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“Nature does not hurry, yet everything is accomplished.”

Lao Tzu, (b. 6th century BCE)
Ancient Chinese philosopher

CONTENTS

Editorials

341 Hepatitis—Cure and Prevention

Chee Kiat [Tan](#)

343 Paediatric Services: The Future Direction

Daniel YT [Goh](#)

Original Articles

346 A Comparison of the Short-term Morbidity and Mortality Between Late Preterm and Term Newborns

Justin HT [Tan](#), Woei Bing [Poon](#), Wee Bin [Lian](#), et al

355 Neonatal and Paediatric Extracorporeal Membrane Oxygenation (ECMO) in a Single Asian Tertiary Centre

Angela SH [Yeo](#), Jin Ho [Chong](#), Teng Hong [Tan](#), et al

362 Validation of the Paediatric Hearing Impairment Caregiver Experience (PHICE) Questionnaire

Lynne HY [Lim](#), Ling [Xiang](#), Naomi LY [Wong](#), et al

371 Hearing Loss in Newborns with Cleft Lip and/or Palate

Enrica EK [Tan](#), Karen YM [Hee](#), Annie [Yeoh](#), et al

Commentary

378 Internet Addiction in Young People

Say How [Ong](#), Yi Ren [Tan](#)

Please see inside Contents for the full list of articles.

Hepatitis—Cure and Prevention

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World Hepatitis Day has been celebrated annually on 28 July since 2008. This day was chosen as it was the birthday of Professor Baruch Blumberg who won a Nobel Prize in 1976 for his discovery of the hepatitis B virus (HBV). World Hepatitis Day is an official World Health Organisation (WHO) awareness day, one of only 4 official disease-specific world health days endorsed by WHO (the other 3 being World Tuberculosis Day, World Malaria Day and World AIDS Day). This year marks the 7th World Hepatitis Day.

Why a World Hepatitis Day? Hepatitis is a preventable chronic disease and yet it is the world's 8th biggest killer with the same mortality as the human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS), but without the equivalent level of awareness and global political resolve to contain the disease unlike that for HIV/AIDS.¹ There are 240 million people in the world with chronic hepatitis B infection and 185 million with chronic hepatitis C infection.^{2,3} World Hepatitis Day is pertinent in Singapore as chronic hepatitis B and C infections are significant diseases locally with important healthcare sequelae of liver cirrhosis, end-stage liver disease and hepatocellular carcinoma (HCC).

Besides the usual hepatitis B and C campaign staples regarding modes of acquisition and prevention, and the need for regular medical follow-up, when one discusses about hepatitis this year, the limelight will inevitably be on chronic hepatitis C, in particular the delicate issue of access to care. Sofosbuvir is a "miracle" oral drug for chronic hepatitis C infection belonging to the new class of oral hepatitis C direct-acting antivirals (DAAs). It has recently been approved by the drug authorities in the United States and Europe i.e. the Food and Drug Administration (FDA) and European Medicines Agency (EMA) respectively. This drug has revolutionised the landscape of chronic hepatitis C treatment from a 24 to 48 week regime of weekly pegylated interferon (Peg-IFN) injections and thrice-daily

oral medications with a cure rate of up to 75% in the most difficult to treat genotype 1 to current sofosbuvir once daily together with ribavirin twice daily and weekly Peg-IFN injections for just 12 weeks to yield an unprecedented superior cure rate of 89%.^{4,5} There is more in the pipeline with an upcoming sofosbuvir-ledipasvir (another new DAA) once-daily monotherapy combination pill that gives a cure rate of 99% after 12 weeks of treatment.⁶ It is difficult to imagine that we now have a once-daily all-oral monotherapy bereft of significant adverse effects that will give a near total cure rate in just 12 weeks of a disease that hitherto required weekly injections that had multiple side effects for up to 48 weeks in return for a cure rate of only up to 75%. This combination pill is on the threshold of approval by FDA which is expected in the fourth quarter of this year.

However, the cost of a course of treatment with sofosbuvir is USD 80,000 which works out to about SGD 1000 a tablet. Furthermore, we do not know the price of the superior sofosbuvir-ledipasvir combination pill which will obviously be higher than sofosbuvir alone. Paradoxically, nearly 90% of the approximately 185 million chronic hepatitis C sufferers worldwide reside in low- and middle-income countries that are unable to afford these new wonder drugs.³ Thus the irony is that new superbly efficacious drugs for chronic hepatitis C will not be used in places that require them the most because of the high cost of the medications. This situation is reminiscent of the time when new effective drugs for HIV were first made available.

Unlike the situation with chronic hepatitis C, there is little significant recent treatment advancement in chronic hepatitis B. Satisfactory once-daily oral antiviral monotherapy treatment for chronic hepatitis B at a reasonable price has been around for some time. However, there are still targets to be achieved in the prevention of hepatitis B i.e. in hepatitis B vaccination programmes. Hepatitis B vaccination is highly efficacious and more importantly,

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it has been shown to reduce the incidence of HCC.⁷ Hepatitis B vaccine is a true anticancer vaccine. In 2011, 180 countries have included hepatitis B vaccination in their routine vaccination schedules and achieved a coverage of about 80%.⁸ However, the coverage is not uniform worldwide, with only 58% of the countries in the African region reporting the existence of a hepatitis B control and prevention (vaccination) programme. More needs to be done globally for the prevention of hepatitis B infection in view of the availability of a highly efficacious vaccine against hepatitis B. Cost of vaccine and poor infrastructure for delivery of vaccination are major obstacles to achieving better hepatitis B vaccination coverage.⁸

So, as we celebrate and commemorate this year's World Hepatitis Day on 28 July 2014, we should be mindful of the two basic pillars of any disease management – prevention and cure, and what needs to be done in the arena of hepatitis. We have the tools viz hepatitis B vaccine for prevention of hepatitis B infection and new super-efficacious DAA agents for cure of hepatitis C infection but the devil is in how to get them realised at the ground levels where they are most needed.

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Paediatric Services: The Future Direction

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Medical care in Singapore has progressed significantly over the past few decades; we have achieved a world class healthcare system with a standard of care comparable with the best in the world in many disciplines. Singapore's healthcare system is designed to ensure that everyone has access to different levels of healthcare in a timely, cost-effective and seamless manner. Singapore has achieved several notable firsts in the world in the arena of medical care but medical excellence is not just about doing cutting edge research and procedures, but also about doing the common things well.

Changing trends of diseases in childhood has seen infectious diseases make way for chronic diseases such as childhood malignancies and other chronic illnesses to be the major causes of death in children today. The top causes of disease burden in childhood in Singapore today include autism spectrum disorder, asthma and attention-deficit hyperactivity disorder (ADHD).¹

With a rapidly ageing population, there is a justifiable increase in the focus on healthcare for the elderly today. It is however important to remember that how we care for the child today will impact on his well-being tomorrow as an adult. The positive impact of paediatric care on the future health of the adult population reinforces the importance of investing in excellent paediatric care today for long-term benefits and future cost savings.

The paediatric services of the future will have to address the changing needs, expectations, as well as the increasing affluence and demands of the population.

Integrated Care in Paediatrics

Integrated care is centred on the patient's needs and its service delivery principle focuses on making the patient's journey through the system of care as simple and smooth as possible. It presents to the patient a health care provision that is personalised and seamless, and is particularly beneficial for those patients whose current care provision is disjointed and fragmented, especially those with multiple comorbidities.²

With increasing chronic disease burden and complex conditions in childhood, there is a growing recognition of fragmentation of healthcare services that is aggravated by the rapidly emerging trend of increasing subspecialisation—a phenomenon seen by our adult counterpart years earlier. Without integration, healthcare performance suffers—patients get lost, needed services fail to be delivered or are delayed, quality and patient satisfaction decline, and the potential for cost-effectiveness diminishes. Integration allows for greater efficiency and effectiveness, less duplication and waste, and better coordination and continuity of care.

Medical and technological advancements have improved the survival of even the very premature and critically ill; this has however resulted in an increase in disabled children with complex healthcare needs. With this are the social, financial and emotional stresses that commonly accompany childhood disability. Parents, siblings and the children themselves struggle to experience a normal family life as time-consuming and sometimes distressing medical and therapeutic routines are regularly required. Social support, advice, information and respite from the routines of care are much needed. Medical care itself, which often involves multiple specialty disciplines and allied health fields, add on to the complexity of care and the burden on the caregivers.³ Unfortunately, the latter is often fragmented between different services and professionals. The major tasks of accessing and coordinating these different sources of help are additional sources of stress. Integrated care programmes will thus help facilitate coordination of services and resources, and enable more convenient and efficient care.

