CPD BULLETIN

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Foreword

By Prof Lee Yung Seng (President)
College of Paediatrics & Child Health, Singapore

The College of Paediatrics and Child Health and Deanery of the Academy of Medicine are pleased to present this edition of the CPD bulletin which includes several recent articles we hope will be informative and applicable to your clinical practice.

One of the articles reported the increased suicide ideation and attempts among youths presenting to an overseas paediatric emergency department during the COVID-19 pandemic, which struck a chord as we are also grappling with a similar sombre situation in our community.

The current COVID-19 pandemic and the resulting restrictions are taking a mental toll on Singaporeans and our children are not spared. There is fear and worry not just about the deadly virus but also on our livelihood; and the need for social distancing has led to social deprivation and isolation. Families have to respond to changes forced upon them by the pandemic and make major adjustments to their lifestyle and habits. These stressors have led to many problems in our society where we are witnessing increasing domestic violence and suicides. There are also numerous reports of deteriorating mental health in both the young and old.

Anecdotally we are seeing more children presenting with psychosomatic complaints, adjustment disorders, depression, and worryingly, suicide ideation and attempts, which reflect the elevated distress experienced by our youths, especially those in the more vulnerable socio-economic strata. COVID-19 is not going away anytime soon, and we need to do more to help our children and their families build their resilience, manage the stress positively, and stay focused on the light at the end of the tunnel.

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COVID-19

ARTICLES

1 **Titers and neutralizing capacity of SARS-CoV-2-specific antibodies in human milk: a systematic review** FULL ARTICLE ACCESS

Low JM, Low YW, Zhong Y, Lee CYC, Chan M, Ng NBH, Amin Z, Ng YPM.
Arch Dis Child Fetal Neonatal Ed. 2021 Jul 13:fetalneonatal-2021-322156.
PMID: 8282417

Synthesise evidence on production of SARS-CoV-2 antibodies in human milk of individuals who had COVID-19, and antibodies' ability to neutralise SARS-CoV-2 infectivity. A systematic review of studies published from 1 December 2019 to 16 February 2021 without study design restrictions. Data were sourced from PubMed, MEDLINE, Embase, CNKI, CINAHL and WHO COVID-19 database. Search was also performed through reviewing references of selected articles, Google Scholar, and preprint servers. Studies that tested human milk for antibodies to SARS-CoV-2 were included. Individuals with COVID-19 infection and human milk tested for anti-SARS-CoV-2 neutralising antibodies. The presence of neutralising antibodies in milk samples provided by individuals with COVID-19 infection. Individual participant data from 161 persons (14 studies) were extracted and re-pooled.

Milk from 133 (82.6%) individuals demonstrated the presence of anti-SARS-CoV-2 immunoglobulin A (IgA), IgM and/or IgG. Illness severity data were available in 146 individuals; 5 (3.4%) had severe disease, 128 (87.7%) had mild disease, while 13 (8.9%) were asymptomatic. Presence of neutralising antibodies in milk from 20 (41.7%) of 48 individuals neutralised SARS-CoV-2 infectivity in vitro. Neutralising capacity of antibodies was lost after Holder pasteurisation but preserved after high-pressure pasteurisation. Human milk of lactating individuals after COVID-19 infection contains anti-SARS-CoV-2-specific IgG, IgM and/or IgA, even after mild or asymptomatic infection.

Current evidence demonstrates that these antibodies can neutralise SARS-CoV-2 virus in vitro. Holder pasteurisation deactivates SARS-CoV-2-specific IgA, while high-pressure pasteurisation preserves the SARS-CoV-2-specific IgA function.

2 **Seroprevalence of anti-SARS-CoV-2 IgG antibodies in children with household exposure to adults with COVID-19: Preliminary findings** FULL ARTICLE ACCESS

Buonsenso D, Valentini P, De Rose C, Pata D, Sinatti D, Speziale D, Ricci R, Carfì A, Landi F, Ferrari V, De Maio F, Palucci I, Sanguinetti M, Sali M; Gemelli Against COVID-19 Post-Acute Care Study Group.
Pediatr Pulmonol. 2021 Jun;56(6):1374-1377.
PMID: 33470561

Weather and the susceptibility of children to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is still a debated question and currently a hot topic, particularly in view of important decisions regarding opening schools. Therefore, we performed this prospective analysis of anti-SARS-CoV-2 immunoglobulin G (IgG) antibodies in children with known household exposure to SARS-CoV-2 and compared their IgG status with the other adults exposed to the index case in the same household.

