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End of the COVID Pandemic: Time to Move On

About half a year ago in August of 2022, the American Academy of Pediatrics (AAP) and the Children's Hospital Association had jointly reported over 14 million children in the United States affected with coronavirus disease (COVID), and children represented 18.4% of all confirmed cases.[1] Pediatric COVID cases spiked dramatically across the United States during the Omicron variant surge. It is important to recognize that there are immediate effects of the pandemic on children's health, but importantly, we need to identify and address the long-lasting impacts of COVID on the physical, mental, and social well-being of this generation of children and youth, as suggested by the AAP.

Needless to say, the implementation of a vaccination program played a positive role in the ongoing battle against COVID. While an increased number of infections was seen in pediatric population across the world, severe cases were not common. However, risk factors for severe COVID disease in children were described in studies, such as preterm babies, obesity, and diabetes mellitus.[2] This Journal has played an active role in bringing COVID to an end, and I trust this contribution will continue in the future under the able leadership of the editorial board led by Prof. Gary Wong.

In this issue, several authors discuss a wide range of topics from the use of bleach baths in atopic dermatitis and fetal intervention in diaphragmatic hernia to the use of high flow in COVID.

Eczema is most commonly seen among infants and children, although adults can also suffer from the condition. Eczema can take several forms, with the most frequent being atopic dermatitis, which is a severe chronic disease that causes itchy, inflamed skin. Infection follows frequently and contributes to flare-ups, along with various other complications. The exact cause of eczema is unknown—although a genetic link is suggested—but a number of external factors are believed to be at work during an eczema episode.[3] It is true that there is no cure for the condition, but there are a number of possible treatments for those suffering from eczema. A medical student from the Chinese University of Hong Kong, Chan Jeffrey Yi Ming, reviewed the use of bleach baths as a treatment for atopic dermatitis.[4] Diluting bleach into a bath of warm water kills the bacteria and lessens the chance of new super germs emerging. Parents should consult their pediatricians for advice before starting a bleach bath regimen, but a general recommendation is to use half a cup of bleach in a full standard-sized bathtub, bathing twice a week and possibly more often during an acute episode. When properly mixed, the odor of bleach should not be detectable and bleach bath works best in combination with other treatments. The author reviewed the current literature for the effectiveness of bleach bath as a treatment for atopic dermatitis and compares water and bleach baths. After carefully analyzing the cost, tolerance, and possible risks of bleach bath, the author concludes that it could be a treatment option for atopic dermatitis to control *Staphylococcus aureus* colonization in pediatric and adult patients.

The second paper by Dr. Kason WH Lin addresses the issue of congenital diaphragmatic hernia (CDH) and local Hong Kong experience in the treatment of CDH.[5] When CDH occurs, the respiratory, circulatory, digestive, and other systems will change, and the clinical manifestations are varied. The author reviewed the approach to neonatal surgical repair, including methods of surgical repair, the shift from early to delayed repair, and relevant controversies in the practice. The author then addressed the current consensus in delayed surgical repair, which suggested a period of preoperative stabilization. High-frequency oscillatory ventilation and extracorporeal membrane oxygenation were analyzed by the author in terms of rationale, benefits, and controversies. Finally, the author discussed the advent of fetal surgeries, which is introduced for patients who are predicted to have favorable clinical outcomes. The author explained the history of fetal intervention, its evolution, fetal endoscopic tracheal occlusion, and the Hong Kong experience with the new technique of a flutter-valve design to allow tension-free repair.

The third paper by Huang *et al*. discussed the use of respiratory therapy in COVID.[6] In most pediatric COVID cases, clinical symptoms are mild, and the hospitalization rate is low. In a situation when a child is hospitalized and receives treatment for acute respiratory failure, such as in severe COVID cases, it is critical that the utility and safety of other forms of respiratory support devices be explored, including high-flow nasal cannula oxygenation (HFNCO). The physiological benefits of HFNCO are improved oxygenation, decreased anatomical dead space, decreased metabolic demand of breathing, decreased production of carbon dioxide, superior comfort and improved work of breathing, positive nasopharyngeal and tracheal airway pressure, and better secretion clearance. HFNCO is an effective treatment modality for COVID-19-associated acute respiratory failure. Particularly in patients with mild-to-moderate acute respiratory distress

syndrome and in negative pressure rooms, it could be a viable initial alternative to mechanical ventilation. In this article, the authors discussed heated humidified high-flow nasal cannula (HHHFNC) in prone position, which has shown reduction of aerosol spreading in comparison with noninvasive positive pressure ventilator and other oxygen therapy. However, the authors also advised that if a patient does not show adequate saturation under HHHFNC, early intubation with video laryngoscope is suggested.

I hope that these interesting topics presented in this issue may open up further discussions and studies on these issues. As we continue to understand more about concerning pediatric issues, especially under the ever-evolving COVID variants and their impact on short-term and long-term child health, safety, and well-being, we as pediatricians and pediatric researchers will be better equipped to identify possible solutions and alternatives.

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Review Article

Treatments of Congenital Diaphragmatic Hernia: The Paradigm Shift, Controversies, and The Hong Kong Experience

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Abstract

Despite continuous effort in developing treatments of congenital diaphragmatic hernia (CDH), the high morbidity and mortality of the disease and lack of standardization of managements remain to be a formidable challenge. This article aims to review the current controversies of treatments of CDH and the Hong Kong experience.

Keywords: Congenital diaphragmatic hernia, pediatric surgery, respiratory medicine, respiratory surgery

Introduction

Congenital diaphragmatic hernia (CDH) describes a developmental abnormality of the diaphragm, which causes herniation of the abdominal viscera into the thoracic cavity. The emergence of early surgical treatments in the early 20th century shed light on the subsequent development of a myriad of treatments.[1] Despite the continuing evolvement of medical and surgical treatments, the management of CDH has still not been standardized. Many of the novel treatments were only found effective in experimental animal models and were practiced based on conventionalism without support from randomized controlled trials.[1-5] Whether there exists an evidence-based practice for the treatment of CDH remains to be a conundrum. This article, therefore, aims to review the paradigm shift, the controversies, and the local Hong Kong experience in treatments of CDH.

Neonatal Surgical Repair

Surgical repair was the first documented successful modality in the development of treatments of CDH. In 1940, Ladd and Gross demonstrated a survival of 9 of 16 patients that were operated on.[1] Many aspects of surgical repair have now been consistently improved and modified, including the techniques and timing of the surgery.