Another important and increasingly important group of patients is the growing numbers of adolescents with chronic conditions. Transition from paediatric to adult care must consider the patients' and caregivers' needs and expectations. Integrated care programmes can better package services to facilitate convenience and achieve greater acceptance hence improving adherence, translating to better and more successful clinical outcomes.⁴

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Child-friendly and Family-centred Services and Facilities

The clinic or hospital visit need not (and should not) be scary or unpleasant; it is important that paediatric facilities be child-friendly and not just generic-looking spaces. This extends beyond just cartoon murals or provision of a play corner, but encompasses the overall design and layout, fittings, atmosphere, environment and ambience. Work processes, communications and procedures should be made conducive to the child and family. The physical, psychological and emotional needs of the child and their families should also be taken into consideration. This would enhance the child's (and families') acceptance of medical therapy which translates to better compliance and ultimately enhancing the outcomes of care.⁵

More than just the child, paediatric care actively involves the family unit and caregivers. Through close partnership, respect, and negotiation between the healthcare team and caregiver, the desired outcome is a successful collaboration that enhances communication and thus helps the family and caregivers navigate the healthcare system effectively.⁶ This also reduces the level of anxiety and stress (and fear of the unknown), and improves the overall level of satisfaction.⁷ Giving more attention to the voices of parents and children goes a long way to ensure that their priorities and needs are addressed and enables optimal care in the context of family and community.^{8,9}

Supporting the family and caregivers during the course of the child's illness is essential; it enables the parents to be well rested and to be available by the child's side to provide reassurance and support. This will aid the recovery process and also help strengthen the parent-child bonding. These provisions can range from residential facilities for caregivers (e.g. Ronald McDonald House), to programmes providing psychological support as well as physical sustenance (e.g. refreshments and meals), within a family-centred and family-oriented framework. The love and care of the family during such difficult times can certainly make a significant difference to the child in aspects no amount of medicine can; truly it is love that heal wounds and knits the family together.

Towards Ambulatory Care

When a child is hospitalised, the parents or caregivers and family are significantly impacted. Keeping the child out of the hospital reduces the hospital resource utilisation, increases convenience for the child and the family (reduces or avoids disruption to the family unit), improves quality of life, reduces the incidence of healthcare-related infections and also reduces direct and indirect costs. Hence a redesign of the care delivery with a focus on ambulatory versus

inpatient care is especially beneficial in paediatrics. There is growing evidence such ambulatory care is cheaper, and yet equally safe and effective compared to traditional inpatient care.¹⁰

The care of technologically-dependent children with complex medical needs (including children on ventilatory assistance, continuous tube feeding, parenteral nutrition) can be managed within the home environment. Medical care can be performed by the home-care team, reducing the strain on already overburdened parents and caregivers, and reducing the risk of deterioration during transfers. Prompt and proper medical assessment and intervention by the visiting home-care team can often reduce the need for re-hospitalisation, and hence reduce total cost and burden on limited inpatient healthcare resources.

With the fast growing demand for hospital beds in Singapore from both an ageing and growing population, the current hospital bed crunch highlights the importance of keeping patients healthy and out of hospital, and for sick patients to remain stable and be cared for at home; this is something that is especially relevant in paediatrics.

The Human Touch

At the heart of paediatric care provision is the healthcare team: the doctors, nurses, allied health workers, educators, researchers and administrators. The team-based model of paediatric care seeks to provide high quality, cost-effective care by minimising duplication of clinical effort and promoting the appropriate and timely use of all healthcare providers and resources on the team.¹¹ Each member of the team should embrace their responsibility to educate patients, their families, and their caregivers; even policy makers, the media, and the public on common childhood conditions, health promotion, disease prevention, and child safety. The training of healthcare providers must also keep pace with the changing needs, inculcating a strong desire to serve patients, demonstrate empathy and compassion as well as good verbal and nonverbal communication skills.

Children Are Not Just Small Adults

Just as medical assessments and treatments differ significantly between a child and the adult, applying the four E's—engagement, empathy, enlistment, and education—to paediatric patients and their families requires a much different approach than with adults. Paediatric medical interaction has unique aspects that differ in structure, format, and content from adult patient medical communication. The paediatric facility, environment and approach to care are also necessarily different and the healthcare delivery models must adapt to the changing needs and expectations of the child, his/her family and the community.

Traditional organisation of medical care has been very much provider-centred. We need a different paradigm of patient- and family-centredness to give our patients our best. This needs much hard work, hard thinking and rethinking; but isn't this what good medical care is all about?

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A Comparison of the Short-term Morbidity and Mortality Between Late Preterm and Term Newborns

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Abstract

Introduction: Late preterm babies are defined as those born between 34 to 36 completed weeks. There has been a recent increased awareness that this group of babies has a higher incidence of morbidity as compared to term babies. The aim of this study was to evaluate the short-term morbidities occurring in this group of babies managed in the neonatal unit at Singapore General Hospital (SGH). **Materials and Methods:** A retrospective study was done of babies managed in the neonatal unit at SGH from January 2005 to December 2008. Maternal, perinatal and neonatal data were obtained from the departmental database. The outcomes of late preterm infants were compared with term infants. **Results:** A total of 6826 babies were admitted. Ten percent (681 out of 6826) of babies were late preterm babies, making up 63% (681 out of 1081) of all preterm babies. Late preterm babies had significantly greater need for resuscitation at birth. They also had statistically significant increased risks of developing hyaline membrane disease (2.5% vs 0.1%), transient tachypnoea of the newborn (TTN) (8.1% vs 1.7%), pneumonia (7.0% vs 2.8%), patent ductus arteriosus (PDA) (4.3% vs 1.1%), hypotension (0.7% vs 0%), apnoea (3.7% vs 0%), gastrointestinal (GI) bleeding (1.5% vs 0.3%), polycythaemia (2.2% vs 1.0%), anaemia (3.4% vs 1.2%), thrombocytopenia (3.2% vs 0.6%), hypoglycaemia (6.6% vs 1.7%), neonatal jaundice requiring phototherapy (41.1% vs 12.2%) and sepsis (1.7% vs 0.6%). **Conclusion:** Late preterm infants are indeed a vulnerable group of infants with significant morbidities that need to be addressed and treated. Despite their relatively large size and being almost term, the understanding that late preterm infants are not similar to term infants is important to both obstetricians and neonatologists.

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Key words: Moderate preterm, Near term infants, Outcome, Prematurity, Preterm birth

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A Comparison of the Short-term Morbidity and Mortality Between Late Preterm and Term Newborns

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Abstract

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Introduction

Late preterm infants are defined as those who are born between the gestational age (GA) from 34 weeks and 0/7 days through 36 weeks and 6/7 days.

Worldwide, late preterm birth has increased since the last decade. In the United States (US), there are approximately 500,000 preterm births annually.¹ These account for 12.5% of all live births in the US every year. Of these preterm births, three-quarters are late preterm births.¹ The rate of late preterm birth in the US has increased nearly 15% since the last decade. The World Health Organization (WHO) reported an estimated 12.9 million preterm births

worldwide annually.² Out of these, 54% occurred in Asia.² Therefore, we believe that Asia has the largest group of late preterm infants worldwide. However, to date, little has been reported with regards to the outcome of this group of infants in Asia. It is important to know whether we observe similar morbidity and mortality amongst our late preterm infants in Asia as compared to those in other continents. There are various reasons for the increase of late preterm births. The increase is largely due to the increase in obstetric interventions, either as a result of pregnancy-related complications or maternal pre-existing medical

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conditions. The increase in obstetric interventions is also due to the advancement in obstetrical technology resulting in early detection and surveillance of foetal abnormalities or foetal distress, consequently leading to earlier delivery of the baby. The advancement of reproductive technologies over the decade has also contributed to the increase of late preterm births due to the increase of multiple pregnancies.

Why have late preterm infants become a huge concern for many perinatologists, obstetricians and neonatologists worldwide over the last decade? We observe vast publications on late preterm infants over the last 5 years. These publications do not merely focus on the morbidity or mortality during the neonatal period but also the long-term outcome of this group of infants. Why are late preterm infants more vulnerable as compared to their 'term' infants? Late preterm infants are believed to be vulnerable due to the immaturity of their body system, either physiologically or metabolically. The decision to deliver should be prioritised in delivering babies who are physiologically mature and capable of transition to extrauterine life without compromising the health of the mother. Hence, the decision to deliver early should always be made conscientiously after balancing the risks of prematurity versus those of continuing the pregnancy.

The aim of this study was to ascertain the incidence of late preterm births in our institution, to determine the maternal, antenatal and intrapartum factors associated with late preterm births as well as to compare the neonatal morbidity and mortality of the late preterm babies with the term infants.

Materials and Methods

Singapore General Hospital (SGH), established in 1821, is a public restructured hospital in Singapore with 1600 beds, providing mainly adult tertiary care services. A retrospective review of infants managed in the neonatal unit at SGH between 1 January 2005 to 31 December 2008 was performed. The infants were identified from the departmental database, and relevant antenatal, intrapartum and postnatal data were retrieved. The departmental database was approved by SingHealth Centralised Institutional Review Board (CIRB).

For all infants managed in our unit, GA was confirmed at the time of delivery. GA was usually based on the mother's last menstrual period (LMP) together with early ultrasonographic dating information in the first trimester. All preterm infants (less than 37 weeks GA), with the exception of infants conceived by in vitro fertilization (IVF), were scored clinically using the Dubowitz or modified Ballard score. GA scoring was also done if the mother's LMP was uncertain and there was no early dating scan done or there

was clinical suspicion about the GA of the infant. If there was a discrepancy of more than 2 weeks between the scored dates and the maternal dates, the GA determined by scoring was taken, after confirmation by an independent scorer.