A total of 30 families with a documented COVID-19 index case were included. A total of 44 out of 80 household contacts (55%) of index patients had anti SARS-CoV-2 IgG antibodies. In particular, 16/27 (59,3%) adult partners had IgG antibodies compared with 28/53 (52,3%) of paediatric contacts ($p > .05$). Among the paediatric population, children ≥5 years of age had a similar probability of having SARS-CoV-2 IgG antibodies (21/39, 53.8%) compared to those less than 5 years old (7/14, 50%) ($p > .05$). Adult partners and children also had a similar probability of having SARS-CoV-2 IgG antibodies. Interestingly, 10/28 (35.7%) of children and 5/27 (18.5%) of adults with SARS-CoV-2 IgG antibodies were previously diagnosed as COVID-19 cases.

Our study shows evidence of a high rate of IgG antibodies in children exposed to SARS-CoV-2. This report has public health implications, highlighting the need to establish appropriate guidelines for school openings and other social activities related to childhood.

3 **Suicide Ideation and Attempts in a Pediatric Emergency Department Before and During COVID-19** FULL ARTICLE ACCESS

Hill RM, Rufino K, Kurian S, Saxena J, Saxena K, Williams L.
Pediatrics. 2021 Mar;147(3):e2020029280.
PMID: 33328339

Elevated rates of mental health concerns have been identified during the coronavirus disease 2019 (COVID-19) pandemic. In this study, we sought to evaluate whether youth reported a greater frequency of suicide-related behaviours during the 2020 COVID-19 pandemic as compared with 2019.

We hypothesized that rates of suicide-related behaviours would be elevated between the months of March and July 2020 as compared with 2019, corresponding to the onset of the COVID-19 pandemic. Routine suicide-risk screening was completed with youth aged 11 to 21 in a paediatric emergency department. Electronic health records data for suicide-risk screens completed between January and July 2019 and January and July 2020 were evaluated. A total of 9092 completed screens were examined (mean age 14.72 years, 47.7% Hispanic and/or Latinx, 26.7% non-Hispanic white, 18.7% non-Hispanic Black). Rates of positive suicide-risk screen results from January to July 2020 were compared with corresponding rates from January to July 2019.

Results indicated a significantly higher rate of suicide ideation in March and July 2020 and higher rates of suicide attempts in February, March, April, and July 2020 as compared with the same months in 2019. Rates of suicide ideation and attempts were higher during some months of 2020 as compared with 2019 but were not universally higher across this period. Months with significantly higher rates of suicide-related behaviours appear to correspond to times when COVID-19-related stressors and community responses were heightened, indicating that youth experienced elevated distress during these periods.

4 **Multisystem Inflammatory Syndrome in Children Associated with Coronavirus Disease 2019 in a Children's Hospital in New York City: Patient Characteristics and an Institutional Protocol for Evaluation, Management, and Follow-Up** FULL ARTICLE ACCESS

Jonat B, Gorelik M, Boneparth A, Geneslaw AS, Zachariah P, Shah A, Broglie L, Duran J, Morel KD, Zorrilla M, Svoboda L, Johnson C, Cheng J, Garzon MC, Silver WG, Gross Margolis K, Neunert C, Lytrivi I, Milner J, Kernie SG, Cheung EW.

Pediatr Crit Care Med. 2021 Mar 1;22(3):e178-e191.

PMID: 33003176

The disease caused by severe acute respiratory syndrome coronavirus 2, known as coronavirus disease 2019, has resulted in a global pandemic. Reports are emerging of a new severe hyperinflammatory syndrome related to coronavirus disease 2019 in children and adolescents.

The Centres for Disease Control and Prevention has designated this disease multisystem inflammatory syndrome in children. Our objective was to develop a clinical inpatient protocol for the evaluation, management, and follow-up of patients with this syndrome. The protocol was developed by a multidisciplinary team based on relevant literature related to coronavirus disease 2019, multisystem inflammatory syndrome in children, and related inflammatory syndromes, as well as our experience caring for children with multisystem inflammatory syndrome in children.

