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Overcoming COVID-19 in Children

Although the coronavirus disease 2019 (COVID-19) pandemic is still ongoing, the overall number of new daily cases has declined worldwide, especially in the countries that have received a large number of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines. More than 170 million people have been infected globally with more than 3.5 million deaths. In comparison to the high mortality rate in adults, children are usually asymptomatic or have moderate symptoms.[1] In the review article "Children are not little adults," Professor Goh reviewed the possible mechanisms for this difference between children and adults. Professor Nong performed a comprehensive review of mucoactive agents that have commonly been used in respiratory diseases for decades, according to the different mechanisms of overproduction and clearance of sputum. In addition, critical infants are an especially fragile pediatric population. Professor Chee reported that the clinical outcomes of critical infants could be improved if interhospital transportations were performed by a specialized transport team and a standard neonatal referral workflow. This new strategy was implemented in July 2019 and is still being used during the COVID-19 pandemic.

The presentations of the COVID-19 infection are less severe in children than in adults. Professor Goh[2] reviewed the pathophysiological mechanisms underlying the differences between children and adults and found that they were caused by a lower number of angiotensin-converting enzyme 2, a strong immune response, and a lower inflammatory response in children. In addition, multisystem inflammatory syndrome, which mainly affects children and adolescents but not adults, is also discussed. Good innate antiviral defenses and lower cytokine responses than adults explain the milder COVID-19 infection in children.

Hsu *et al*.[3] reviewed mucoactive agents, which are widely used to treat respiratory diseases by changing the properties of sputum or decreasing its production. Professor Nong provides an overview of mucoactive agents according to the different pathophysiologies of mucus hypersecretion and clearance.

Infants are an especially fragile pediatric population. From 2013 to 2016, a complication rate of 44.1% in critically ill infants during interhospital transportations was reported on admission in Hong Kong.[4] After July 2019, a standard neonatal referral workflow and specialized neonatal transport team were implemented at the Hong Kong Children's Hospital. One year after implementation, Chee *et al.*[5] reported a marked improvement. Compared to the previous cohort, the rate of documented physiological parameters increased, serious complication rate decreased, and the intervention rate during transport (or within 1 h after transport) also significantly decreased. This significant improvement emphasizes the importance of establishing standard protocols including a designated and specialized transport team when a critically ill infant requires interhospital transport and that this is especially important during the COVID-19 pandemic.

The SARS-CoV-2 vaccines are helping to overcome the COVID-19 pandemic. I sincerely hope we can see each other in the near future.

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There are no conflicts of interest.

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Review Article

Children Are Not Little Adults

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Abstract

Coronavirus has caused a pandemic affecting both adults and children. Although mortality rates in adults are high, that in children has been low, with many children experiencing only mild disease. This article looks at the pathophysiologic mechanisms that may account for the differences observed in children, namely a strong immune response, a lower number of angiotensin-converting enzyme 2, and a lower inflammatory response. Though children in general have mild disease, there is a hyperinflammatory condition known as multisystem inflammatory syndrome, which is likely a postinfectious immunologic response, which is seen mainly in children and adolescents and not adults.

Keywords: COVID-19, paediatric, pathophysiology, SARS-CoV-2

Coronavirus disease 2019 (COVID-19) caused by coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China but has since swept round the world with more than 20 million people infected and causing the death of over 700,000 people. The disease initially presents as a mild respiratory illness that can progress to a viral pneumonia with acute respiratory distress syndrome and multiple organ failure and death in adults especially in the elderly.[1,2] In children, the course of the disease is generally milder with low fatality rates. Reports from Italy where the number of infections with COVID-19 was high with 253,275 cases, the findings have found that children between zero and nine years made up about 0.5% and those between 10–19 years about 0.7% of confirmed cases. There were no deaths reported in children despite 35,825 deaths reported in adults. The majority of children were either asymptomatic or had mild disease.[3] A systematic review of SARS-CoV-2 infection in children and newborns confirms the findings that the disease affects children and even newborns less severely than adults. About 2% were admitted to the intensive care unit, and estimated mortality was 0.08%.[4] What is it about children that makes their response to the coronavirus infection so different from adults?

The three main postulations for this difference observed are firstly, a stronger immune response in children; secondly, a lower number of angiotensin-converting enzyme (ACE) 2 in children; and thirdly, a lower inflammatory response in children.