For the analysis, infants were categorised as late preterm infants (those between 34 to 36 weeks GA) and term infants (those between 37 to 41 weeks GA). Gestational size was classified based on revised intrauterine growth curves by Kitchen et al.³ Small for gestational age (SGA) was defined as birth weight for GA below the 10th percentile. Appropriate for gestational age (AGA) was defined as birth weight for GA below the 10th to 90th percentile. Large gestational age (LGA) was defined as birth weight for GA above the 90th percentile. Factors which were compared between the 2 groups included general characteristics like birth weight, GA and ethnicity, maternal factors such as parity, pre-existing medical conditions and obstetric complications and intrapartum factors like mode of delivery, level of resuscitation and Apgar score. Neonatal outcomes studied included various respiratory outcomes and the level of respiratory support required, cardiovascular, neurological, gastrointestinal (GI), haematological, metabolic and infective morbidities as well as birth-related injuries. These outcomes included pneumonia, feeding intolerance, GI bleeding, necrotising enterocolitis (NEC), anaemia, thrombocytopenia, polycythaemia, hypocalcaemia, hypoglycaemia, soft tissue injuries etc. Pneumonia was diagnosed based on the presence of clinical features and radiological evidence consistent with pneumonia for which the infant was treated with a course of antibiotics. Feeding intolerance included infants who had feeding difficulties like vomiting and high gastric residuals. GI bleeding included both upper and lower GI bleeding with evidence of blood in the gastric aspirate, vomitus or stool. NEC was diagnosed using the Modified Bell Staging Criteria for Necrotizing Enterocolitis. Anaemia was defined as haemoglobin less than 14 g/dL. Thrombocytopenia was defined as the platelet count of less than 150,000/mm³. Polycythaemia was defined as a haematocrit greater than 65%. Hypocalcaemia was defined as a total serum calcium concentration <2 mmol/L or an ionised calcium concentration <1 mmol/L. Hypoglycaemia was defined as a plasma glucose level ≤2.5 mmol/L. Soft tissue injuries included abrasions, lacerations, etc. while scalp injuries included those with cephalhaematomas, subaponeurotic bleeds, etc.

We also compared the resource usage required such as need for lumbar puncture, umbilical vessel catheterisation and central venous catheterisation as well as highest level of care and length of hospitalisation stay.

All data analysis was conducted using the Statistical Package for the Social Sciences (SPSS) software version 16 (SPSS, Chicago, IL). Differences between categorical

variables were analysed using the Chi-square test or Fisher's exact test. Continuous variables were compared using the student's *t* test for normally distributed data and Mann-Whitney *U* test for nonparametric data. A *P* value of less than 0.05 was considered significant.

Results

Between 1 January 2005 and 31 December 2008, a total of 6826 babies managed at SGH were admitted to one of these units — nursery, high dependency or intensive care unit. Out of these babies, 5721 (83.8%) were term infants, 1081 (15.8%) were preterm and 24 (0.4%) were post-term. Of the preterm babies, 681 (63%) were late preterm (Fig. 1).

The mean birth weight for late preterm infants was significantly lower compared with the term infants (2545 ± 470 grams vs 3134 ± 409 grams, $P < 0.001$) (Table 1).

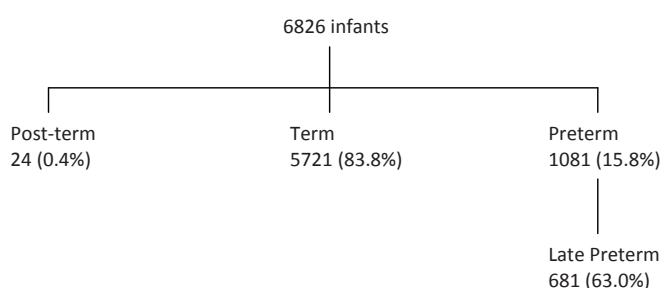


Fig. 1. Concept map showing the cohort profile.

There were significantly fewer late preterm infants who were appropriate for GA (85% vs 88.6%, $P = 0.007$). More late preterm infants were either SGA or LGA compared with the term infants (10.1% vs 8.8%, $P = 0.001$ and 4.8% vs 2.6%, $P = 0.001$ respectively). There were slightly more males in the late preterm group.

Out of the late preterm babies, 36.4% of them were born to mothers who had parity of 3 and above compared to 31.8% who were born to mothers who were primigravida. In contrast, more term babies were born to primip mothers compared to those born to mothers who had parity of 3 and above, 43.7% vs 23.8% ($P < 0.001$) respectively.

Mothers with pre-existing medical problems of any type were noted to deliver earlier. Out of the late preterm babies, 43% of them were born to mothers with pre-existing medical problems of any type compared to 27.4% in term babies (Table 2). Pre-existing hypertension and diabetes as well as pre-eclampsia and gestational diabetes were significantly more prevalent in mothers of late preterm infants. Pre-eclampsia and gestational diabetes mellitus (GDM) were the 2 most frequently reported antenatal conditions among mothers of late preterm and term infants.

Pregnancy conceived via IVF was associated with significantly higher incidence of late preterm deliveries as compared to term deliveries, 10% vs 2% ($P < 0.001$). Other antenatal conditions such as oligohydramnios, polyhydramnios and antepartum haemorrhage were significantly more common with more late preterm births.

Table 1. General Characteristics

	Late Preterm, % (n = 681)	Term, % (n = 5721)	<i>P</i> Value
Birth weight*	2545 ± 470	3134 ± 409	<0.001
Gestational size			
LGA	4.8	2.6	0.001
SGA	10.1	8.8	0.001
AGA	85.0	88.6	0.001
Gender			
Male	55.4	51.2	0.04
Ethnic group			
Chinese	43.0	45.2	>0.05
Malay	41.6	39.2	>0.05
Indian	9.5	9.5	>0.05
Others	5.9	6.1	>0.05
Maternity parity			
1	31.8	43.7	<0.001
2	31.8	32.5	<0.001
3 and above	36.4	23.8	<0.001

LGA: Large for gestational age; SGA: Small for gestational age; AGA: Appropriate for gestational age

*Mean ± SD

Table 2. Maternal/Antenatal Factors

	Late Preterm, % (n = 681)	Term, % (n = 5721)	P Value	Odds Ratio
Medical problems of any type	43.0	27.4	<0.001	2.0 (1.7,2.4)
Pre-existing hypertension	2.6	1.1	<0.001	2.5 (1.5,4.3)
Pre-existing diabetes	4.7	0.8	<0.001	6.0 (3.8, 9.4)
Pre-eclampsia	13.9	3.1	<0.001	4.6 (3.5, 6.0)
Gestational diabetes	12.9	6.5	<0.001	2.1 (1.7,2.7)
IVF	10.0	2.0	<0.001	5.3 (3.9,7.2)
Multiple pregnancy	16.0	0.5	<0.001	35.0 (23.2,52.6)
Antenatal foetal anomaly	2.9	3.8	0.281	0.8 (0.5,1.2)
Oligohydramnios	5.1	3.3	0.012	1.6 (1.1,2.3)
Polyhydramnios	0.9	0.2	<0.001	5.6 (2.0,15.9)
Antepartum haemorrhage	4.3	1.0	<0.001	4.6 (2.9,7.2)

IVF: In vitro fertilisation

Intrapartum factors such as maternal pyrexia and meconium stained liquor were more common in term deliveries. However, mothers with prolonged rupture of membrane requiring antibiotics tended to deliver earlier (Table 3).

Late preterm infants had significantly more major malformations and chromosomal abnormalities as compared to the term infants.

More late preterm infants were delivered via caesarean section. They also required more resuscitation at birth and had poorer Apgar scores (Table 4).

Respiratory Outcome

Out of the late preterm infants, 28.5% of them had respiratory disorders of any type after birth compared to 14.5% in the term infants (Table 5). Transient tachypnoea of the newborn (TTN) was the most common respiratory morbidity in our late preterm cohort (8.1%). This was followed by pneumonia (7.0%) and apnoea of prematurity (AOP) (3.7%). There was no significant difference in the incidence of air leak and meconium aspiration syndrome (MAS) between the 2 groups.

The late preterm infants needed significantly more respiratory support as compared to the term infants. Comparing the late preterm and the term group, 1.7% vs 0.7% required oxygen therapy, 6.8% vs 1.1% required continuous positive airway pressure (CPAP) and 0.3% vs 0.1% required mechanical ventilation.

Cardiovascular Outcome

In terms of cardiovascular outcome, 4.3% of the late preterm infants had patent ductus arteriosus (PDA) compared to 1.1% in the term group ($P < 0.001$). Late preterm infants had a significantly higher rate of hypotension (0.7%).

Neurological Outcome

There was no significant difference in the rates of hypoxic ischaemic encephalopathy (HIE), intraventricular haemorrhage (IVH), periventricular leucomalacia (PVL) and seizures between the 2 groups.

Gastrointestinal Outcome

The late preterm infants had higher rates of GI complications; 26.4% had GI problems of any type compared to 14.9% in the term group. There were more late preterm infants who had GI bleeding and feeding intolerance. We did not find any statistical difference in NEC between the 2 groups. More late preterm infants had neonatal jaundice requiring phototherapy compared to the term infants, 41.1% vs 12.2% ($P < 0.001$).