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Methods of surgical repair

Surgical repair can be performed via a transthoracic or transabdominal route, in an open or minimally invasive manner. The most important determinant of postoperative outcome is the characteristic of diaphragmatic defect.[6] Defect of CDH can be considered as a spectrum: a small muscular defect will have minimal recurrence after primary approximation, whereas the agenesis of diaphragm will require a patch closure. The latest systematic review comparing primary and patch repair showed a higher risk of surgical complications, including recurrence, chylothorax, and small bowel obstruction, in patch-repaired patients.[7] The minimally invasive approach was also shown to have a higher recurrence rate and gastroesophageal reflux.[8]

The shift from early to delayed repair

Historically, emergency surgical repair was advocated as justified by the presence of large amounts of gas in the bowel and thorax, causing lung compression and respiratory

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distress.[9] It was then noted that there was no improvement in gas exchange and a deterioration in thoracic compliance and $PaCO_2$ immediately after operation in seven of nine CDH patients.[10] Furthermore, surgery is associated with a reduction in cerebral blood volume and oxygenation due to an increase in right-to-left shunt and a decrease in venous return from the compression of inferior vena cava by the repositioned viscera into the abdominal cavity.[11] As such, more surgeons begin to use a strategy of delayed surgical repair, which may minimize the compromise of cerebral circulation and oxygenation without worsening pulmonary compliance.[9]

However, evidence that supports the practice of delayed surgical repair and its benefit of improving survival appears controversial. Several studies concluded there was no clear evidence favoring delayed surgical repair.[9,12-14] A systematic review in 2002 identified two small randomized trials with sample sizes of less than 90, and neither showed a significant difference in mortality.[9] A more recent review by Yunes *et al.*[14] included 4 systematic reviews with a total of 38 studies. They also concluded that there appeared to be no clear disadvantage of immediate surgical repair in terms of increased mortality due to the low certainty of evidence demonstrated in the systematic reviews. Such a controversy might be due to the difficulty of generalizing findings from studies that investigate the influence of the timing of repair on outcomes.[6] Many of these studies are in the form of retrospective design with a heterogeneous patient group, which may dent their reliability.[6]

Preoperative Stabilization

The current consensus of delayed surgical repair thereby encourages a period of preoperative stabilization based on the rationale that stabilization of hemodynamic and pulmonary functions prior to surgery could improve surgical outcomes.[15] Two modalities of preoperative stabilization warrant particular attention, as controversies remain concerning their survival benefits.

High-frequency oscillatory ventilation

High-frequency oscillatory ventilation (HFOV) operates in a "safe window" during the cycle changes between inspiration and expiration phases, thus achieving homogenous aeration of the lung to recruit collapsed alveoli and to prevent atelectasis.[16] This is primarily performed using rapid tiny oscillations from a reciprocating piston. Compared to conventional ventilation, HFOV prevents ventilator-induced lung injury while preserving adequate ventilation. As iatrogenic lung injury by conventional ventilation further exacerbates the lethality of CDH in which patients are already susceptible to pulmonary hypoplasia, HFOV is increasingly used as a management strategy for preoperative stabilization.[17]

The benefits of HFOV were substantiated in early studies with a documented increase in survival rates.[18-21] Somaschini *et al.*[21] further extrapolated the benefit by showing infants maintained an optimal neurodevelopmental outcome when they had reached the age of 1 year. Furthermore, the use of HFOV was extended into perioperative stabilization in an attempt to optimize surgical outcomes. Ventilation of 22 newborn infants with HFOV during surgery was shown to facilitate diaphragmatic repair.[17]

However, the survival benefits of HFOV as preoperative stabilization have been challenged in recent years. The conventional ventilation in infants with congenital diaphragmatic hernia: an international randomised clinical trial recruited 171 newborns to determine the optimal initial ventilation mode in CDH.[22] No statistically significant difference in terms of mortality rate and bronchopulmonary dysplasia was noted between patients who received conventional mechanical ventilation and those with HFOV. The perioperative benefits of HFOV were also challenged in a recent retrospective cohort study by Derraugh *et al.*[23] They concluded that no significant difference was observed between conventional ventilation and HFOV in oxygen dependency or death at 28 days. In light of the small sample size in many of the studies, it remains early to conclude or refute the beneficial effects of HFOV, either as preoperative or as perioperative stabilization.

Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) is considered a rescue therapy to restore cardiac and pulmonary functions in severe cases of CDH when conventional treatments with ventilation and vasoactive drugs failed. Despite its first use in 1977, the benefits of ECMO in CDH remain to be substantiated by representative randomized controlled trials, since neonates who require ECMO are often in critical condition with a high mortality rate.[24]

The rationale for using ECMO as a rescue therapy stems from the ultimate development of pulmonary hypertension in CDH. Pulmonary hypertension is said to be a significant predictor and cause of mortality necessitating ECMO.[25] There are mainly two pathophysiological mechanisms of pulmonary hypertension in CDH, one is the reduction of lung volume from herniation of organs and the other is the presence of right-to-left shunt and persistent pulmonary hypertension after birth. Both of which give rise to hypoxemia, causing thickened pulmonary arteries and vasoconstriction.[25] Subsequent pulmonary and cardiac dysfunctions would, therefore, necessitate the use of ECMO to provide temporary artificial support.

The survival benefit from the use of ECMO has long been debated. There were only two remote studies investigating the role of ECMO in CDH with randomized controlled trials.[24,26] The UK Collaborative ECMO Trail Group undertook a randomized controlled trial of 185 mature

infants with severe respiratory failure to compare ECMO and conventional intensive management.[27] A striking difference of 22% survival rate was seen in the ECMO group when compared to the conventional management group. However, the actual survival benefits brought by ECMO might be lower, as the presence of late-term mortality (death at more than 90 days after ECMO) needs to be accounted for.[28] ECMO has also been shown to bring a myriad of complications, including hemorrhage, metabolic derangements, and renal insufficiency in up to 70% of neonates.[29] Even when an infant is weaned from ECMO, the risk of pulmonary hypertension and recurrent hypoxia remains.[30]

Another controversial issue is deciding whether to operate when patients are put on ECMO. While patients' conditions might be severe enough to warrant intraoperative ECMO during repair for cardiopulmonary support, one major concern is how to meticulously balance the risk of intraoperative bleeding brought by the anticoagulation needed for the ECMO circuit.[31] Studies vary on the effects of intraoperative ECMO on the neonates' survival rate, and the latest cohort study demonstrated a lower mortality rate in patients who underwent early repair after ECMO cannulation.[31-33]

The Advent of Fetal Surgeries

Despite the advance in preoperative stabilization and surgical techniques, there remains a portion of patients who are not fortunate enough to survive until postnatal treatments. Whether a fetus can survive after birth depends mainly on the presence of pulmonary hypoplasia and the development of pulmonary hypertension.[34,35] Improvement of prenatal diagnostic modalities has led to the development of prognostic indicators that can stratify fetuses with better chances of survival.[36] This allows the introduction of fetal surgeries to those who are predicted to have favorable outcomes.

