocytic villitis resulting in chorionic vascu-litis and subsequent fresh (e) and already organizing thrombosis (f) (H&E, 100×). g Intervillous increase of fibrin as result of ma-ternal malperfusion (H&E, 100×). h Presence of SARS-CoV-2 in decidual cells (red) (in situ hybridization for SARS-CoV-2, 200×).

SURGICAL SUBSPECIALTIES

PRE-OPERATIVE CT CHEST AS A SCREENING TOOL FOR COVID-19: AN APPRAISAL OF CURRENT EVIDENCE

Agrawal V, Yadav SK, Sharma D.. Br J Surg. 2020 Sep 8. doi: 10.1002/bjs.12039. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A review of studies between February 1, 2020 and July 31, 2020 by surgeons in India assessed the efficacy of chest computed tomography (CT) as a preoperative COVID-19 diagnostic tool for patients undergoing elective surgeries and found early studies indicated chest CT as an effective screening tool, but further evaluation of subsequent studies (Table 1) showed low predictive value and potentially unnecessary surgery delay. Authors suggest chest CT is not practical in settings where RT-PCR is readily available, recommending its use only for symptomatic patients with high post-operative complication risk or pulmonary sequelae after COVID-19.

FIGURES

Author	Month of Publication	No of patients undergoing Chest CT	Positive on CT	Positive on RT-PCR	Remarks
Callaway *et al*[3]	June	677	90(13·49%)	13/643(2·02%)	Sensitivity- 68·4%, Specificity- 88%, Disease prevalence- 2·95% Difficult to justify this additional examination.
Chetan *et al*[4]	June	439	32(7·28%)	7(1·59%)	Altered surgical management in 7% of the elective surgical cohort, but not in the acute abdominal emergency cohort requiring surgery.
Hernigou *et al*[5]	July	298	16(5·36%)	20/227(8·81%)	Chest CT scan is no longer useful outside the pandemic period Most accurate diagnostic test for COVID-19 pneumonia in patients who needed surgery in emergency Useful in patients who had a previous symptomatic infection with recovery and may have pulmonary sequels
Huybens *et al*[6]	July	374	18(4·81%)	3(0·80%)	CT chest has no added value in a low prevalence population.
Ikehara *et al*[7]	July	21	2(9·52%)	0	54% of asymptomatic patients have Pneumonic changes on CT, chest CT screening before procedural endoscopy may contribute to identify COVID-19 patients.
Shah *et al*[8]	July	625	105(16·8%)	1(0·16%)	Chest CT scanning did not provide valuable information in detecting asymptomatic cases of COVID-19 in low prevalence populations.

Table 1. Summary of Findings in studies using preoperative CT chest screening in a surgical setting.

THORACIC SURGERY

MANAGEMENT OF CONGENITAL CARDIAC SURGERY DURING COVID-19 PANDEMIC

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Level of Evidence: 4 - Case-series

BLUF

A case series by pediatric cardiothoracic surgeons at Ankara City Hospital in Turkey from March 18 to May 18, 2020 found patients with congenital heart disease who received emergent (n=16) or semi-emergent (n=13) surgery had a higher than normal mortality rate (13.8%; Table 1), which was attributed to case severity and limited resources during the pandemic. Authors argue for adjustments in guidelines regarding emergency care criteria through the Turkish Pediatric Cardiology and Cardiac Surgery Association (Tables 2,3) to better categorize and address congenital valve disease, acquired heart disease, and childhood cardiac tumors.

ABSTRACT

The new Coronavirus infection, which was first seen in China in late December 2019 and eventually became a worldwide pandemic, poses a serious threat to public health. After a high spike in the number of new COVID-19 infection cases following increase in overall daily death toll in Turkey, Turkish Ministry of Health has taken immediate precautions to postpone elective surgeries in order to reduce the burden to the healthcare system which might be challenged. Whereas different areas of medicine were able to suspend their operative procedures during this period, this was not completely possible in pediatric cardiovascular surgery due to the severity and urgency of congenital heart disease patients requiring operation. Based on the guideline that was published by the Turkish Pediatric Cardiology and Cardiac Surgery Association, in which the patients requiring surgical intervention during the Covid-19 pandemic period are ranked according to the priority, directions were given regarding the operations that hereby, be delayed, we report our experience in 29 cases retrospectively, regarding the preoperative evaluation of these patients, makings of an emergency operation decision, and strategies taken about intraoperative and postoperative management and arrangements during the pandemic period. In this article, we present crucial precautions that was applied in pediatric cardiovascular surgery and extensive list of cases in order to deliver highest level of the patient safety and protection for the surgical team.