Haematological, Metabolic and Infection Outcome

Late preterm infants were at higher risk for anaemia, polycythaemia and thrombocytopenia as compared to term infants. They were also at higher risk for hypocalcaemia, metabolic acidosis and hypoglycaemia. There was no difference in the rate of hypothermia between the 2 groups. There was also more late preterm infants who had infection of any time as compared to term infants, 10% vs 4.8% ($P < 0.001$). Out of our cohort of late preterm infants, 1.7% of them had sepsis (clinical or culture positive) compared to 0.6% in the term infants.

Birth-Related Injuries

There was no difference in the rates of birth-related injuries such as soft tissue injuries, nerve injuries and fractures between the groups. Nevertheless, there was a greater tendency for term infants to suffer from scalp injuries than late preterm infants (3.6% vs 1.3%, $P = 0.002$) (Table 6).

Table 3. Intrapartum Factors

Intrapartum Factors	Late Preterm % (n = 681)	Term % (n = 5721)	Odds Ratio	P Value
Maternal pyrexia	1.3	3.3	0.4 (0.2 – 0.8)	0.004
Prolonged rupture of membrane requiring antibiotics	7.0	3.4	2.0 (1.5 – 2.7)	<0.001
Fetal distress	5.1	4.0	1.3 (0.9 – 1.9)	0.166
Meconium stained liquor	2.6	12.0	0.2 (0.1 – 0.3)	<0.001

Table 4. Mode of Delivery, Resuscitation at Birth and Apgar Scores

Intrapartum Events	Late Preterm, % (n = 681)	Term, % (n = 5721)	P Value
Mode of delivery			
Vaginal	46.7	66.8	<0.001
Instrumental	4.4	8.9	<0.001
Caesarean	48.9	24.3	<0.001
Resuscitation at birth			
No resuscitation	73.3	89	<0.001
Oxygen/stimulation	17.9	7.7	<0.001
Bag and mask	8.1	3.0	<0.001
Intubation/external cardiac massage/drugs	0.7	0.3	<0.001
Apgar scores			
<5 at 1 min	2.5	0.4	<0.001
<7 at 5 min	0.6	0.2	0.029

Mortality

The rate of mortality was 0.1% in the late preterm group compared with no mortality in the term group ($P = 0.004$).

Resource Utilisation

Late preterm infants required significantly more interventions and had greater rates of admission to the neonatal intensive care unit as compared to term infants (Table 7). Out of the late preterm infants, 11.9% of them required intensive care as compared to 1.9% in term infants ($P < 0.001$). Late preterm infants also required longer hospital stay with median of 4 days (range, 1 to 42 days) as compared to term infants who had a median stay of 2 days (range, 1 to 101 days) ($P < 0.001$).

Discussion

In our cohort of 6826 infants, 681 (10%) of them were born late preterm and this accounted for 63% of all preterm births. These figures are similar to those reported in the US where, in 2005, there were 377,000 late preterm births which accounted for 9.1% of all births and 70% of all preterm births.

In a study carried out by Carrie et al, late preterm birth and maternal condition exposure were independent risk factors for newborn morbidity.⁴ The risk for neonatal morbidity was higher if both risk factors were present. Comparing both, late preterm birth was the stronger risk. Mothers with medical problems of any type are at higher risk of late preterm births. These medical problems include pre-existing hypertension or diabetes or even common antenatal conditions such as pre-eclampsia or gestational diabetes. Other antenatal conditions like oligohydramnios, polyhydramnios and antepartum haemorrhage often lead to premature deliveries as well.

In our cohort, more late preterm infants were delivered via caesarean section as compared to the term infants, likely due to indications for earlier delivery such as maternal medical/ antenatal conditions, multiple pregnancy or intrapartum events like premature rupture of membrane, foetal distress etc. However, we were not able to determine whether there were cases of caesarean section being performed without clear medical indications. Reddy et al recently reported that 23% of late preterm births had no clear recorded indications for delivery in the birth certificate.⁵

Respiratory morbidity is one of the most important health

Table 5. Neonatal Morbidity

	Late Preterm, % (n = 681)	Term, % (n = 5721)	Odds Ratio	P Value
Respiratory				
Any type	28.5	14.5	2.3 (2.0 – 2.8)	<0.001
Hyaline membrane disease	2.5	0.1	24.4 (9.6 – 62.1)	<0.001
TTN	8.1	1.7	5.2 (3.7 – 7.3)	< 0.001
MAS	0.3	0.7	0.4 (0.1 – 1.6)	0.188
Pneumonia	7.0	2.8	2.4 (1.7 – 3.3)	<0.001
Air leak	0.3	0.2	1.7 (0.4 – 7.7)	0.498
Persistent pulmonary hypertension	0.7	0.1	10.6 (2.8 – 39.5)	<0.001
AOP	3.7	0.0		<0.001
Respiratory support				
Oxygen	1.7	0.7	2.5 (1.3 – 4.9)	<0.001
CPAP	6.8	1.1	6.5 (4.4 – 9.6)	<0.001
Mechanical ventilation	0.3	0.1	2.8 (0.5 – 13.9)	<0.001
Cardiovascular				
PDA	4.3	1.1	4.1 (2.7 – 6.4)	<0.001
Hypotension	0.7	0.0		<0.001
Neurological				
HIE	0.0	0.1		0.490
Seizures	0.0	0.1		0.490
IVH/PVL	0.0	0.0	-	-
Gastrointestinal				
Any type	26.4	14.9	2.1 (1.7 – 2.5)	<0.001
Feeding intolerance	23.5	14.9	1.7 (1.4 – 2.1)	
NEC	0.3	0.1	2.1 (0.4 – 9.9)	0.337
GI bleeding	1.5	0.3	5.0 (2.3 – 11.0)	<0.001
Neonatal jaundice				
Neonatal jaundice requiring phototherapy	41.1	12.2	5.0 (4.2 – 5.9)	<0.001
Neonatal jaundice requiring exchange transfusion	0.1	0.1	2.8 (0.3 – 27.0)	0.351
Haematological				
Anaemia	3.4	1.2	2.8 (1.8 – 4.6)	<0.001
Polycythaemia	2.2	1.0	2.1 (1.2 – 3.8)	0.008
Thrombocytopenia	3.2	0.6	5.4 (3.2 – 9.3)	<0.001
Metabolic				
Hypocalcaemia	5.7	1.9	3.2 (2.2 – 4.7)	<0.001
Metabolic acidosis	1.0	0.2	6.6 (2.4 – 17.8)	<0.001
Hypoglycaemia	6.6	1.7	4.1 (2.8 – 5.8)	<0.001
Hypothermia	1.2	1.2	1.0 (0.5 – 2.1)	0.975
Infection				
Any type	10.0	4.8	2.2 (1.8 – 2.9)	<0.001
Sepsis (clinical/culture positive)	1.7	0.6	2.9 (1.5 – 5.6)	0.001
Meningitis	0.0	0.1	0.9 (0.1 – 17.3)	0.490

TTN: Transient tachypnoea of newborn; MAS: Meconium aspiration syndrome; AOP: Apnoea of prematurity; CPAP: Continuous positive airway pressure; PDA: Patent ductus arteriosus; HIE: Hypoxic ischaemic encephalopathy; IVH: Intraventricular haemorrhage; PVL: Periventricular leucomalacia; NEC: Necrotizing enterocolitis; GI: Gastrointestinal

Table 6. Birth-Related Injuries

Birth-Related Injuries	Late Preterm, % (n = 681)	Term, % (n = 5721)	Odds Ratio	P Value
Soft tissue injuries	4.8	4.9	1.0 (0.7 – 1.4)	0.956
Scalp injuries	1.3	3.6	0.4 (0.2 – 0.7)	0.002
Nerve injuries	0.1	0.2	0.8 (0.1 – 6.6)	0.868
Fractures	0.3	0.6	0.5 (0.1 – 2.1)	0.321

Table 7. Resource Utilisation

Resource	Late Preterm, % (n = 681)	Term, % (n = 5721)	Odds Ratio	P Value
Lumbar puncture	3.2	0.6	5.4 (3.2 – 9.3)	<0.001
Umbilical artery catheterisation	2.6	0.3	8.6 (4.4 – 16.6)	<0.001
Umbilical vein catheterisation	1.3	0.3	3.8 (1.7 – 8.4)	<0.001
Central venous line	1.5	0.1	12.2 (4.6 – 32.1)	<0.001
Level 3 (Neonatal Intensive Care)	11.9	1.9	7.1 (5.3 – 9.7)	<0.001

morbidities affecting the late preterm infants. Wang et al from Massachusetts, United States reported that respiratory morbidity occurred in 28.9% of their late preterm cohort.⁶ Our findings were similar with 28.5% of our late preterm cohort having respiratory morbidity. Infants born late preterm may have immature lungs which lead to inefficient gaseous exchange resulting in respiratory distress. Escobar et al and Gilbert et al reported that 10.7% and 3.6% of their cohorts respectively had respiratory distress,^{7,8} while Judith et al reported a rate of 9% in their late preterm cohort.⁹