For the first postulation, the milder disease observed in children could be due to "trained immunity." Trained immunity represents an innate immune memory formed after antigen exposure.[5] Repeat viral infections with cytomegalovirus and influenza A have been shown to trigger a stronger natural killer (NK) cell–mediated secondary innate immune response on reinfection.[6] Trained immunity represents a crossprotection against various pathogens, and it can also be activated by vaccines.[5] In children who have frequent viral infections, the increased activation of antigen-presenting cells led to a nonspecific resistance of the host to reinfection, providing crossprotection to other infections. Children too receive many vaccinations, and it is assumed that vaccines can also induce crossreactivity, thus training the innate immune system. It has been found that vaccinations elicit an NK cytotoxic response. Myśliwska, *et al.*[7] investigated the relationship between NK activity

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in the vaccinated population with influenza vaccine and specific immune protection against influenza virus as well as immune protection against other infections. They found that NK activity remained elevated one month after vaccination and concluded that NK cell activation may confer protection against influenza and other respiratory viral infections. Hence, frequent viral infections and vaccination in children could induce an innate immune system with an enhanced state of activation that protects them against different pathogens.[8] Furthermore, children with SARS-CoV-2 infection usually demonstrate normal levels of peripheral blood lymphocytes, which suggest less immune dysfunction.[5]

ACE2 mediates the entry of coronavirus (CoV) into host cells in two independent ways. The first way involves ACE2 receptor–mediated clathrin-dependent endocytosis. When the CoV connects to ACE2, the extracellular domain is cleaved off by specific proteases, such as metalloproteinase ADAM17, and the transmembrane domain is internalised. With the assistance of clathrin, viral particles and host cells fuse that aids viral transport from the cell membrane to the cytoplasm. The second way involves ACE2 receptor-mediated transmembrane serine protease 2 (TMPRSS2)-dependent membrane fusion. TMPRSS2 has been found to compete with the ADAM17 metalloprotease for ACE2 processing, but only cleavage by TMPRSS2 was found to enhance SARS-S protein–driven entry.[9,10]

A publication looking at nasal gene expression of ACE2 in children and adults found an age-dependent expression in nasal epithelium. ACE2 gene expression was lowest in young children below the age of 10 years and increased with age.[11] The low levels of ACE2 could suggest a lower affinity for the virus resulting in milder infection. Adolescents and young adults have high levels of ACE2, but most have mild disease. ACE2 expression decreases with increasing age, thus it is higher in young adults than in the elderly, yet the elderly are at greatest risk of severe disease.[12] In a mouse model, membrane-bound ACE2 was demonstrated to play a critical role in anti-inflammation through the renin-angiotensin system (RAS) signalling and the conversion of Ang II to Ang (1–7), which protected the animal against acute lung injury.[13] Hence, it is not just the level of ACE2 expression but the downregulation in ACE2 expression seen in the elderly and adults with comorbidities resulting in increased activity of RAS that promotes the inflammation in the lung and the subsequent severe lung disease.

Thirdly, a lower inflammatory response as evidenced by lower interleukin-6 (IL-6) levels in children. A review of all paediatric cases with reported cytokine levels showed that the majority of children had IL-6 within the normal range (mean: 86.3%; range: 67%–100%)[14] in contrast to adults.[15] The less mature immune system of children may result in a lower capability to elicit a cytokine release against viral infections.

Taken together, these immune pathophysiologic mechanisms in children protect them from severe disease from the SARS-CoV-2. Children also have fewer comorbidities and also do not smoke, which upregulates the ACE2. The upregulation of ACE2 activates the immune system inducing the expression of a variety of inflammatory cytokines resulting in the "cytokine storm" caused by COVID-19.[16]

Are children with chronic illnesses at increased risk of COVID-19? The commonest chronic illness in childhood is allergic diseases such as asthma. Fortunately, allergic disease appears to be "protective" against COVID-19. Children with allergic disease and asthma have eosinophilia. Eosinophils clear viral load, thus improving recovery from viral infections. It was also found that allergic sensitisation was inversely related to ACE2 expression and allergen exposure and challenges significantly reduced ACE2 expression.[17] Even in immunocompromised children, the disease is no worse.[18]

There have been reports of an emerging hyperinflammatory shock syndrome resembling Kawasaki's disease, which has been termed multisystem inflammatory syndrome (MIS). This is likely to be a postinfectious inflammatory syndrome as most of the children did not have evidence of viral replication.[19,20] Thus, though children have mild disease with COVID-19, paediatricians have to be aware of this rare sequelae of COVID-19 infection.

In summary, children have milder disease from COVID-19 infection because of their good innate antiviral defences and less exuberant inflammatory cytokine responses than adults. However, children are at higher risk of developing postinfectious hyperinflammatory disease such as MIS compared with adults.