FIGURES

CASE number	SEX	AGE	WEIGHT	DIAGNOSIS	PROCEDURE	INTUBATION DURATION (days)	TIME IN ICU (days)	MORTALITY (yes/no)
1	Male	3 months	4800 gr	Complete AVSD+CHF	Single patch repair	1	2	No
2	Male	1.5 years	6500 gr	VSD+Severe PH+Reversibility+	VSD closure	0.5	3	No
3	Male	13 years	52 kg	Constrictive perikarditis+CHF+need ECMO support	Total Pericardiectomy	1	17	No
4	Male	15 days	3500 gr	Interrupted Aortic Arch+VSD	Arcus repair+pulmonary banding	8	8	No
5	Female	1.5 years	11 kg	DORV+TGA+VSD+PS	Nikaidoh Procedure	4	10	No
6	Male	8 months	7500 gr	TOF+Hypoxic Spell	Total correction with RV-PA Conduit	1	4	No
7	Female	7 years	23 kg	Severe MR+ Decompensated CHF	MVR	18	18	Yes
8	Female	2 days	2500 gr	Unbalanced AVSD+Pulmoner Atrezi	4 mm BT shunt	3	3	No
9	Female	4 months	3800 gr	VSD+Severe PH+CHF	Correction with pericardial patch	1	4	No
10	Female	11 years	40 kg	Tamponade+Cardiogenic Shock	Tamponade revision	0.5	1	No
11	Female	6 days	2900 gr	d-TGA+VSD	JATENE procedure+VSD closure	3	3	Yes
12	Male	15 months	5.500 gr	Complete AVSD+Severe PH+Trizomy 21	Single patch repair	2	11	No
13	Female	7 days	3000 gr	TOF+Pulmonary Hypoplasia	4 mm BT shunt	3	3	No
14	Male	7 days	4000 gr	HLVS	Norwood stage 1	8	8	No
15	Male	20 days	3200 gr	d-TGA+VSD	JATENE procedure+VSD closure	6	6	No
16	Female	2.5 months	4000 gr	Swiss Cheese VSD+Severe PH+KKY	Pulmonary banding+pda ligation	1	11	No
17	Male	26 days	3500 gr	Truncus Arteriosus Type 1+CHF	Rastelli type correction	7	7	No
18	Female	4 days	3200 gr	Ebstein Anomaly+Pulmoner Atresia	4 mm BT shunt	3	3	Yes
19	Male	19 days	3200 gr	Taussig Bing Anomaly+Arcus Hypoplasia	JATENE procedure+Arcus repair	1	1	Yes
20	Male	35 days	1100 gr	Hemodynamically important PDA	PDA ligation	23	Bedside	No
21	Female	26 days	1300 gr	Hemodynamically important PDA	PDA ligation	15	bedside	No
22	Male	13 days	3200 gr	Truncus Arteriosus Type 1+CHF	Rastelli type correction	7	7	No
23	Female	5 days	3200 gr	TOF+Pulmonary Atresia	4 mm BT shunt	14	14	No
24	Female	19 days	3400 gr	HLVS	Norwood stage 1	15	15	No
25	Female	2.5 months	3300 gr	VSD+Severe PH+CHF	Pulmonary banding	2	7	No
26	female	16 days	3000 gr	Coarctation of Aorta−Arcus Hypoplasia	extended sidetoside anastomosis	2	2	No
27	female	4 monhts	5600 gr	VSD+ASD+severe PH+CHF	VSD closure via patch	2	8	No
28	male	5 monhts	5000 gr	VSD+ASD+PH+Down Syndrome	VSD closure via patch	3	6	No
29	male	11 days	3300 gr	d-TGA	Jatene	4	4	No

Table 1. Registry of Cases.