In our late preterm cohort, TTN is the commonest respiratory morbidity which accounted for 8.1%. This is likely due to the delayed intrapulmonary fluid absorption.¹⁰ Out of the late preterm babies, 2.5% of them had respiratory distress syndrome (RDS) as compared to 0.1% in the term group. It can be difficult to differentiate between RDS, TTN and pneumonia as these often overlap. Rubaltelli FF et al reported that the incidence of RDS in his cohort was 12% at 33 to 34 weeks, 2% at 35 to 36 weeks and 0.11% at term, while incidence of TTN was 11.6% at 33 to 34 weeks, 5% at 35 to 36 weeks and 0.7% at term.¹¹

Previous studies reported the incidence of apnoea in late preterm infants of between 4% to 7% compared to less than 1% in term infants.^{12,13,14,15} Our study shows 3.7% of late preterm infants had apnoea while none of the term infants had apnoea. Late preterm infants are at higher risk for developing apnoea as their central nervous systems are structurally immature and generally smaller with less myelination.¹⁶ Apnoea is also more common in the late preterm due to the immature lung volume, feeding-related problems and anaemia.¹⁷

Late preterm infants are also at higher risk of persistent pulmonary hypertension (PPHN) compared to term infants. Out of the late preterm infants, 0.7% of them developed PPHN while 0.1% of the term infants developed PPHN. Judith et al reported 0.5% of her 34 weeks cohort developed pulmonary hypertension, followed by 0.3% at 35 weeks, and 0.5% at 36 weeks compared to 0.1% in their term cohort.⁹ In pulmonary hypertension, there is a maladaptation to the circulatory transition whereby there is reduced responsiveness to vasodilators such as prostacyclin and nitric oxide. This results in vasoconstriction of the pulmonary vasculature, which in turn causes persistent high pulmonary pressure. This is also contributed by a relative surfactant deficiency in this group of infants in addition to the maladaptation.¹⁸ Our late preterm babies required more ventilatory support such as oxygen therapy, continuous nasal positive airway pressure support or mechanical ventilation. Gilbert et al reported that 3.4% of their late preterm infants required mechanical ventilation as compared to 0.9% in the term group.⁸

Out of the late preterm infants, 4.3% of them had patent ductus arteriosus compared to 1.1% in term infants. Late preterms were also at higher risk for hypotension. It has been postulated that late preterm infants do not have adequate cardiovascular reserve to handle stress postnatally.

In our cohort, there was no difference in the rates of HIE, seizures, IVH and PVL between the 2 groups of infants. However, there are reported concerns of the association between late preterm births with long-term adverse neurodevelopmental sequelae. Late preterm infants are at higher risk of cerebral palsy,¹⁹ neurodevelopmental

disability²⁰ and speech delay.²¹ Therefore, there is a need for long-term follow-up for this group of infants.

Late preterm infants tend to have poorer peristaltic functions and sphincter controls compared with term infants.²² They are less able to achieve effective sucking and swallowing.²³ This often leads to delay in establishing feeds and results in poor weight gain. They also have immature GI function.²⁴ The GI tract continues to develop with increasing maturity and the more mature infants tend to have less GI problems. In our cohort, 26.4% of the late preterm infants had GI disorders of any type compared to 14.9% in the term cohort which included feeding intolerance and GI bleeding. Wang et al reported that 32.2% of their late preterm infants had feeding difficulties.⁶

In our study, the late preterm infants were also at higher risk for anaemia, polycythaemia and thrombocytopenia. Very few studies have looked at haematological outcomes in late preterm infants. The immaturity of the bone marrow results in ineffective and inadequate erythropoiesis and platelet production. Maternal conditions and intrapartum factors may also have contributed to the increased rates of haematological problems in the late preterm cohort.

The late preterm infants were at higher risk of developing hypoglycaemia, metabolic acidosis and hypocalcaemia. Wang et al found that late preterm infants tend to require more glucose infusion for hypoglycaemia than in term infants.⁶ Out of their cohort of late preterm infants, 15.6% had hypoglycaemia compared with 6.6% in our cohort. Preterm infants are at risk of hypoglycaemia due to the immaturity of liver gluconeogenesis and glycogenolysis, and adipose tissue lipolysis. As the GA increases, the incidence of hypoglycaemia decreases.

Our study did not show any difference between late preterm and term infants in the occurrence of hypothermia. Physiologically, however, late preterm infants are at higher risk for hypothermia as they have a larger surface area to weight ratio as well as less adipose tissue for metabolism.

In our cohort, there were significantly more late preterm infants who had neonatal jaundice requiring phototherapy compared to term infants. Due to the immaturity of liver, the ability to conjugate bilirubin is impaired. Co-existing feeding difficulties also result in impairment of the enterohepatic circulation, decreased stool frequency and dehydration which further aggravates hyperbilirubinaemia.²⁵

Late preterm infants are at higher risk of infection. Out of our cohort of late preterm infants, 10% had an infection of any type which included documented bacteraemia, skin/subcutaneous infection, meningitis, pneumonia etc. These can be explained by the lower immunity in late preterm infants especially in the maturation of T-cell and granulocyte functions.²⁶

Our study did not show any significant difference between the groups in terms of birth-related injuries such as soft tissue injuries, nerve injuries and fractures. There were more term infants who suffered scalp injuries as compared to late preterm infants. This was possibly because more term infants required instrumental deliveries as compared to our late preterm infants, 8.9% vs 4.4% respectively.

Tomashek et al reported that mortality in late preterm infants is approximately 3 times higher than it is among term infants.²⁷ However, we did not observe a statistical difference in mortality in our cohort. The mortality in the late preterm group was a 36 weeker who was antenatally diagnosed with holoprosencephaly with multiple dysmorphic features. The parents of this infant declined termination of pregnancy antenatally despite dismal prognosis. Conservative management and comfort case was offered postnatally.

Our late preterm cohort required more interventions including lumbar punctures, umbilical artery catheterisations, umbilical venous catheterisations and central venous lines. More interventions mean higher financial costs and greater resource utilisation. They also required more intensive care. Gilbert et al in his population study in 1996 showed that avoiding 'non-medically indicated births' among the late preterm births could have saved \$49.9 million in California alone.⁸ By preventing unnecessary late preterm births, we could save on our resource utilisation.

Conclusion

Late preterm infants are indeed a vulnerable group of infants. Despite their relatively large size and being almost term, they should not be regarded as being similar to term infants. This is an important understanding that obstetricians and neonatologists need to have when they decide and plan for late preterm deliveries. Management strategies should be planned based on adequate understanding of the health morbidity which late preterm infants face after birth.

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Neonatal and Paediatric Extracorporeal Membrane Oxygenation (ECMO) in a Single Asian Tertiary Centre

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Abstract

Introduction: Extracorporeal membrane oxygenation (ECMO) is a cardiopulmonary bypass technique (CPB) which provides life-saving support in patients with refractory cardiorespiratory failure until cardiopulmonary recovery or organ replacement. **Materials and Methods:** This is a single centre retrospective study reporting the largest series of paediatric patients in Singapore who received ECMO support over an 11-year period from January 2002 to December 2012. The objective is to describe the characteristics of the patients and to report the survival to hospital discharge, complications during ECMO and other long-term complications. **Results:** Forty-eight patients received ECMO during the study period. ECMO was initiated for myocarditis in majority of the paediatric patients whereas postoperative low cardiac output state was the most common indication in the neonatal population. The overall survival rate to hospital discharge was 45.8%. Survival was highest in the neonates with respiratory failure (75%). Haematological and cardiac complications were most common during ECMO. Age group, gender, duration of ECMO, need for renal replacement therapy, acute neurological complications were not associated with mortality. Those needing inotropic support during ECMO had poorer survival while those with hypertension requiring vasodilator treatment had a higher survival rate. The survival rates for ECMO patients more than doubled from the initial 6 years of 23% to 54% in the last 5 years of the study period. Long-term complications encountered included neurological, respiratory and cardiac problems. **Conclusion:** ECMO is a life-saving modality for neonatal and paediatric patients with cardiopulmonary failure from diverse causes. Patients with persistent need for inotropes during ECMO had poorer outcome. Centre experience had an impact on ECMO outcome.

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Key words: Complications, Retrospective, Survival

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Introduction

Extracorporeal membrane oxygenation (ECMO) is a cardiopulmonary bypass technique (CPB) introduced by Bartlett in 1972, which provides life-saving support in patients with refractory yet reversible cardiorespiratory failure until organ recovery or organ transplantation. Since the first report of successful ECMO support in an adult was published by Hill in 1972, there have been over 45,000 cases in the ECMO Registry of Extracorporeal Life Support Organization (ELSO), including over 27,000 newborns and 9000 children.¹

KK Women's and Children's Hospital (KKH) is an 830-bed tertiary institution for women and children in Singapore with about 26,000 paediatric hospital admissions per year. It is both a local and a regional tertiary referral centre for women and children. It has a 16-bedded multidisciplinary Paediatric Intensive Care Unit (PICU) with about 700 admissions per year and a 32-bedded Neonatal Intensive Care Unit (NICU) with similar yearly admissions. The PICU admits all postoperative cardiac surgical patients weighing more than 2 kg. During the study duration, there was an average of 186.4 cardiac operations per year. ECMO was first

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introduced in KKH in 2002 and our experience has increased significantly over the years. As there was no paediatric heart and lung transplant programme in Singapore, the use of ECMO was only as a bridge to organ recovery.