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Conflicts of interest
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Review Article

An Overview of Mucoactive Agents

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Abstract

Mucus production of the respiratory tract is our first defense against microbes and allergens. However, overproduction of the sputum and difficulty with airway clearance could lead to many respiratory tract diseases. Mucoactive agents are medications that either change the properties of the sputum or decrease its production. This article aims to provide an overview of common mucoactive agent.

Keywords: Expectorants, mucoactive, mucolytics, sputum

Introduction

Our airway epithelium defends against the inhaled irritants such as dusts, microbes, and allergens. The first defense is the production of mucus, by goblet cells lining the surface epithelium, and seromucous gland beneath the mucosal epithelium. The mucus is composed of water, carbohydrates, proteins (glycoprotein), and lipids (surfactant) and forms a thin film on the surface of the airways. Normally, the mucus entraps the foreign debris, microbes, and dust and clears them from the airway by ciliary movement, termed mucociliary clearance. Rhythmic vibrations of the cilia propel it toward the pharynx from where it is swallowed unnoticeably. However, when the mucus is produced excessively and changed in nature, mucociliary clearance is impaired. Cough becomes essential for airway clearance in this pathologic state. The expectorated mucus, along with microorganisms, cell debris, and other foreign particles, together formed the sputum.[1-3]

Medications that affect mucus properties and promote the clearance are said to be mucoactive. Mucoactive medications include expectorants, mucolytics, mucoregulatory drugs, and mucokinetic drugs. They can help expectorating the sputum or decrease mucus hypersecretion.[4] As these medications are used widely clinically, this review article aims to discuss the mechanism and efficacy of them [Table 1].

Pathophysiology

The surface epithelium of intrapulmonary airways is composed of ciliated cells and secretory cells. Secretory cells release not only mucins but also antimicrobial molecules (e.g., defensins, lysozyme, and immunoglobulin A), immunomodulatory molecules (e.g., secretoglobins and cytokines), and protective molecules (e.g., trefoil proteins and heregulin). Submucosal gland is constituted of mucous cells and serous cells. Mucous cells secret mucin while serous cells secret proteoglycans and antimicrobial proteins.[5]

Normal mucus consists of 97% water and 3% solids (mucins, nonmucin proteins, salts, lipids, and cellular debris). There are two mechanisms for the expulsion of mucus from the airway – mucociliary clearance and cough clearance. The efficacy of mucus clearance is determined by the viscous and elastic properties of mucus. Healthy mucus has low viscosity and elasticity, whereas pathologic mucus has higher viscosity and elasticity (which may contains up to 15% solids) and is less easily cleared. Impaired mucus clearance results in the accumulation of mucus, which in turn may lead to infection and inflammation by providing an environment for microbial growth.[5]

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Table 1: Categories of mucoactive agents

Categories	Function	Examples
Expectorants	Hydration and increase the volume of airway secretions	Hypertonic saline inhalation
		Guaifenesin
		Ambroxol
Classic mucolytics	Hydrolyzes the disulfide bonds of mucus proteins and decrease mucus viscosity	Acetyl cysteine
Peptide mucolytics	Degrade DNA, F-actin polymers in sputum	Dornase alfa
		Thymosin β4
Mucoregulatory agents	Anti-inflammation or inhibit mucus secretion	Glucocorticosteroids
		Macrolide antibiotics
		Anticholinergic drugs
Mucokinetic agents	Increase mucociliary clearance	β2-adrenoceptor agonist bronchodilators
		Surfactant

Expectorants

The efficiency of mucus clearance depends on an adequate volume of airway surface liquid.[6] Airway surface dehydration may increase the adhesivity of secretions to the epithelium of airway and thus make it more difficult to expectorate.[7] Hydration is thought to aid sputum expectoration.[4] Expectorants can help expectorate purulent secretions, by increasing airway water or the volume of airway secretions. For example, hypertonic saline or dry powder mannitol acts through hydration of luminal secretions.

The inhalation of hypertonic saline produces an osmotic force and draws water from the interstitium to the airway surface layer[8] and therefore improves airway hydration and accelerates mucus transportability.[5,7,9] Inhalation of hypertonic saline promotes greater sputum expectoration than isotonic saline.[9] Inhaled hypertonic saline is generally safe and well tolerated, except for some mild adverse reactions, such as unpleasant salty taste, throat irritation, excessive coughing, or airway narrowing.[8] Immediate adverse reactions resolve rapidly. Cough typically decreases over time. Bronchodilator may be used before administration of hypertonic saline to prevent or minimize airway narrowing.[10] Addition of hyaluronic acid can decrease bronchospasm and balance water homeostasis in airways. The adverse reactions during inhalation are less frequent and milder in inhalation of hypertonic saline and hyaluronic acid than inhalation of hypertonic saline alone. Combination of hypertonic saline and hyaluronic acid is the preferred solution for treatment.[9]