From animals to humans

Areechon and Reid[37] first postulated the feasibility of fetal interventions in lung hypoplasia in CDH in 1963. However, it was until 1980 that the first animal model of fetal intervention was created.[35] Compression of intrathoracic abdominal organs was mimicked by inflating a balloon in the hemithorax of a sheep. Increased lung growth and survival were noted when the balloon was subsequently deflated. Such a surgical model was then extended to rabbits, which were more easily available with lower costs.[38] *In utero* interventions that have been attempted in animal models include primary closure with a patch or secondary closure with silo reduction.[38] Further modification and iteration of the animal model led to the first successful *in utero* CDH correction in humans in 1990. Harrison *et al.*[39] performed open fetal surgery on six fetuses with severe CDH. Three died intraoperatively from kinking of umbilical veins during the attempt to reduce the herniated liver, whereas one died postoperatively. The remaining two successful cases had optimal lung growth *in utero* and good postnatal lung functions.

Evolution of fetal interventions

A major shortcoming of the open approach by Harrison *et al.* was its difficulty in reducing the herniated liver. Kinking and compression of the umbilical vein during the reduction process was the major obstacle, and it was later demonstrated that only 5 of 21 fetuses with herniated livers survived after open fetal surgery.[39] Attempts had been made to limit the open approach to fetuses without liver herniation, yet disappointingly, the use of open fetal surgery in those patients failed to increase survival when compared to standard postnatal interventions.[41] As the difficulty to reduce liver herniation was technically insurmountable, and the failure of demonstrating survival benefits in fetuses without liver herniation, the open approach was then abandoned.[40]

The technique of tracheal occlusion was then introduced. The birth of such an idea was dated back in 1970 when it was shown that serial ligation and drainage of fetal lamb lungs led to pulmonary hyperplasia.[35,42] When the tracheal was ligated, fluid produced by the lungs would accumulate, causing an elevated hydrostatic pressure, thereby promoting lung growth.[43] This technique was termed PLUG, or Plug the Lung Until it Grows. The group later attempted the PLUG technique in eight fetuses of 25–28 weeks gestation. Five fetuses were found to have dramatic lung growth after the procedure, a much more promising result when compared to the open approach. It proved to be a breakthrough in fetal surgery in CDH, stimulating the rapid improvement of the technique of tracheal occlusion in the late 1990s and early 2000s.[35]

Fetal endoscopic tracheal occlusion

Fetal endoscopic tracheal occlusion (FETO) is considered the state-of-the-art fetal surgery for CDH. It is performed percutaneously with local anesthesia. Fetal position is first ascertained with intraoperative ultrasound; the fetus is then anesthetized via ultrasound-guided intramuscular route injection of narcotics and muscle relaxants. A 10-Fr cannula is then introduced into the amniotic cavity toward the fetus' mouth, which serves as a guide for the introduction of the fetoscope with a catheter containing the occlusion balloon. Advancement of the fetoscope into the fetal pharynx, larynx, and trachea allows deployment and inflation of the balloon. Postoperative imaging will be performed routinely to confirm its position and to monitor fetal lung volume and fetal growth until the balloon is removed 5–7 weeks after its placement.[35]

There have been some remarkable successes in the FETO procedure in Europe and America.[35,40] A notable multicenter study in 2009 demonstrated substantial

improvement in survival in fetuses with severe CDH.[44] FETO was performed on 210 cases from Belgium, London, and Spain. Evaluation with regression analysis showed a striking difference between the expected survival and observed survival after FETO, with 49.1% and 35.3% of observed survival after FETO for left- and right-sided CDH, respectively, compared to 24.1% and 0% of expected survival in the same group. Furthermore, FETO appeared to be able to circumvent the insurmountable obstacle of reducing liver herniation in severe CDH in open surgery. Placement of endotracheal balloon in 21 fetuses with liver herniation was successful without major maternal complications, with increased lung echogenicity within 48-h after operation demonstrated on ultrasound scans.[45]

Harrison *et al.* demonstrated contradictory findings in their 2003 study, which was described as "the most significant report in the history of fetal surgery."[40,46] It was a randomized controlled trial comparing fetal tracheal occlusion with standard postnatal care. Inclusion criteria were fetuses between a gestation of 22–27 weeks with severe left-sided CDH. The primary and secondary outcome was the 90-day survival. It demonstrated an unexpectedly high survival rate in the standard postnatal care arm, necessitating the termination of the trial. Overall, 77% of the fetuses with postnatal neonatal care survived, compared to that 73% with FETO. Thus, the authors concluded there was no improvement in survival in fetuses with severe left-sided CDH. More recently, a similar randomized controlled trial was performed on fetuses with moderate left-sided CDH.[47] The trial also failed to demonstrate a significant benefit of FETO at 30–32 weeks of gestation in fetuses with moderate left-sided CDH. It remains early to conclude that FETO should be recommended as a routine *in utero* intervention, given the contradictory results.

The Hong Kong Experience

A few studies have evaluated the management of CDH in the local Hong Kong population with encouraging results. Tam *et al.*[48] reviewed 22 patients at Prince of Wales Hospital with neonatal CDH between 1999 and 2009. Their survival after receiving the latest treatment modalities (namely, HFOV, inhaled nitric oxide, exogenous surfactant, and delayed surgical operation) was documented at the expense of ECMO (which was not available during that time). A promising overall survival rate of 82% was shown. They had particularly highlighted that such a figure was comparable with tertiary centers in the United States equipped with ECMO services. It was until 2014 that ECMO was first used as a bridge to surgical repair. Lau *et al.*[3] reported a 37-week Caucasian boy with left-sided CDH complicated by respiratory distress and pulmonary hypertension. ECMO was subsequently performed after failure of surfactant, inhaled nitric oxide, and HFOV. Stabilization was achieved, and the ECMO was weaned off on day 31 of life. This was the first and only documented success of ECMO as a bridging therapy for surgery, yet the authors particularly emphasized the controversy and the doubtful beneficial effects of ECMO in patients with CDH, in particular, the high costs.