This retrospective descriptive review aims to report the characteristics of the patients who received ECMO, the primary outcome of survival to hospital discharge and the secondary outcomes of short-term and long-term complications of ECMO.

Materials and Methods

We performed a retrospective chart review on all patients who received ECMO in the PICU and NICU between January 2002 and December 2012. The first patient was a child with viral myocarditis and complete heart block. In 2006, we started ECMO in NICU on neonates with refractory respiratory failure secondary to meconium aspiration syndrome (MAS) and congenital diaphragmatic hernia (CDH). In 2008, we did our first case of extracorporeal cardiopulmonary resuscitation (ECPR) on a child with myocarditis. The medical record of each patient was reviewed to determine demographic history (age on admission and gender), primary diagnoses, indications for ECMO, occurrence of cardiac arrest prior to ECMO initiation, location of ECMO initiation, type of ECMO (veno-venous or veno-arterial) and duration of ECMO support as detailed below, complications while on ECMO (neurological, respiratory, mechanical, cardiac, haemorrhagic), survival to hospital discharge, and long-term complications. Indications for ECMO were categorised into respiratory, cardiac or ECPR. Respiratory and cardiac indications were defined by the primary organ system involvement. We classified the complications during ECMO into haemorrhagic, neurological, mechanical, renal and cardiac complications. Long-term complications were classified into neurological, respiratory, developmental or behavioural and late deaths (defined as death any time after hospital discharge) and other problems.

The indications for placement on veno-arterial ECMO (VA ECMO) included poor systemic perfusion with metabolic acidosis and impaired ventricular function by transthoracic echocardiography (TTE) despite optimising inotropic support and fluid status. Patients were started on ECMO flows of about 20 to 30 ml/kg/min and increased to achieve flows according to the body weight: infants – 120 to 150 ml/kg/min; children – 100 to 120 ml/kg/min; and adolescents – 70 to 80 ml/kg/min. Inotropic support would be weaned while maintaining a central venous oxygenation of >65% and then discontinued after commencement of ECMO as far as possible. When there was absence of aortic valve opening due to poor left ventricular function, a left atrial vent would be inserted if the patient had central

cannulation with an open chest. We did not perform atrial septal dilatation.

Veno-venous ECMO (VV ECMO) was indicated when there was severe respiratory failure despite high ventilator pressures and fractional inspired oxygen (FiO_2). ECMO flows were started as per VA ECMO flows.

ECMO was performed using centrifugal pumps RotaFlow (Maquet) or Levitronix with a membrane oxygenator Lilliput (Sorin) or Hilite® (Medos). Arterial cannulae used in our institution are from Medtronic DLP® or Maquet, while venous cannulae are the Medtronic Bio-Medicus®, Medtronic DLP® or Maquet.

Management while on ECMO involved ventilatory settings of PIP <30 cm H_2O , PEEP 6 cm to 12 cm H_2O , ventilator rates 15 to 25 breaths per minute and FiO_2 21% to 40%.

ECMO patients were managed by a multidisciplinary team of intensive care physicians, cardiologists, cardiothoracic surgeons and pulmonologists. Daily patient care was performed by both intensive care nurses and the ECMO circuit management, which was carried out by perfusionists trained in cardiopulmonary bypass and ECMO. Systemic anticoagulation was done with intravenous unfractionated heparin infusion to achieve an activated clotting time (ACT) of between 180 to 220 seconds. When there was severe bleeding, the ACT target would be reduced to 160 to 180 seconds until the bleeding was controlled. Blood products were transfused to maintain a platelet level more than $80 \times 10^{12}/\text{L}$, a haemoglobin level more than 10 g/dL, a prothrombin time less than 17 seconds and a fibrinogen level more than 1 g/L.

ECMO circuits were changed if there were indications of haemolysis evidenced by haemoglobinuria, decreasing haematocrit and rising indirect bilirubin or evidence of clots in the circuit.

Duration of support was determined by readiness to wean, and was in turn based on assessment of the recovery of cardiopulmonary function by clinical assessment, chest X-ray and TTE. ECMO flow rates were weaned over a few hours to a day and the decision to decannulate was based on the stability of the patient on conventional treatment for about 30 minutes off ECMO. For patients with irreversible organ failure, the decision to discontinue ECMO was made by a multidisciplinary team of intensive care physicians, cardiologists and pulmonologists together with the families.

All records were reviewed as hard or digital copies. Descriptive statistics were reported as median, range, and interquartile range (IQR) for continuous variables and as frequencies and percentages for categorical variables. Categorical variables were analysed using a Fisher's exact test or Pearson chi-square test, whereas continuous variables

were analysed using a Mann-Whitney U test or the Kruskal-Wallis test when comparing more than 2 groups. All statistical analysis was performed using SPSS 19.0. Significance was determined as $P < 0.05$.

Results

During the 11-year period, there were a total of 48 patients who received ECMO in both the PICU and NICU. Twenty-six were females and 22 were males. The median age at ECMO initiation was 20 months (range, newborn to 23 years). The 23-year-old was admitted to the PICU after surgery for congenital heart disease and had ECMO initiated in PICU postoperatively. Our first case of ECMO was performed in 2002 and numbers increased with a peak in ECMO use in 2008 (Fig. 1). The median duration of ECMO was 6 days (IQR, 4.0 to 8.8).

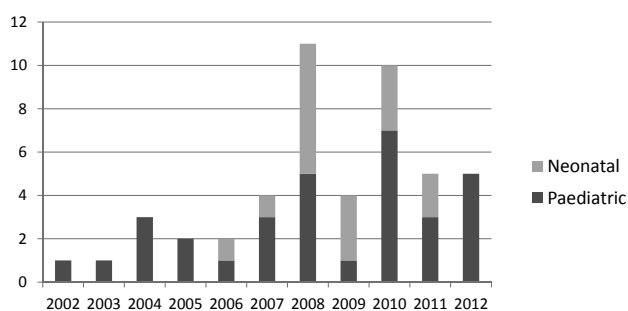


Fig. 1. Number of ECMO cases by year.

Among the neonates, the most common underlying diagnoses were congenital heart disease (CHD) (35.7%), CDH (28.6%) and MAS (28.6%). In the paediatric patients, acute myocarditis (55.9%) and CHD (29.4%) including 2 cases of left pulmonary artery (LPA) sling were the more common diagnoses (Table 1).

Overall, ECMO was initiated mainly for cardiac indications (60.4%). However, respiratory ECMO was more commonly performed in the neonatal population (Table 1). Majority (91.7%) received VA ECMO, both in the paediatric and neonatal group (Table 2).

Thirty-three patients (68.8%) had ECMO initiated in the ICUs, 28 in the PICU and 5 in the NICU. Thirteen patients (27.1%) had central cannulation and ECMO initiation in the operating room. Of the 2 remaining patients, one had ECMO started in our Emergency Department and another in a separate tertiary hospital before being transferred back to our ICU.

Data on complications during ECMO was missing in 1 patient. Of the 47 patients with available data, all except 1 experienced at least 1 complication during ECMO. Haemorrhagic complications, especially around the cannula site and mucosal bleeding, were common (Table 3). One-third of the patients required renal replacement therapy. Neurological complications occurred in 6 patients, 4 of whom were declared brain dead during ECMO. All of these patients had myocarditis and the mortality rate was 80%.

Table 1. Survival Outcomes by Age Group and Indications

	No. of Infants	Survive ECMO		Survive to Discharge	
		n	%	n	%
Neonatal					
Respiratory	-	-	-	-	-
MAS	4	4	100.0	4	100.0
CDH	4	3	75.0	2	50.0
Cardiac (postcardiotomy)	5	2	40.0	1	20.0
ECPR (arrhythmia)	1	1	100.0	1	100.0
Total	14	10	71.4	8	57.1
Paediatric					
Respiratory	-	-	-	-	-
ARDS	2	2	100.0	2	100.0
Interstitial lung disease with pulmonary hypertension	1	0	0.0	0	0.0
LPA sling with tracheostenosis	2	0	0.0	0	0.0
Cardiac	-	-	-	-	-
Myocarditis	19	13	68.4	10	52.6
Postcardiotomy	8	5	62.5	1	12.5
Sepsis	2	25	100.0	2	100.0
Total	34	21	61.8	14	41.2
Grand Total	48	31	64.6	22	45.8

ARDS: Acute respiratory distress syndrome; CDH: Congenital diaphragmatic hernia; ECMO: Extracorporeal membrane oxygenation; ECPR: Extracorporeal cardiopulmonary resuscitation; LPA: Left pulmonary artery; MAS: Meconium aspiration syndrome

Table 2. Indications and Types of ECMO

	Indications	n	Types	n
Neonatal (n = 14)	Cardiac	5	VA	13
	Pulmonary	8	VV	1
	ECPR	1		
Pediatric (n = 34)	Cardiac	24	VA	30
	Pulmonary	6	VV	3
	ECPR	4	VA → VV	1

ECMO: Extracorporeal membrane oxygenation; ECPR: Extracorporeal cardiopulmonary resuscitation; VA: Veno-arterial ECMO; VV: Veno-venous ECMO; VA → VV: Veno-arterial ECMO with subsequent conversion to veno-venous ECMO