EMERGENT/EARLY SURGERY Immediate or in 1 to 2 weeks	SEMI- ELECTIVE SURGERY In 1 to 3 months	ELECTIVE Wait > 3 months
- Drainage of Pericardial Tamponade - Ductus dependent newborn with systemic circulation (IAA, HLHS, critical COA, critical AS etc.) - Ductus dependent newborn with pulmonary circulation (PA-VSD, PA-IVS, PA-Univentricular heart) - Simple cTGA - Obstructive TAPVR - Severe hypoxic cyanotic CHF - Severe newborn with Shone complex - Extremely large PDA in preterm - Postoperative complication and revision - ECMO/assist device need - OHT	- Non-obstructive TAPVD - Large VSD and TGA with PH - Truncus arteriosus - AP window - Complete AV septal defect - Tetralogy of Fallot with spell history - Functional univentricule requiring pulmonary banding - VSD-PH; with CHF unresponsive to medical therapy - PDA; baby with PH and heart failure - Uncontrolled infective endocarditis - High risk cardiac tumor cases - Severe LVOT obstruction; symptomatic or LVH - HLHS stage II	- Secundum/sinus venosus ASD closure - Partial/intermediate AV septal defect repair - VSD closure; normal development, without PH , presence of indication due to extensive shunt or AR - Asymptomatic Tetrology of Fallot - Subaortic ridge resection; due to moderate stenosis and mild-moderate AR - Glenn operation - Completion to Fontan - Complex TGA operations without profound hypoxia

Table 2. Sorting the patients who will require surgical intervention in the COVID-19 pandemic according to urgency and the operations that can be postponed.
IAA: "Interrupted" aortic arch, COA: Coarctation, AS: Aortic stenosis, PA: Pulmonary Atresia, TGA: Transposition of great arteries, TAPVR: Total anomalous of pulmonary venous return, ECMO: Extra-corporeal membrane oxygenation, OHT: Orthotopic heart transplantation, PH: pulmonary hypertension, AP: Aorto-pulmonary, AV: Atrioventricular, CHF: Congestive heart failure, LVOT: Left ventricle outflow tract LVH: left ventricle hypertrophy, AR: Aortic Regurgitation.
*2nd column in the table may vary according to institutes, A multi-disciplinary committee should decide on early operations, taking into account features such as COVID-19 load / density in the hospital and surrounding area as well as whether the hospital is a pandemic hospital.

For Newborns		
Emergent (in 24-48 hours)	Urgent (in 1 to 2 weeks)	Elective (Beyond 2 weeks)
Obstructed TAPVR	TGA with IVS	TGA+VSD
Obstructed Cor Triatriatum	Symptomatic TOF	Stabile Truncus Arteriosus
TOF with Spell	Ebstein resistant to medical therapy	HLVS
Coarctation unstable with PGE	Coarctation stable with PGE	
Aortic Stenosis unstable with PGE	Aortic Stenosis stable with PGE	
HLHS with restricted ASD	IVS+PA with PDA(stenting not possible)	
Shunt Thrombosis	HLHS	
	Shunt stenosis	
For Infants		
Emergent (in 24-48 hours)	Urgent (in 1 to 2 weeks)	Elective (Beyond 2 weeks)
Acute unstable Aortic Regurgitation	VSD+CHF resistant to medical therapy	VSD+CHF
Prosthetic valve thrombosis	TOF with Spell (Despite medical therapy)	TOF resistant to medical therapy
Shunt thrombosis	Shunt Stenosis	AVSD+Trizomy 21+ Pulmonary blood overflow resistant to medical therapy requiring surgery
	DCM resistant to medical therapy, restrictive CMP	Ebstein Anomaly + right heart failure
		Mitral insufficiency+CHF
		Symptomatic Aortic Insufficiency+enlarged left ventricle/decrased LVEF
		Symptomatic Aortis stenosis /LVOTO+ decreased LVEF
		RVOTO+ impaired right ventricle functions
		Despite shunting, increased cyanosis or shunt stenosis in bi-directional cavopulmonary anastomosis candidates
For Children		
Emergent (in 24-48 hours)	Urgent (in 1 to 2 weeks)	Elective (beyond 2 weeks)
Acute unstable aortic insufficiency	Worsening CHF with DCM despite medical therapy	Symptomatic Heart failure+ Mitral insufficiency despite medical therapy
Prosthetic valve thrombosis	ARCAPA/ALCAPA+angina with minimal exercise	Aortic Insufficiency + decrease in LVEF /LV enlargement
Severe RV dysfunction in patients with RV-PA conduits /conduit stenosis with ventricular arrythmia	Severe stenosis in RV-PA conduit	Symptomatic AS/LVOTO+ decrease in LVEF
Despite maximal medical therapy, endocarditis in cardiogenic or septic shock	Stable but uncontrolled endocarditis with ongoing infection	Worsening right heart failure in patients with RV-PA conduits
ARCAPA/ALCAPA+ resuscitated cardiac arrest		Fontan candidates with worsening cyanosis

Table 3. Congenital lesions and surgical priorities

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