A team of Hong Kong cardiothoracic surgeons had recently pioneered a novel diaphragmatic reconstruction technique for recurrent diaphragmatic hernia.[49] A xenograft of dermal collagen implant with a flutter-valve design on the medial neo-diaphragm was designed to allow tension-free repair with an adequate seal while avoiding adjacent organ injury. It is hoped that this new technique will be further extended to cases with a large diaphragmatic defect with an insufficient rim.

Conclusion

Treatments of CDH have evolved from neonatal surgical repair to preoperative stabilization and fetal interventions. Although there have been various treatment successes, controversies remain owing to the complexity of the disease spectrum and the diversity of patients. Furthermore, data from Hong Kong on epidemiology and management appear sparse. We eagerly await future clinical trials, in particular for the Hong Kong population, to address the remaining concerns in treating CDH.

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Conflicts of interest

There are no conflicts of interest.

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Review Article

Chest Care and Respiratory Therapy in Pediatric SARS-CoV-2 Acute Infection

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Abstract

Most pediatric patients infected with severe acute respiratory syndrome coronavirus-2 show mild clinical symptoms, and hospitalization rate in the United States is about 0.05%. Most cases with hospitalization need respiratory therapy to keep saturation and relieve symptoms including tachypnea or chest tightness. According to a recent study, heated humidified high-flow nasal cannula (HHHFNC) is effective treatment opinion and reduce aerosol spreading comparing with noninvasive positive pressure ventilator and other oxygen therapy. Respiratory rate-oxygen index is a useful tool to predict patient's respiratory function whether intubation is needed or not. Besides, chest care with appropriate position change improves respiratory status. Prone position is suggested if no clinical improvement is seen after use of HHHFNC. Earlier decision for intubation prevents sudden deterioration and gets enough time for protective equipment concerned about strong transmission by severe acute respiratory syndrome coronavirus-2.

Keywords: Chest care, heated humidified high-flow nasal cannula, intubation, severe acute respiratory syndrome coronavirus-2

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has infected more than 180 million cases globally since abruption in 2019.[1] Among all infected cases, pediatric patients accounted for 15% case ratio.[2-4] Incidence of SARS-CoV-2 is much lower in pediatric population compared to adult. Besides, current reports show most pediatric cases only present mild symptoms of upper airway infection. The difference in presentation between adult and pediatric is presumed due to the pathway of SARS-CoV-2 entering host cell. SARS-CoV-2 uses spike protein at virus surface to bind angiotensin converting enzyme-2 receptor of host cell. In pediatrics, angiotensin converting enzyme-2 receptor at superficial cell of respiratory tract is immature and the different characteristics decrease infection possibility.[2-4] Common symptoms during disease course include tachypnea and dyspnea. Adequate chest care and oxygen therapy strategy relieve discomfort and correct desaturation. Although clinical symptoms subside and resolve within few days after infection in most cases, moderate-to-severe symptoms with respiratory distress and failure are reported increasingly as infected population increase. A recent study has noticed kinds of therapy strategy and protocol. Except for medical treatment by antivirus agent and anti-inflammation agent to inhibit cytokine reaction, an adequate respiratory treatment in acute phase is important especially for the scenario in the intensive care units. Concerned about air-borne transmission characteristic for SARS-CoV-2 and protection for medical staff. Efficacy and safety from current respiratory treatment are discussed comprehensively. This review article summarizes current consensus for respiratory therapy in pediatric SARS-CoV-2 patients.

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Severity Classification in Pediatric SARS-CoV-2

Like other upper respiratory tract infection, common symptoms after infection with SARS-CoV-2 include fever, cough, rhinorrhea, tachypnea, chest retraction, and sore throat. In progressive cases, cyanosis, low saturation, dehydration, and even hypotension present.[5] Carlotti *et al.* classify severity in pediatric SARS-CoV-2 infection by clinical manifestation and image finding including chest X-ray or chest computed tomography.[6] Severity is defined to five stages from asymptomatic to critical case.[5,7] For all stages, a patient gets positive SARS-CoV-2 polymerase chain reaction finding, then severity progressed from upper respiratory tract infection symptoms to respiratory distress. The most undesirable case present symptoms including respiratory failure, shock, encephalopathy, heart failure, coagulopathy, or multiple organ dysfunction. Besides, we should notice that this disease course could begin from any stage after infection and disease progression may be not in the sequence. Most patients need hospital care if severity progresses to pneumonia. Intensive care unit is usually needed if severity progresses to respiratory distress or shock.[2,6,8,9]

Oxygen Therapy

Oxygen therapy begins with one of the following settings.

a. Oxygen saturation < 94%
b. Tachypnea corrected by age [Table 1]

Tachypnea is defined by World health organization suggestion. Devices' choice includes oxygen nasal cannula, simple mask, non-rebreathing mask, and venturi-mask. Flow rate or oxygen fraction adjusts according to a patient's saturation. If aforesaid setting does not maintain patient's saturation, we advises heated humidified high-flow nasal cannula (HHHFNC).[3,4,9-12]

Comparing to noninvasive positive pressure ventilator (NIPPV), HHHFNC has less spreading range of aerosol. It declines the risk of infection to medical staff. Dispersion distance of aerosol while using ventilator is only one-ninth distance from HHHFNC to NIPPV.[13] Besides, HHHFNC offers better comfort level compared to NIPPV. NIPPV is only suggested to use while qualified negative-pressure isolation room is available.

Respiratory rate-oxygen (ROX) index is used to predict successful rate weaning from high-flow nasal cannula in patients with acute hypoxemic respiratory failure syndrome before. Figure 1 shows its formula. Lots of study show good sensitivity and specificity by using ROX index to decide intubation in adult patients.[14,15] Chandel *et al.*[10] reported in their study outcome by using ROX index at 2, 6, and 12 h after the initiation of HFNC for adult patients. A total of 85.3% sensitivity is noted to maintain a patient's clinical condition with HFNC. Webb *et al.*[16] used the same criteria in patients whose age are lower than 24 months. ROX index <3 is a significant marker to predict failure rate by HHHFNC treatment.