Table 3. Complications During ECMO

Complications	n (% of Total Cases)
Mechanical	Cannula kinking 2 (4.2)
	Clots 6 (12.5)
Haemorrhagic	GIT 7 (14.6)
	Cannula site 18 (37.5)
	Surgical site 2 (4.2)
	DIC 6 (12.5)
	Mucosal 14 (29.2)
	Lung 5 (10.4)
	Haemothorax 3 (6.3)
Neurologic	Brain Death 4 (8.3)
	Cerebral infarction 1 (2.1)
	Intracranial bleed 2 (4.2)
	Seizures 1 (2.1)
Renal	Needing renal replacement therapy 15 (31.3)
Cardiovascular	Inotropes 11 (22.9)
	Vasodilators 11 (22.9)
	CPR 2 (4.2)
	Pericardial effusions 2 (4.2)
Others	Pneumothorax 4 (8.9)
	Pericardial clot 3 (6.3)
	Wound site infection 1 (2.2)

ECMO: Extracorporeal membrane oxygenation; CPR: Corporeal cardiopulmonary resuscitation; CPR: Cardiopulmonary resuscitation; DIC: Disseminated intravascular coagulation; GIT: Gastrointestinal tract

Thirty one (64.6%) patients survived ECMO decannulation but eventually 22 patients (45.8%) survived to hospital discharge. Survival was highest in the group of neonates who required ECMO for respiratory indications at 75%, with 100% survival in patients with MAS and 50% in those with CDH (Table 1). The survival rates in postcardiotomy patients who required ECMO were low for both the neonatal and paediatric groups (20% and 12.5%).

Of the 22 survivors, 6 (28.6%) had long-term neurological deficits which included foot drop, sensorineural deafness, left hemiplegia, epilepsy and oropharyngeal dysphagia. Developmental problems such as poor attention and speech delay were seen in 2 patients (9.5%) and 4 others (19.0%) developed reactive airway disease after discharge. Late death occurred in 2 of our patients (9.1%) who survived hospital discharge. One patient had complex CHD who died after 5 months despite repeated surgeries, and the other had myocarditis that progressed to end-stage cardiomyopathy and died 17 months later due to decompensated cardiac failure.

We performed univariate analysis comparing age group (paediatric or neonatal), gender, pre-ECMO cardiac arrest, duration of ECMO, occurrence of cardiac arrest before ECMO (ECPR included), time period (2002 to 2007, 2008 to 2012), need for renal replacement therapy, need for inotropic support, hypertension requiring vasodilators and acute neurological complication while on ECMO with survival to hospital discharge (Table 4). Need for inotropic support during ECMO was associated with lower survival. Patients with hypertension had better survival.

Discussion

This is the largest series of paediatric and neonatal patients who received ECMO support in a single centre over an 11-year period in Singapore. In the early years of our experience, ECMO was considered primarily for patients who were in cardiac failure refractory to maximum medical therapy.

Our survival rates in MAS and CDH patients did not differ from international experience of 94% and 50% respectively.¹ In a Cochrane meta-analysis of neonatal ECMO for respiratory failure, ECMO was shown to have a clear benefit on survival.² The relative risk of death before discharge was 0.44 with ECMO compared to conventional treatment. This effect was more pronounced when CDH was excluded from the analysis. The utility and benefit for ECMO in CDH was therefore less clear. While the acute lung injury and associated pulmonary hypertension in MAS is often reversible, underlying pulmonary hypoplasia

Table 4. Age Group, Pre-ECMO Arrest, Time Period, Renal Replacement Therapy and Inotropic Support on ECMO — Survivors Compared with Non-Survivors

	Survivors (n = 22, %)*	Non-Survivors (n = 26, %)*	Significance (P Value)
Age group			
Paediatric	14 (63.6)	20 (76.9)	0.31
Neonatal	8 (36.4)	6 (23.1)	
Gender			0.38
Female	10 (45.5)	16 (61.5)	
Male	12 (54.5)	10 (38.5)	
Duration of ECMO	7.0 (5.0, 9.0)	5.0 (2.8, 8.2)	0.17
Pre-ECMO arrest	7 (31.8)	14 (53.4)	0.19
Period			
2002-2007	3 (13.6)	10 (38.5)	0.1
2008-2012	19 (86.4)	16 (61.5)	
Renal replacement therapy	5 (22.7)	10 (38.5)	0.24
Inotropic support on ECMO	1 (4.5)	10 (38.5)	0.006
Hypertension requiring vasodilators	10 (45.5)	1 (3.8)	0.001
Neurological complications	2 (9.1)	5 (19.2)	0.43

ECMO: Extracorporeal membrane oxygenation

*Data are represented as median (IQR)

and persistence of pulmonary hypertension affect the reversibility of pulmonary failure in CDH. Risk factors identified to be associated with in-hospital mortality in patients with CDH on ECMO were prenatal diagnosis of CDH, low 5-minute Apgar score of ≤ 6 , low birth weight (< 2 kg), PaCO₂ higher than 60 mm Hg during the 6-hour period before ECMO, total ECMO duration of 15 days or longer, and the complications of intracranial haemorrhage, PDA right-to-left shunt, requirement of CPR, haemolysis with plasma haemoglobin of more than 0.5 g/L, surgical site haemorrhage, disseminated intravascular coagulation (DIC), and requirement of dialysis while on ECMO.³

Survival rates in postcardiotomy patients improved from 0% in the earlier period (2002 to 2007) to 25% in the later period and this could be accounted for by the higher threshold for starting ECMO in the earlier period with patients at a physiologically poorer pre-ECMO state. ECMO was considered when the patients had failed maximal medical treatment with high inotropic and ventilatory support. Many of them likely had profound circulatory failure before ECMO was commenced. Pre-ECMO severe metabolic acidosis, in addition to underlying cardiac diagnoses and complexity of the cardiac surgery, had been found to influence survival for postcardiotomy patients supported on ECMO.^{4,5} The absence of a heart and lung transplant programme in our centre also precluded the option of organ replacement as an exit strategy for ECMO.

All but 1 had at least 1 complication while on ECMO. Our incidence of mechanical, haemorrhagic and cardiovascular complications were generally lower than reported in the

ELSO Registry, while neurological and renal complications were similar to international rates.

Known significant pre-ECMO predictors of mortality include severe metabolic acidosis,^{4,6} single ventricle physiology and history of stage-1 procedure for cardiac disease.⁴ During ECMO, complications such as neurological injury,^{4,7,8} renal dysfunction,^{5,6,7} persistent metabolic acidosis,^{4,6} arrhythmias⁸ and bleeding⁸ as well as prolonged duration of extracorporeal life support (ECLS),^{5,7,9} repeat need for ECLS,⁷ absence of heart transplantation⁷ and need for inotropes^{6,10} had been found to be significant factors for hospital mortality. In a series of paediatric ECPR cases, acute neurological injury defined as brain death, intracranial bleed and cerebral infarction was not uncommon (22%), with a high mortality rate of 89%.¹¹ Those with cardiac disease, less metabolic acidosis pre-ECMO and uncomplicated ECMO course had reduced odds of neurological injury.

We analysed various factors including age groups, gender, pre-ECMO cardiac arrest, duration of ECMO, need for inotropic support during ECMO, hypertension, acute neurological injury, need for renal replacement therapy and duration of ECMO with survival to discharge. Similar to other studies,^{6,10} the need for inotropic support during ECMO was a poor prognostic indicator and the converse was true for hypertension requiring vasodilator use. The need for renal replacement therapy, however, was not associated with a survival difference.

Systemic hypertension is a recognised complication of ECMO, especially in the neonatal patients. It occurred in 38.4% to 88% of neonatal ECMO patients in reported

series.^{12,13,14} The mechanism of hypertension in ECMO patients is not entirely clear. It is believed that the augmented stroke volume in VA ECMO from the return flow into the aorta contributes to the increase in blood pressure.^{12,13} Alteration in water and sodium handling has also been postulated to be a potential cause.¹³ Intracranial haemorrhage (ICH) was shown to be more common in neonates on ECMO with hypertension.¹³ Similar finding was not found in a paediatric series of VV ECMO.¹⁵ Significant hypertension was also not significantly associated with survival.^{14,15} In our study, 1 of the 2 patients with ICH had hypertension requiring vasodilator therapy. However, the temporal relationship of the onset of hypertension and ICH was not clear as this patient had radiological confirmation of ICH only after ECMO was discontinued. Intracranial hypertension as the cause of systemic hypertension, therefore, could not be excluded. Interestingly, hypertensive patients in our cohort had better survival. This was true even after excluding patients who required inotropic support. We treated hypertension readily with afterload reduction agents which could have augmented cardiac output from the external ECMO flow and the native heart.

Although not statistically significant in our small sample, the survival more than doubled in the later period compared to the first 6 years of our experience, from 23% to 54%. The improvement through experience of the ICU team and better coordination of multidisciplinary teams were the likely contributory factors.