Data were obtained on patients with multisystem inflammatory syndrome in children at our institution from the pre-protocol and post-protocol periods. Our protocol was developed in order to identify cases of multisystem inflammatory syndrome in children with high sensitivity, stratify risk to guide treatment, recognize co-infectious or co-inflammatory processes, mitigate coronary artery abnormalities, and manage hyperinflammatory shock. Key elements of evaluation include case identification using broad clinical characteristics and comprehensive laboratory and imaging investigations. Treatment centres around glucocorticoids and IV immunoglobulin with biologic immunomodulators as adjuncts. Multidisciplinary follow-up after discharge is indicated to manage continued outpatient therapy and evaluate for disease sequelae. In nearly 2 months, we admitted 54 patients with multisystem inflammatory syndrome in children, all of whom survived without the need for invasive ventilatory or mechanical circulatory support. After institution of this protocol, patients received earlier treatment and had shorter lengths of hospital stay.

This report provides guidance to clinicians on evaluation, management, and follow-up of patients with a novel hyperinflammatory syndrome related to coronavirus disease 2019 known as multisystem inflammatory syndrome in children. It is based on the relevant literature and our experience. Instituting such a protocol during a global pandemic is feasible and is associated with patients receiving treatment and returning home more quickly.

5 **COVID-19 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review of critically unwell children and the association with underlying comorbidities** FULL ARTICLE ACCESS

Williams N, Radia T, Harman K, Agrawal P, Cook J, Gupta A.
Eur J Pediatr. 2021 Mar;180(3):689-697.
PMID: 32914200

Data show that children are less severely affected with SARS-Covid-19 than adults; however, there have been a small proportion of children who have been critically unwell.

In this systematic review, we aimed to identify and describe which underlying comorbidities may be associated with severe SARS-CoV-2 disease and death. The study protocol was in keeping with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. A total of 1726 articles were identified of which 28 studies fulfilled the inclusion criteria. The 28 studies included 5686 participants with confirmed SARS-CoV-2 infection ranging from mild to severe disease. We focused on the 108 patients who suffered from severe/critical illness requiring ventilation, which included 17 deaths. Of the 108 children who were ventilated, the medical history was available for 48 patients. Thirty-six of the 48 patients (75%) had documented comorbidities of which 11/48 (23%) had pre-existing cardiac disease.

Of the 17 patients who died, the past medical history was reported in 12 cases. Of those, 8/12 (75%) had comorbidities. Whilst only a small number of children suffer from COVID-19 disease compared to adults, children with comorbidities, particularly pre-existing cardiac conditions, represent a large proportion of those that became critically unwell.

What is Known:
• Children are less severely affected by SARS-CoV-2 than adults.
• There are reports of children becoming critically unwell with SARS-CoV-2 and requiring intensive care.

What is New:
• The majority of children who required ventilation for SARS-CoV-2 infection had underlying comorbidities.
• The commonest category of comorbidity in these patients was underlying cardiac disease.

6 **Childhood vaccinations: Hidden impact of COVID-19 on children in Singapore** FULL ARTICLE ACCESS

Zhong Y, Clapham HE, Aishworiya R, Chua YX, Mathews J, Ong M, Wang J, Murugasu B, Chiang WC, Lee BW, Chin HL.
Vaccine. 2021 Jan 29;39(5):780-785.
PMID: 7762701

Although the direct health impact of Coronavirus disease (COVID-19) pandemic on child health is low, there are indirect impacts across many aspects. We compare childhood vaccine uptake in three types of healthcare facilities in Singapore - public primary care clinics, a hospital paediatric unit, and private paediatrician clinics - from January to April 2020, to baseline, and calculate the impact on herd immunity for measles.

We find a 25.6% to 73.6% drop in Measles-Mumps-Rubella (MMR) uptake rates, 0.4 – 10.3% drop for Diphtheria-Tetanus-Pertussis-inactivated Polio-Haemophilus influenza (5-in-1), and 8.0–67.8% drop for Pneumococcal conjugate vaccine (PCV) across all 3 sites. Consequent herd immunity reduces to 74–84% among 12-month- to 2-year-olds, well below the 95% coverage that is protective for measles. This puts the whole community at risk for a measles epidemic.