Table 1: Tachypnea definition corrected by age

Age	Rate
<2 months	>60 breaths/min
2–12 months	>50 breaths/min
1–5 years	>40 breaths/min
≥5 years	>20 breaths/min

HHHFNC Setting

Previously, HHHFNC was used mostly in neonatal intensive care unit for preterm and term neonates with the diagnosis of respiratory distress syndrome. Studies showed HHHFNC provided equivalent nasopharyngeal pressure compared to nasal continuous positive airway pressure.[17,18] Flow rate is set at 2–8 L/min for preterm baby and infant. However, flow rate for elder children and calculation formula by body weight has not established generally. Chisti *et al.*[19] treat children younger than 5 years of age with severe pneumonia and hypoxemia by HHHFNC at flow rate 2 L/kg/min (up to the maximum of 12 L/min). Testa *et al.*[20] used HHHFNC in pediatric cardiac surgical patients younger than 18 months at flow rate 2 L/kg/min. Long *et al.*[11] set flow rate 2 L/kg/min for the first 10 kg then 0.5 L/kg/min for every kilogram thereafter at emergent department without serious adverse effect. In our experience, it is safe to set maximal flow rate to 2.5 L/kg/min for infants. If a patient's body weight is over 10 kg, we use the same formula as Long *et al.*[11] used. Flow rate should be set at least 80% of maximal level, whereas, patients diagnosed with SARS-CoV-2 need oxygen therapy and step down gradually according to improvement of clinical symptoms.

$$\text{ROX index} = \frac{\text{SpO2} / \text{FiO2}}{\text{Respiratory rate}}$$

Figure 1: ROX index

Table 2: Mechanical ventilator setting for pediatric SARS-COV-2 patient

Parameter	Value
Tidal volume	6 mL/kg
PIP	Peak inspiration pressure ≤ 30 cmH_2O
PEEP	Setting: 6–7 cmH_2O
I/E ratio	1:3~1:4

PIP = peak inspiration pressure, PEEP = positive end-expiratory pressure, I/E ratio = inspiratory-to-expiratory time

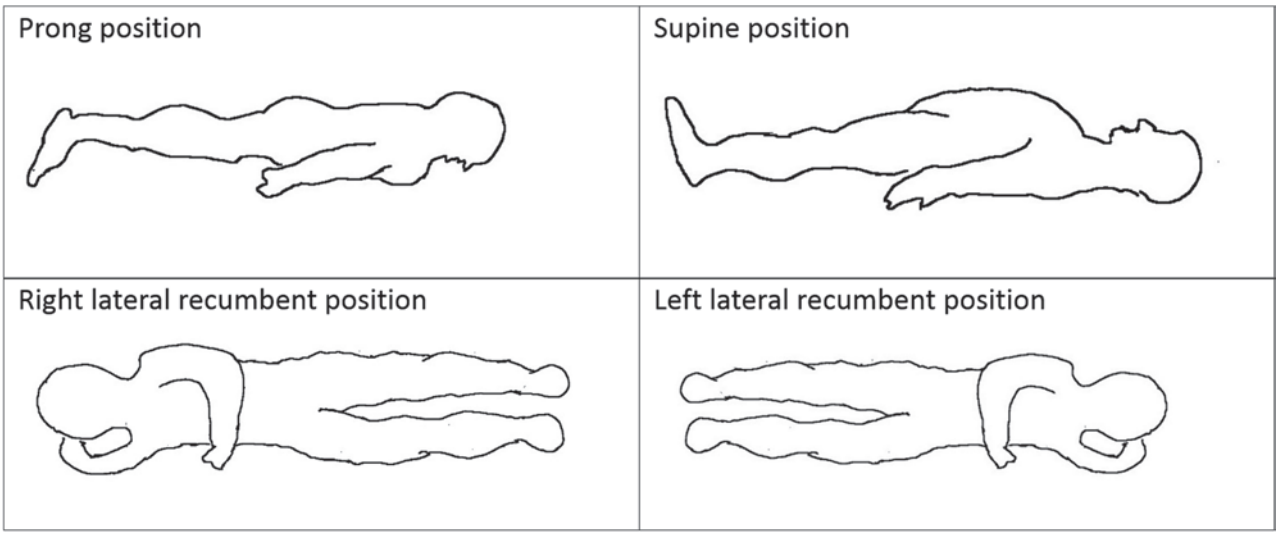

Figure 2: Example for 4 position change

Intubation and Mechanism Ventilator

Current consensus for intubation is "early intubation." It means earlier decision for intubation to prevent an emergent procedure. Infection risk is relatively higher while establishing advanced airway. Thus, enough time of preparation including taking protective equipment, contacting experienced practitioner, and setting ventilator are important. Advice for clinical practice is intubation, whereas saturation could not keep over 94% under high-flow rate of oxygen therapy setting (such as non-rebreathing mask or HHHFNC). In addition to earlier decision-making, both rapid sequence intubation and video laryngoscopy help practitioner successfully intubated in less contacting time, reducing infection risk. We do not suggest to use bag-valve-mask for preoxygenation concerned about aerosol spread. After intubation, mechanical ventilator with virus filter is recommend if device is available.[3,6,15,21-23]

Ventilator setting is similar acute respiratory distress syndrome caused by other etiology. "Gentle ventilator" is the most important principle. Setting target is shown in Table 2. Mild hypercapnia is tolerated (pH > 7.2).

Position

Recent study reported that prone position could improve saturation with high effect especially while PaO_2/FiO_2 < 150 mmHg. While patient's position is supine, the upper alveoli overdistend and lower alveoli collapse. Prone position helps closed alveoli to distend physically and improves oxygenation function.[22-25] We suggest changing patient's position by two following settings:

- Rotate four positions [Figure 2] in a sequence. Each position keeps from 30 min to 2 h.
- Prone position for 4 h then supine position for 1 h, alternately.

Conclusion

For pediatric patients with SARS-CoV-2 acute infection, we need adequate respiratory therapy strategy to maintain patients' condition. We suggest to use non-rebreathing mask and HHHFNC to improved patients' hypoxia because both the devices spread aerosol with limited distance and decreased the infection risk to medical staff. We also advice medical staff should wear complete protective equipment while taking care these patients. If a patient cannot maintain adequate saturation under HHHFNC or non-rebreathing mask, we suggest intubation earlier with video laryngoscope. Prone position is another physical chest care, which helps to improve patients' saturation effectively.

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Conflicts of interest

There are no conflicts of interest.