Guaifenesin, or glyceryl guaiacolate ether, is an oral expectorant that is once thought to stimulate cholinergic muscarinic receptors via the vagus nerve in the gastric mucosa and therefore stimulate submucosal glands (also called gastropulmonary reflex).[11,12] However, its precise mechanism of action has remained unclear.[12] Other studies found that guaifenesin reduces mucin production, decreases mucus viscoelasticity, and increases mucociliary transport.[13] Moreover, it has significant better efficacy in decreasing mucin production, mucus viscosity, and elasticity, and increasing mucociliary clearance rate, than N-acetyl cysteine (NAC) or ambroxol.[14] It is approved by the US Food and Drug Administration as an effective expectorant with a good safety profile.[15] It is also sold as over-the-counter cold and cough medicines. Recently, an extended-release formulation of guaifenesin was launched. It combines immediate-release guaifenesin with an extended-release feature, to provide sustained blood levels for 12 h. Studies revealed that it improves cough and other discomfort related with excess mucus.[16] It is also shown to have safe and well tolerated.[11]

Ambroxol is a mucoactive agent that increases bronchial secretions,[17] stimulates ciliary activity,[18] activates the surfactant system of the lung,[19] and owns antioxidative/anti-inflammatory activities[20] in animal models. Ambroxol has been used for years, and early studies showed that it improves respiratory symptoms, such as ease of expectoration, phlegm loosening, and decrease in sputum volume and sputum viscosity, in adults.[21,22] In studies regarding children with acute respiratory disease, both ambroxol and acetyl cysteine (NAC) were effective in improving symptoms (cough and expectoration), but ambroxol was either more effective or had a more rapid effect than NAC.[23,24] In conclusion, its secretolytic and secretomotoric actions restore the physiological clearance mechanisms of the respiratory tract, and its clinical efficacy and safety in the management of acute and chronic lower respiratory diseases were well documented.[25]

Classic Mucolytics

Mucolytics degrade the mucin polymers, deoxyribonucleic acid (DNA), fibrin, or filamentous actin (F-actin) in airway secretions and therefore decrease viscosity of the mucus.[4] Classic mucolytics, such as acetyl cysteine (NAC), hydrolyze the disulfide bonds of mucus proteins to decrease mucus viscosity, thereby facilitating its clearance.[26] However, studies reported no significant differences in sputum volume, ease of expectoration, and atelectasis between acetyl cysteine and placebo.[27] Oral acetyl cysteine is rapidly inactivated and does not appear in airway secretions. It is probably the reason why acetyl cysteine is effective *in vitro* but ineffective *in vivo*.[4] One study found aerosolized NAC to decrease sputum viscosity (subjective assessment), but there is no significant change in daily sputum volume or pulmonary function.[28]

Due to lack of high-level evidence, routine use of aerosolized NAC to improve airway clearance is not recommended in hospitalized adult and pediatric patients without cystic fibrosis.[29]

Peptide Mucolytics

Peptide mucolytics degrade polymers in the sputum, which are composed of DNA, F-actin polymers, and mucin gel.[30] Dornase alfa, a human recombinant DNase, digests extracellular DNA released during infection, which contributes to viscosity of exudates.[31] Several case reports demonstrated the use of dornase alfa in patients having status asthmaticus with mucus plugging and refractory to traditional therapy.[32-35] However, in the setting of acute bronchiolitis or airway malacia with a respiratory tract infection in children, studies found no benefit in clinically meaningful outcomes with nebulized dornase alfa.[36,37]

Thymosin β4 (Tβ4) is another peptide mucolytic that degrades F-actin. There was a direct relationship between actin filament length and sputum cohesivity. One study found that Tβ4 depolymerizes sputum actin in both a dose-dependent (between 0.3 and 3.0 μg/mL) and a time-dependent manner.[38] Synergy with Tβ4 and dornase alfa at a concentration of 1.5 μg/mL of each was also observed.[38]

Mucoregulatory and Mucokinetic Agents

Mucoregulatory agents such as glucocorticosteroids and macrolide antibiotics own the anti-inflammatory activity. Anticholinergic drugs not only act as bronchodilator but also inhibit cholinergic nerve-induced mucus secretion. These medications therefore may reduce chronic mucus hypersecretion.[7]

Mucokinetic agents increase mucociliary clearance, generally by acting on the cilia.[4] These medications include β2-adrenoceptor agonist bronchodilators and surfactant. β2 agonists increase airflow and ciliary beat and therefore facilitate mucus movement. Surfactant reduces the adherence of mucus to the epithelium.[7]

Summary

In both acute and chronic airway diseases, mucus hypersecretion and retention cause variable degrees of discomfort to the patients and therefore are a frequent complaint. Mucoactive agents hence play an important role in treating our patients, and it is important for us to understand the pathophysiology of mucus hypersecretion and the mechanisms of different types of mucoactive agents.