Public health efforts are urgently needed to maintain efficacious coverage for routine childhood vaccines during the COVID-19 pandemic.

PRACTICE-CHANGING UPDATES

ARTICLES

1 **Initial Guidance on Use of Monoclonal Antibody Therapy for Treatment of Coronavirus Disease 2019 in Children and Adolescents** FULL ARTICLE ACCESS

Wolf J, Abzug MJ, Wattier RL, Sue PK, Vora SB, Zachariah P, Dulek DE, Waghmare A, Olivero R, Downes KJ, James SH, Pinninti SG, Yarbrough A, Aldrich ML, MacBrayne CE, Soma VL, Grapentine SP, Oliveira CR, Hayes M, Kimberlin DW, Jones SB, Bio LL, Morton TH, Hankins JS, Maron GM, Timberlake K, Young JL, Orscheln RC, Schwenk HT, Goldman DL, Groves HE, Huskins WC, Rajapakse NS, Lamb GS, Tribble AC, Lloyd EC, Hersh AL, Thorell EA, Ratner AJ, Chiotos K, Nakamura MM.

J Pediatric Infect Dis Soc. 2021 May 28;10(5):629-634.

PMID: 33388760

In November 2020, the US Food and Drug Administration (FDA) provided Emergency Use Authorizations (EUA) for 2 novel virus-neutralizing monoclonal antibody therapies, bamlanivimab and REGN-COV2 (casirivimab plus imdevimab), for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adolescents and adults in specified high-risk groups. This has challenged clinicians to determine the best approach to use these products.

A panel of experts in paediatric infectious diseases, paediatric infectious diseases pharmacy, paediatric intensive care medicine, and paediatric haematology from 29 geographically diverse North American institutions was convened. Through a series of teleconferences and web-based surveys, a guidance statement was developed and refined based on review of the best available evidence and expert opinion.

The course of COVID-19 in children and adolescents is typically mild and there is no high-quality evidence supporting any high-risk groups. There is no evidence for safety and efficacy of monoclonal antibody therapy for treatment of COVID-19 in children or adolescents, limited evidence of modest benefit in adults, and evidence for potential harm associated with infusion reactions or anaphylaxis. Based on evidence available as of December 20, 2020, the panel suggests against routine administration of monoclonal antibody therapy (bamlanivimab, or casirivimab and imdevimab), for treatment of COVID-19 in children or adolescents, including those designated by the FDA as at high risk of progression to hospitalization or severe disease.

Clinicians and health systems choosing to use these agents on an individualized basis should consider risk factors supported by paediatric-specific evidence and ensure the implementation of a system for safe and timely administration that does not exacerbate existing healthcare disparities.

2 **Prevention and treatment of anticipatory chemotherapy-induced nausea and vomiting in paediatric cancer patients and hematopoietic stem cell recipients: Clinical practice guideline update** FULL ARTICLE ACCESS

Patel P, Robinson PD, Devine KA, Positano K, Cohen M, Gibson P, Holdsworth M, Phillips R, Spinelli D, Thackray J, van de Wetering M, Woods D, Cabral S, Sung L, Dupuis LL.
Pediatr Blood Cancer. 2021 May;68(5):e28947.
PMID: 33686754

This 2021 clinical practice guideline update provides recommendations for preventing anticipatory chemotherapy-induced nausea and vomiting (CINV) in paediatric patients. Recommendations are based on systematic reviews that identified

(1) if a history of acute or delayed CINV is a risk factor for anticipatory CINV, and

(2) interventions for anticipatory CINV prevention and treatment.

A strong recommendation to optimize acute and delayed CINV control to prevent anticipatory CINV is made. Conditional recommendations are made for hypnosis, systematic desensitization, relaxation techniques, and lorazepam for the secondary prevention of anticipatory CINV. No recommendation for the treatment of anticipatory CINV can be made.