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Review Article

Revisit on the Use of Bleach Baths as a Standardized Treatment for Atopic Dermatitis

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Abstract

Background: Atopic dermatitis is known to be associated with the colonization of *Staphylococcus aureus* and topical antiseptics, such as bleach bath, have been hypothesized to be effective in the treatment of atopic dermatitis. **Method:** This essay aimed to summarize the current literature on the effectiveness of bleach bath as a standard treatment for patients with atopic dermatitis. The essay also explored the relationship between *S. aureus* colonization and atopic dermatitis with the latest literature to understand the effects of *S. aureus* colonization. **Results:** The current literature seemed to suggest whereas bathing was useful in improving the severity of atopic dermatitis, bleach bath did not offer superior results when compared to water bath. **Conclusions:** Although bleach bath may not be more effective than water bath, bleach bath could still be offered to patients at the discretion of the attending clinician because bleach bath is relatively inexpensive and adverse events are rare.

Keywords: Atopic dermatitis, bleach bath, antiseptic, eczema

Introduction

Atopic dermatitis (AD) is a common inflammatory skin disease that affects around 5%-20% of children, and the prevalence is expected to increase globally.[1] The global prevalence of AD, according to a 2010 estimate, was 229,761,000 and was the leading skin disease cause of DALY (disability adjusted life years) worldwide.[2] Despite the mounting burden of AD, there is no definitive cure for the skin disease.[3] Instead, treatment usually involves the use of moisturizing emollients and topical corticosteroids to alleviate the symptoms.[4] Studies have also hypothesized the causality between AD with predominant *Staphylococcus aureus* colonization in AD skin,[5] where topical antiseptics might be prescribed to patients to reduce *S. aureus* colonization. Among other topical antiseptic methods, bleach baths are commonly recommended to patients due to its accessibility and low cost. However, studies evaluating the efficacy of bleach baths have been inconsistent.[4] The essay will explore the potential relationship between AD and *S. aureus* colonization, in the context of different literature evidences for bleach baths in AD patients. This essay will also discuss the use of bleach baths as a standardized treatment for AD patients in the context of Hong Kong.

Relationship between *Staphylococcus aureus* and atopic dermatitis

A systemic review published in 2016 suggested 70% of the AD patients (5231 patients in 81 studies) carried *S. aureus* on their skin lesions, as compared to 10%-20% in normal controls.[6] The study showed the significant increase in susceptibility of *S. aureus* colonization in AD patients, but what does it mean to patients? In this section, the effects of S aureus colonization on AD patients will be elaborated.

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Severity scores and the density of *S. aureus*

A study published in 2016 concluded that the "*S. aureus* density on both lesional and non-lesional skin appears to be the most important factor associated with AD severity." The study compared the density of *S. aureus* on both lesioned and non-lesioned skin of adult AD patients with the Scoring Atopic Dermatitis (SCORAD) index and Nottingham Eczema Severity Score (NESS). They found that the density of *S. aureus* was a significantly better predictor for both eczema severity scores.[7] Similar findings were also observed in younger patients. Travers *et al.*[8] recruited 59 participants (4 months to 6 years) and concluded that the *S. aureus* CFU/mL was correlated with clinical severity of pediatric patients using Eczema Area and Severity Index (EASI). Older studies also showed a linear relationship between density of *S. aureus* and clinical severity.[9]

An observational study published in 2018 discovered the type 2 inflammatory biomarkers (eosinophil count, tIgE, CCL17 and periostin) were higher in AD patients colonized with *S. aureus* than those without colonization. The severity was also higher in patients colonized with *S. aureus* according to the EASI score.[10] Although the association did not imply cause-and-effect relationship due to the observational nature of the study, it provided potential scientific explanation of the severity.

Severity and the decreased microbiome biodiversity with *S. aureus* dominance

Not only is the density of *S. aureus* associated with increased severity in AD patients, but the microbial diversity also inversely correlates with the disease severity. Byrd *et al.* [11] found the predominance of *S. aureus* was associated with greater severity AD patients, while *S. epidermis* predominance was associated with less severe disease. A 2019 study found the significant reduction in skin microbial community diversity and the prominent abundance of *S. aureus* were "distinctly correlated with disease severity."[12]

Pruritus and staphylococcal enterotoxin

AD is known to induce intense pruritus. IL-31 expression was identified as an itch-inducing factor and triggered intense scratching behavior in multiple animal trials (in rodents, dogs and monkey).[13,14] In AD patients, the expression of IL-31 was found to be significantly overexpressed (in lesioned skin and in blood) than non-pruritic psoriasis patients.[15] In the same study, Sonkoly *et al.*[15] found that, *in vitro*, staphylococcal enterotoxin B (superantigen) was responsible for inducing the expression IL-31. Hence, the significantly increased expression of IL-31 in AD patients due to Staphylococcal enterotoxin B was believed to cause the intense pruritus.[16] IL-31 was also found to be responsible for decreased expression of anti-microbial peptides (AMPs) such as β-defensin 2 and 3 and RNAse7, whereas such a change was not seen in psoriasis patients. Hence, *S. aureus*-induced IL-31 expression also weakened the normal skin barrier and increased *S. aureus* colonization.[17] Thus, *S. aureus* colonization leads to increased IL-31 expression, which leads to pruritus, decreased AMPs, and predisposition to *S. aureus* colonization. In other words, the colonization of *S. aureus* leads to a vicious cycle by inducing IL-31 expression.

Novel treatment for AD using anti-IL-31 receptor antibody (nemolizumab) showed promising results with significant, dose-dependent decrease in EASI, and affected body-surface area when compared with placebo group.[18] This further proven that IL-31 plays a crucial role in AD.

Flares and *S. aureus*

Flares could be associated with the abundance of *S. aureus* colonization on the skin without clinical signs of infection. A study published in 2012 found a selective shift of microbiome during flares to *Staphylococcus* spp., especially for *S. aureus*, in 12 pediatric patients with moderate-to-severe AD patients with an age range of 2-15 years. The mean proportion of *S. aureus* during flares was significantly higher than that detected before and after flares, as well as controls in antecubital and popliteal creases. Similarly, the proportion of *S. epidermidis* also increased during flares but to a lesser extent when compared with *S. aureus*. On the other hand, there was a selectively decreased in Streptococcus, Corynebacterium, and Propionibacterium.[19] The preferential increase in *S. aureus* during flares might suggest special correlation of flares and *S. aureus*, and provided important insights for future etiology studies on acute flares of AD.