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Reduction of Complications in Interhospital Transport of Critically Ill Infants: Impact of a Standardized Neonatal Referral Workflow and Specialized Neonatal Transport Team at the Hong Kong Children's Hospital

An article "Clinical Outcomes of Critically Ill Infants Requiring Interhospital Transport to a Paediatric Tertiary Centre in Hong Kong" was previously published by Leung *et al*. at the *Pediatric Respirology and Critical Care Medicine* in 2019.[1] This paper retrospectively reviewed the characteristics and clinical outcomes of all infants transported from the neonatal units of different regional hospitals to a tertiary neonatal intensive care unit (NICU) or cardiac intensive care unit in Hong Kong from August 1, 2013, to July 31, 2016. During that review period, no specialized neonatal transport team has been formed yet. Salient findings from this review included inadequate documentation of physiological parameters during transport (91.4% with missing documentation), while close to half of the patients (44.1%) had complications on admission.

Commencement of clinical service of the NICU at the newly opened Hong Kong Children's Hospital (HKCH) was started in July 2019. HKCH NICU mainly takes care of neonates transferred from other hospitals with neonatal surgical problems. A standardized protocol is developed comprising workflow on case referral, systematic clinical handover via telephone conferencing, and pre-transportation preparation (with specific neonatal transport equipment bag, medications for use during transport together with body-weight specific resuscitation chart to minimize medication error). Interhospital transport of critically ill infants are now performed by a designated and specialized critical care transport team, comprising medical and nursing staff equipped with training on neonatal transport. Critical care transport will be performed by at least one doctor who is a pediatric specialist and one nurse from transport roster (nurses with prior training on neonatal transport at HKCH). We reviewed our interhospital neonatal intensive care transport data from July 2019 to July 2020 [Table 1]. The data only included neonatal transport from the referring hospital to the HKCH. A total of 48 infants with a mean gestational age of 32.2 ± 5.0 weeks and birth weight of 1800 ± 951 g were included in the study. Patient characteristics and medical complexity (including ventilator and/or inotropic support) during transport were comparable to the previous cohort.[1] Documentation of physiological parameters during transport was available for all cases (compared with only 8.6% in the previous cohort [$P < 0.05$]). Serious or critical (or both) complications were significantly lower in our current cohort (25%) compared with the previous cohort (44.1%, $P < 0.05$). Significantly less interventions were needed during transport (or within 1 h after transport) in our cohort (6.3%) compared with the previous cohort (23.0%, $P < 0.05$).

To conclude, complications of transport of critically ill infants could be significantly reduced if the transport is performed by a designated and specialized critical care transport team, with fewer unplanned events during transport.

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Conflicts of interest

There are no conflicts of interest.

Table 1: Comparison of complication rates and intervention during transport or within 1 h of admission of our study with previous study

	Leung 2013-2016	Our study 2019-2020	*P*
Gestational age at birth (week), mean±SD	31.7±5.5	32.2±5.0	0.56
Birth weight (g), mean±SD	1732±1007	1800±951	0.67
Age at transport (days), median (range)	13.1 (0.4-150.6)	8 (0-240)	0.98
Ventilatory support during transport (invasive or noninvasive ventilation) (%)	175/256 (68.4)	27/48 (56.3)	0.13
Inotropic support during transport (%)	37/256 (14.5)	2/48 (4.2)	0.06
Monitoring during transport (%)	22 (8.6)	100	<0.05
Intervention during/within 1 h post transport (%)	59/256 (23.0)	3/48 (6.3)	<0.05
Serious or critical (or both) complications (%)	113/256 (44.1)	12/48 (25)	<0.05

SD=Standard deviation

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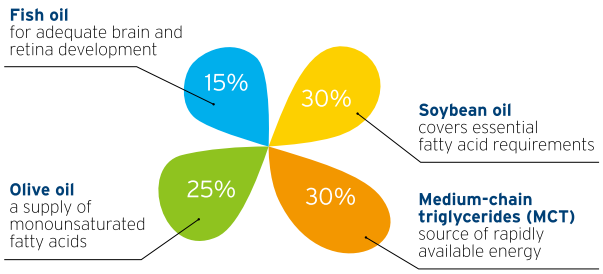

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