FEATURED ARTICLES

	ARTICLES
1	**Delayed referral is common even when new-onset diabetes is suspected in children. A Swedish prospective observational study of diabetic ketoacidosis at onset of Type 1 diabetes** FULL ARTICLE ACCESS Wersäll JH, Adolfsson P, Forsander G, Ricksten SE, Hanas R. **Pediatr Diabetes. 2021 Sep;22(6):900-908.** *PMID: 33978305* Delayed treatment for new-onset diabetes Type 1 (T1D) can lead to diabetic ketoacidosis (DKA) with potentially devastating consequences. This prospective observational study aimed to characterize paediatric patients with DKA at hospital admission, regarding parental awareness of diabetes-related symptoms and delayed referrals from primary health care providers to paediatric emergency wards. Patients 0-18 years admitted to hospital with new-onset T1D and DKA between 2015 and 2017 were invited to participate. Questionnaires were filled out separately by the caregivers and by the attending hospital staff. Data from the Swedish National Diabetes Registry (SWEDIABKIDS) were used for comparison. Delayed referral was defined as a primary healthcare contact due to diabetes-related symptoms 0-4 weeks before hospital admission without immediate referral or registered elevated glucose levels at primary healthcare centres without immediate referral. The study included 237 patients, among which parental suspicion of new-onset diabetes before healthcare contacts was reported in 39%. Parental suspicion of diabetes was associated with higher pH values at diagnosis. Patients in contact with primary health care providers before hospital admission had a delayed referral in 43% of the cases. Delayed referral was associated with lower pH values at hospital admission. Symptoms leading to primary healthcare contacts were similar regardless of whether delay occurred or not. Parental suspicion of diabetes was associated with milder DKA at hospital admission. Delayed referral was seen in a considerable proportion of children with primary healthcare contacts for symptoms associated with diabetes. Increased awareness of diabetes symptoms is of paramount importance.

2 **Clinical Features, Treatment Strategies, and Outcomes in Hospitalized Children with Immune-Mediated Encephalopathies** FULL ARTICLE ACCESS

McGetrick ME, Varughese NA, Miles DK, Wang CX, McCreary M, Monson NL, Greenberg BM.

Pediatr Neurol. 2021 Mar;116:20-26.

PMID: 33388545

Autoimmune encephalitis (AE) and acute disseminated encephalomyelitis (ADEM) are immune-mediated brain conditions that can cause substantial neurological sequalae. Data describing the clinical characteristics, treatments, and neurological outcomes for these conditions are needed.

This is a single-centre retrospective review of children diagnosed with AE or ADEM over a nine-year period with discharge outcomes measured by the Modified Rankin Score. Seventy-five patients (23 with ADEM and 52 with AE) were identified.

Patients with ADEM had a higher percentage of abnormal magnetic resonance imaging findings (100% vs 60.8%; $P < 0.001$) and a shorter time from symptom onset to diagnosis (6 vs 14 days; $P = 0.024$). Oligoclonal bands and serum and cerebrospinal fluid inflammatory indices were higher in patients with AE. Nearly all patients received corticosteroids followed by plasmapheresis or intravenous immunoglobulin, and treatment strategies did not differ significantly between groups. Second-line immune therapies were commonly used in patients with AE. Finally, patients with AE had trends toward longer hospital lengths of stay (21 vs 13 days) and a higher percentage of neurological disability at hospital discharge (59.6% vs 34.8%).

Although patients with ADEM and AE may have similar presenting symptoms, we found significant differences in the frequency of imaging findings, symptom duration, and laboratory and cerebrospinal fluid profiles, which can assist in distinguishing between the diagnoses. Patients in both groups were treated with a combination of immunomodulating therapies, and neurological disability was common at hospital discharge.

3 **Acute Neurofunctional Effects of Escitalopram in Pediatric Anxiety: A Double-Blind, Placebo-Controlled Trial** FULL ARTICLE ACCESS

Lu L, Mills JA, Li H, Schroeder HK, Mossman SA, Varney ST, Cecil KM, Huang X, Gong Q, Ramsey LB, DelBello MP, Sweeney JA, Strawn JR.

J Am Acad Child Adolesc Psychiatry.