Literature Review

Recent meta-analysis and systemic reviews were used for the evaluation of the use of bleach baths as a treatment for AD patients as they give the best possible precision and power by pooling multiple studies. Searches were conducted on Pubmed, EMBase, and Google scholar, and identified three systemic reviews since 2010. They were published in 2010 (Cochrane),[20] 2017 (Annals of Allergy, Asthma and Immunology),[21] and 2019 (Cochrane),[22] respectively. The 2019 Cochrane review by George *et al.* was an update of the 2010 Cochrane review by Bath-Hextall *et al.*[21]; hence, I would focus on the latest 2019 Cochrane review and the 2017 systemic review. The 2017 systemic review included four RCTs for evaluation, whereasthe 2019 Cochrane review included five RCTs (three of which are included in the 2017 study). Findings from the two studies were summarized with focus on the severity of AD or change of quality of life, *S. aureus* density (to assess its correlation with change in severity), and adverse events associated with bleach baths.

In the 2017 systemic review, it included four RCTs comparing the intervention of bleach baths (one study compared the use of oral and topical antibiotics with bleach against control group with oral and topical antibiotics with water bath only; another study compared bleach baths with topical corticosteroids and water baths with topical corticosteroids) with the control group (water bath). All the four studies reported a significant reduction in AD severity with bleach on at least one time point, but only two found significantly greater decreases with bleach bath. One study found no difference between control and intervention groups, and interestingly, one study found greater decreases with water baths. In pooled analysis (under random effect regression model), the review found no significant difference in the mean decrease in Eczema Area and Severity Index (EASI) and body surface area (BSA) between bleach group and water in AD patients at week 4 when compared with baseline. In terms of *S. aureus* density, all four studies found no significant difference in the decrease of *S. aureus* colonization between groups. Adverse events were rare, including itch, burning and stinging sensation, etc., and no significant difference between intervention and control group was observed.[21]

The 2019 Cochrane systemic review included five RCTs comparing bleach baths (one study used bleach plus topical corticosteroids vs. water plus topical corticosteroids) against control (four with water baths and one with bath emollient). In terms of the reduction of AD severity, the pooled analysis of the decrease in EASI showed a non-significantly lower EASI score at one month in bleach group and the placebo group. In terms of quality of life (QoL), one study reported probably little or no difference in QoL improvement (CDLQI) between groups. In terms of the quantification of *S. aureus*, three studies (which were reported in the 2017 systemic review) reported a decrease in *S. aureus* but no statistically significant difference between groups. In terms of adverse events, there were three participants who withdrew from the study due to worsening itch (2) and dryness (1), two of them were from the placebo group and one of them was from intervention groups. Other minor adverse events included burning/stinging sensation, dry skin, erythema, dizziness, urticaria, and oozing. It should be noted that two out of the four RCTs that recorded adverse events reported no adverse events.[22]

Both systemic reviews were limited by different biases, such as selection bias (single-center trials) and lack of adequate blinding (some are single-blinded), which led to performance bias, etc. Patients recruited were also not standardized, with inconsistent inclusion criteria, such as age (children vs. adults), infective status, diagnostic criteria, degree of severity (all patients were moderate-to-severe AD but were defined under different guidelines, e.g., IGA, R&L, SCORAD, etc.). Stratification should also be ideally conducted, for example, age, sex, socioeconomic background, etc. Heterogeneity in study design also made the review difficult to compare, such as study duration, study intervention, instructions to intervention and placebo groups, frequency, and duration of bath (biweekly vs. triweekly). Outcome assessment was also not standardized; however, different severity scores and assessment methods used made it difficult to perform pooled analysis with limited data available in each scoring system. The quality of evidence from the studies also varied, ranging from very low quality to moderate quality in the Cochrane review according to GRADE Working Group grades of evidence. As Egger *et al*.[23] affectionately put it: "garbage in, garbage out," the conclusion drawn from poor evidences could lead to biases. The number of RCTs for evaluation were also very limited, and the long-term efficacy is yet to be studied.

Chopra *et al*.[24] concluded in the 2017 systemic review that "while bleach baths are effective in reducing AD severity, they do not appear to be more effective than water bath alone." This was further reinforced by the results of the 2019 Cochrane systemic review's results. Interestingly, frequent bathing was not recommended according to the 2016 guideline, but the findings in two systemic reviews evinced that bathing (with or without bleach) would lead to an improvement in severity. In terms of *S. aureus* density, both reported no significant difference in the decrease in density of *S. aureus* between groups, which may explain insignificant difference in the decrease in severity in both the intervention and controlled groups. However, it is surprising that water bath was as effective as bleach in reducing colonization albeit conventional wisdom. Serious adverse effects were rare with few participants quitted, and the most common adverse effects are burning/stinging sensation. Furthermore, Chopra *et al*.[21] concluded that there was no significant difference in adverse events between bleach and water baths. In other words, the risk of adverse events due to bleach baths was statistically the same as the risk of adverse events due to water baths, which is presumably performed by patients daily. Hence, it is reasonable to conclude bleach bath is a safe and well-tolerated intervention.

Discussion

As both water and bleach baths are effective in reducing the severity of AD patients, so which one should be recommended? This is question would be explored in this section.

Adverse events are usually mild in RCTs (usually skin irritation), and there is no significant difference in adverse events between intervention group and control group. Bleach is generally considered safe to use, especially when diluted. However, Chopra *et al*.[21] raised a few concerns about bleach, including ocular exposure to bleach, skin irritation (worsening itch in AD), and that fumes of bleach

might cause acute exacerbations of asthma and stains on towels and clothing. The explanation of procedures of bleach baths would be time consuming as well. These concerns are valid, but such events are avoidable with care (e.g., avoid giving bleach for asthmatic patients). Furthermore, to prevent these events, we would need to advise patients to completely avoid contact with bleach (a common household item) and it seems unwise to give such advice due to these uncommon and avoidable events. However, it does take up precious time to explain the procedures, especially in the time-constrained consultation sessions in Hong Kong. However, the tedious task can be outsourced to technology, such as videos or apps, for the explanation of protocol, especially when the procedures of bleach baths should be standardized.

In terms of practicality, bleach is reasonably inexpensive, especially considering only ½ cup is needed for a full bathtub. Hydroquinone-based bleach liquid are also found in most supermarkets in Hong Kong (HK). However, the living conditions of most public hospital patients should be considered as they might not have a bathtub at home (e.g., public housing or subsidized housing). The availability of bathtubs might pose a unique predicament in populated cities such as HK. Other antiseptic techniques that do not require bathtubs, for example, chlorhexidine or topical antibiotics, could be alternatives, but they would certainly cost more than bleach. The extensive use of topical antibiotics as a standard treatment for AD patients may also predispose the emergence of antibacterial resistance.[25] Baby tub could be used instead of a full tub, especially for pediatric AD patients. However, for adults, especially extensively affected AD patients, the procedure will be significantly more time-consuming and repetitive in baby tubs. The compliance of adult AD patients with these preparations is not going to be ideal, especially in moderate-to-severe patients. However, considering the bleach bath is usually bi-weekly (used in 3 out of 4 RCTs in 2017 systemic review), the inconvenience to patients might be tolerable. Furthermore, given the significant reduction in severity observed in the two systemic reviews, compliance might increase as patients see observable improvement.