PMID: 33548492

Amygdala-ventrolateral prefrontal cortex (VLPFC) circuitry is disrupted in paediatric anxiety disorders, yet how selective serotonin reuptake inhibitors (SSRIs) affect this circuitry is unknown. We examined the impact of the SSRI escitalopram on functional connectivity (FC) within this circuit, and whether early FC changes predicted treatment response in adolescents with generalized anxiety disorder (GAD).

Resting-state functional magnetic resonance (MR) images were acquired before and after 2 weeks of treatment in 41 adolescents with GAD (12-17 years of age) who received double-blind escitalopram or placebo for 8 weeks. Change in amygdala-based whole-brain FC and anxiety severity were analysed. Controlling for age, sex, and pre-treatment anxiety, escitalopram increased amygdala-VLPFC connectivity compared to placebo ($F = 17.79$, $p = .002$ FWE-corrected). This early FC change predicted 76.7% of the variability in improvement trajectory in patients who received escitalopram ($p < .001$) but not placebo ($p = .169$); the predictive power of early amygdala-VLPFC FC change significantly differed between placebo and escitalopram ($p = .013$). Furthermore, this FC change predicted improvement better than baseline FC or clinical/demographic characteristics. Exploratory analyses of amygdala subfields' FC revealed connectivity of left basolateral amygdala (BLA) -VLPFC ($F = 19.64$, $p < .001$ FWE-corrected) and superficial amygdala-posterior cingulate cortex ($F = 22.92$, $p = .001$ FWE-corrected) were also increased by escitalopram, but only BLA-VLPFC FC predicted improvement in anxiety over 8 weeks of treatment. In adolescents with GAD, escitalopram increased amygdala-prefrontal connectivity within the first 2 weeks of treatment, and the magnitude of this change predicted subsequent clinical improvement.

Early normalization of amygdala-VLPFC circuitry might represent a useful tool for identifying future treatment responders as well as a promising biomarker for drug development.

4 **Pulmonary hypertension in bronchopulmonary dysplasia** FULL ARTICLE ACCESS

Hansmann G, Sallmon H, Roehr CC, Kourembanas S, Austin ED, Koestenberger M; European Pediatric Pulmonary Vascular Disease Network (EPPVDN).

Pediatr Res. 2021 Feb;89(3):446-455.

PMID: 32521539

Bronchopulmonary dysplasia (BPD) is a major complication in prematurely born infants. Pulmonary hypertension (PH) associated with BPD (BPD-PH) is characterized by alveolar diffusion impairment, abnormal vascular remodelling, and rarefication of pulmonary vessels (vascular growth arrest), which lead to increased pulmonary vascular resistance and right heart failure. About 25% of infants with moderate to severe BPD develop BPD-PH that is associated with high morbidity and mortality.

The recent evolution of broader PH-targeted pharmacotherapy in adults has opened new treatment options for infants with BPD-PH. Sildenafil became the mainstay of contemporary BPD-PH therapy. Additional medications, such as endothelin receptor antagonists and prostacyclin analogues/mimetics, are increasingly being investigated in infants with PH. However, paediatric data from prospective or randomized controlled trials are still sparse.

We discuss comprehensive diagnostic and therapeutic strategies for BPD-PH and briefly review the relevant differential diagnoses of parenchymal and interstitial developmental lung diseases. In addition, we provide a practical framework for the management of children with BPD-PH, incorporating the modified definition and classification of paediatric PH from the 2018 World Symposium on Pulmonary Hypertension, and the 2019 EPPVDN consensus recommendations on established and newly developed therapeutic strategies. Finally, current gaps of knowledge and future research directions are discussed. IMPACT: PH in BPD substantially increases mortality. Treatment of BPD-PH should be conducted by an interdisciplinary team and follow our new treatment algorithm while kept tailored to the individual patient.

We discuss recent developments in BPD-PH, make recommendations on diagnosis, monitoring and treatment of PH in BPD, and address current gaps of knowledge and potential research directions. We provide a practical framework, including a new treatment algorithm, for the management of children with BPD-PH, incorporating the modified definition and classification of paediatric PH (2018 WSPH) and the 2019 EPPVDN consensus recommendations on established and newly developed therapeutic strategies for BPD-PH.

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