Regarding acute atopic dermatitis flare-ups, there is no RCT using atopic dermatitis solely as a treatment method that could be found. This may require further research effort especially when previous study has found preferential increase in the portion of S. Aureus during acute flare up of atopic dermatitis.[19]

Conclusion

There is also limited evidence suggesting superior outcomes from bleach baths when compared with water bath; however, the RCTs included in the systemic reviews are flawed with biases and small number of participants and studies. Furthermore, in Chopra's systematic review, all four studies showed improvements with two groups suggesting "significantly greater or greater" decrease in AD severity. Given bleach is inexpensive, well tolerated, and with avoidable adverse events, until larger scale, standardized, long-term RCTs are available for evaluation, bleach bath should be a standard treatment for AD to control *S. aureus* colonization in pediatric and adult patients.

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Conflicts of interest

There are no conflicts of interest.

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LIBERTY ASTHMA QUEST Study Design[3]: 1902 patients who were 12 years of age or older with uncontrolled asthma were randomly assigned in a 2:2:1:1 ratio to receive add-on subcutaneous DUPIXENT at a dose of 200 or 300 mg every 2 weeks or matched-volume placebos for 52 weeks. The primary end points were the annualized rate of severe asthma exacerbations and the absolute change from baseline to week 12 in the forced expiratory volume in 1 second (FEV_1) before bronchodilator use in the overall trial population. Secondary end points included the exacerbation rate and FEV_1 in patients with a blood eosinophil count of 300 or more per cubic millimetre. Asthma control and DUPIXENT safety were also assessed.

EOS, eosinophils; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid ; OCS, oral corticosteroid; Q2W, once every 2 weeks; SOC, standard of care.

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Presentation: Dupilumab solution for injection in a pre-filled syringe with needle shield. **Indications:** Atopic Dermatitis (AD): Moderate-to-severe AD in adults and adolescents ≥12 years who are candidates for systemic therapy; severe atopic dermatitis in children 6 to 11 years old who are candidates for systemic therapy. Asthma: In adults and adolescents ≥12 years as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment. Chronic rhinosinusitis with nasal polyposis (CRSwNP): As an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control(for 300mg) **Dosage & Administration:** Subcutaneous injection. AD adults: Initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week. AD adolescents(12-17y/o): Body weight <60 kg- initial dose of 400 mg (two 200mg injections), followed by 200 mg every other week. Body weight ≥60 kg- same dosage as adults. Dupilumab can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, e.g. face, neck, intertriginous and genital areas. Consider discontinuing treatment in patients who have shown no response after 16 weeks. AD Children(6-11y/o): Body weight 15Kg~<60 kg- initial dose of 300mg on Day 1 follow by 300mg on Day 15, then 300mg every 4 weeks. Body weight ≥60 kg- same dosage as adults. * The dose may be increased to 200 mg Q2W in patients with body weight of 15 kg ~ < 60 kg based on physician's assessment. Asthma: Initial dose of 400 mg, followed by 200 mg every other week. For patients with severe asthma and on oral corticosteroids or with severe asthma and co-morbid moderate-to-severe AD or adults with co-morbid severe CRSwNP- initial dose of 600 mg, followed by 300 mg every other week. Patients receiving concomitant oral corticosteroids may reduce steroid dose gradually once clinical improvement with dupilumab has occurred. The need for continued dupilumab therapy should be considered at least annually as determined by a physician. CRSwNP: for adult patients initial dose of 300 mg followed by 300 mg given every other week. Consideration should be given to discontinuing treatment in patients who have shown no response after 24 weeks of treatment for CRSwNP. Some patients with initial partial response may subsequently improve with continued treatment beyond 24 weeks. If a dose is missed, administer it asap and thereafter, resume dosing at the regular scheduled time. **Contraindications:** Hypersensitivity to dupilumab or any of the excipients. **Precautions:** Safety and efficacy in children <6 years or <15kg not been established. Not be used to treat acute asthma symptoms, acute exacerbations, acute bronchospasm or status asthmaticus. Do not discontinue corticosteroids abruptly upon start of dupilumab. Reduction should be gradual and performed under supervision of a physician; it may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy. Biomarkers of type 2 inflammation may be suppressed by systemic corticosteroid use. If systemic hypersensitivity reaction occurs, discontinue dupilumab and initiate appropriate therapy. Be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in patients with eosinophilia. Treat pre-existing helminth infections before initiating dupilumab. If patients become infected while receiving dupilumab and do not respond to anti-helminth treatment, discontinue dupilumab until infection resolves. Patients who develop conjunctivitis and keratitis that does not resolve following standard treatment should undergo ophthalmological examination. AD patients with comorbid asthma should not adjust or stop asthma treatments without consultation with physicians. Carefully monitor patients after discontinuation of dupilumab. Do not give live and live attenuated vaccines concurrently with dupilumab. Patients should be brought up to date with immunisations before starting dupilumab. **Drug Interactions:** Immune responses to TdaP vaccine and meningococcal polysaccharide vaccine were assessed. Patients receiving dupilumab may receive concurrent inactivated or non-live vaccinations. **Pregnancy and lactation:** Should be used during pregnancy only if potential benefit justifies potential risk to foetus. Unknown whether dupilumab is excreted in human milk or absorbed systemically after ingestion. Decision must be made whether to discontinue breast-feeding or dupilumab taking into account benefit of breast feeding for the child and benefit of therapy for the woman. **Undesirable effects:** Most common adverse reactions reported- injection site reactions, conjunctivitis, oral herpes and eosinophilia. Safety profile observed in adolescents consistent with that seen in adults. For other undesirable effects, please refer to the full prescribing information. **Preparation:** 2 x 300mg/2ml in pre-filled syringe with needle shield, 2 x 200mg/1.14ml in pre-filled syringe with needle shield. **Legal Classification:** Part 1, First & Third Schedules Poison **Full prescribing information is available upon request.** API-HK-DUP-22.06

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