Occurrence of cardiac arrest before ECMO in 21 patients, which included 4 ECPR cases, was not found to affect survival. The state of the patient pre-ECMO had a greater impact on survival, which is largely reflected by the presence of severe metabolic acidosis.^{4,7,16} We did not, however, study pre-ECMO acidosis in this study. A recent report from the National Registry of Cardiopulmonary Resuscitation in the United States on ECPR in the neonatal and paediatric population cited a survival of 43% with good neurological outcome in survivors.¹⁶

Long-term outcomes in the neonatal ECMO patients have been studied,¹⁷ but there is a paucity of similar studies in the older paediatric population, especially in children who had non-cardiac indications for ECMO. We studied the long-term complications such as late death, re-admissions, as well as neurological, respiratory, developmental and other complications.

About one-third of our survivors suffered long-term neurological sequelae. The most severe case of neurological injury was seen in an 8-year-old child with fulminant myocarditis who developed intracranial bleed while on ECMO and the complications of epilepsy, left hemiplegia, right vocal cord paresis and oropharyngeal dysphagia. Debilitating neurological injury was also not uncommon

in other paediatric ECMO series.¹⁸

The UK Collaborative ECMO trial is the largest randomised controlled trial in neonatal ECMO to date, with follow-up data up to 7 years.^{19,20} The trial showed a clear benefit of ECMO on survival compared to conventional treatment and this benefit was not offset by increased morbidities at the 7-year follow-up in terms of neurocognitive or behavioural impairment. Long-term effects on neurocognition and behaviour were observed in both ECMO and conventional arms, with 24% exhibiting cognitive delay. This suggested that in these sick neonates, the underlying disease and physiological compromise had a major influence on long-term neurological outcome.

Limitations

This is a case series of a single centre — the results may be specific to the local patient population, surgical expertise and techniques, support strategies and infrastructure. Further limitations include the retrospective nature of this study.

Conclusion

ECMO is a life-saving modality of treatment for patients with refractory cardiopulmonary failure of a diverse aetiology, especially in the neonatal patients with respiratory failure. The overall survival rate in our series was 48.5%. Short-term and long-term complications were not uncommon in ECMO patients. Centre experience appeared to have an impact on patient survival on ECMO, highlighting the need for continuing quality assurance and improvement for the ECMO programme.

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Validation of the Paediatric Hearing Impairment Caregiver Experience (PHICE) Questionnaire

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Abstract

Introduction: The paediatric hearing impairment caregiver experience (PHICE) questionnaire is a 68-item instrument that assesses the stress experienced by caregivers of children with hearing impairment (HI). While the questionnaire has been validated in the United States, it may need to be modified for use in the Singapore context due to the differing healthcare system, costing and culture related to caregiving for children with HI. This study aims to modify and validate the PHICE questionnaire to increase its relevance and ease of use in Singapore. **Materials and Methods:** The original PHICE questionnaire was filled out by 127 caregivers of HI children managed at the otolaryngology clinic of the National University Hospital (NUH). An expert panel was convened to assess the questionnaire for its suitability for use in Singapore. Exploratory factor analysis was conducted to evaluate the underlying factor structure of the original PHICE questionnaire. Items with high cross-loadings were removed and a new factor structure was adopted which was further analysed using confirmatory factor analysis (CFA). Cronbach's alpha (α) was computed to determine the internal consistency of the new subscales. **Results:** Items that are less relevant in Singapore and those with high cross-loadings were removed. A 5-factor structure with only 42 items remaining and corresponding to the factors: "Policy", "Healthcare", "Education", "Support" and "Adaptation" was adopted. CFA suggests a good model fit for the modified questionnaire, improved from the 8-factor structure of the original PHICE. Cronbach's α were high (>0.7) for each new subscale. **Conclusion:** The original PHICE questionnaire has been shortened and reorganised in terms of the subscales composition. The resulting instrument is structurally valid and internally consistent. It is a simple and useful tool for identifying factors related to caregiving that can negatively impact rehabilitation outcomes for children with HI in Singapore. Removal of some sign language items makes this modified version less useful for caregivers, places or countries where sign language is the main focus of rehabilitation for children with HI.

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Key words: Modified, Outcome, Rehabilitation, Stress

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Key words: Modified, Outcome, Rehabilitation, Stress

Introduction

The stress experienced by parents of children with hearing impairment (HI) has been studied over the past 2 decades. Increased parenting stress is often associated with developmental problems such as delay in language acquisition, social and emotional problems.^{1,2} The stress that parents endure fluctuates as they go through the process of meeting and overcoming various challenges associated with their child's HI.³⁻⁸ Increased caregiver stress has been correlated with poorer health functioning outcomes for the child. If healthcare teams can identify the domains of caregiver stress and tailor efforts to mitigate the most important stressors specific to each caregiver, hearing outcomes of the child may also be improved.

The paediatric hearing impairment caregiver experience (PHICE) questionnaire has previously been developed to document the various stressors caregivers may experience related to their child's HI.⁹ PHICE is a 68-item instrument spanning 8 factors of stress: communication (10 questions), education (7 questions), emotional well-being (11 questions), equipment (3 questions), financial (4 questions), healthcare (14 questions), social (8 questions), and support (11 questions). The item is scored on an 8-point Likert scale with the descriptors: "Not applicable", "No stress", "Very low stress", "Low stress", "Moderate stress", "High stress", "Very high stress" and "Extremely high stress". While this instrument has been validated in the United States, it may need to be modified for use in the Singapore context due to

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the differing healthcare system, costing and culture related to caregiving for children with HI. The questionnaire takes about 25 minutes to complete.

This study aims to modify, shorten and validate the PHICE questionnaire to increase its relevance and ease of use in Singapore. As the data used to shorten the questionnaire is collected in Singapore, the validity of the shortened version would be assessed in a Singapore context.

Materials and Methods

Participants

A total of 127 caregivers of children with permanent HI who had been receiving treatment at the Otolaryngology – Head and Neck Surgery Centre of the National University Hospital (NUH) were recruited for the study. Caregiver was defined as a parent, family member or other personnel who takes care of the child with HI. The children were managed at the clinic by otolaryngologists, audiologists, speech and language therapists, auditory-verbal therapists, and multidisciplinary supporting specialists as appropriate. Informed consent was sought and the original 68-item PHICE questionnaire was administered to the caregiver.

Expert Panel Review

An expert panel was convened to assess each item on the original PHICE questionnaire for its suitability for use in Singapore. The expert panel consisted of an otolaryngology surgeon, an audiologist and 2 speech and language/auditory-verbal therapists. Items that were less relevant to the Singapore context were removed. The expert panel has had vast experience with management of children with HI and their caregivers in the Singapore context.

Data Analysis

Data analysis was conducted on the remaining items through R.¹⁰ Missing data was imputed by cross-validation imputation using the package “missMDA”.^{11,12} The amount of missing data was deemed to be small at 0.72%. The imputed data was rounded off to the nearest integer to maintain the ordinal nature of the scale and to make the data interpretable.¹³ The items were recoded such that the “Not applicable” entries were mapped to “No stress”. This is on the assumption that if an item is not applicable to a caregiver, the caregiver has not faced stress in that particular area. This recoding preserves the inherent assumption of equidistant between points on the Likert scale.

Factor analysis was conducted using the package “psych”.¹⁴ Factor analysis is a group of methods that aims to understand the underlying structure of the variables. In the current study, the variables are the items of the PHICE

questionnaire and there is an assumed structure of these variables denoted by their subscales. This assumed structure was derived from expert opinion. The purpose of factor analysis is to validate this opinion or propose an alternative way of grouping the items by analysing the mathematical relationships between the items.¹⁵

Factor analysis was conducted using principal axis factoring (PAF) as we do not want to simply account for all the variance of the items, but are interested in shared variance of the items.¹⁶ This orientation allows us to cater for other sources of variance (e.g. random error) and is more compatible with classical test theory.¹⁷ Oblique rotation was used as the latent factors are expected to correlate with each other.¹⁸ Oblimin was selected as the rotation of choice as it provides flexibility to vary the intercorrelations amongst factors.¹⁸ Non-graphical solutions to the scree test including eigenvalues, parallel analysis, optimal coordinates, and acceleration factor were used to help determine the appropriate number of factors to retain.^{19–20} These analyses were conducted using “nFactors” through R.²¹ Cross-loadings for each item were assessed. A cross-loading difference of less than 0.1 between the 2 highest factors loading was set as the criteria for removal of items. High cross-loading suggests that an item can possibly lie in more than one domain and thus is ambiguous in the actual latent construct it represents. Given the ambiguity, we decided to exclude the items in the shortened version.

Confirmatory factor analysis (CFA) was conducted on the original and new factor models. Goodness-of-fit indices were assessed to evaluate if there is an improvement in the fit of the model. Cronbach’s alpha (α) was computed for the new subscales to determine its internal consistency.

Results

Demographics

A total of 127 PHICE questionnaires were collected between April 2004 and March 2009. Two questionnaires were excluded from analysis as they were largely unfilled. The majority of the questionnaires (78%) were filled out by a mother, 20% of them were filled out by a father, and the rest were filled out by a grandparent or other relatives.

Table 1 shows the demographic, audiological and functioning profile for both the caregivers and their children with different types of hearing devices. The children’s ages ranged from 3 months to 18 years, with an average age of 6 years (median, 5 years). Regarding the type of hearing device used, 9.6% ($n = 12$) of the children were not aided with any device, 65.6% ($n = 82$) were aided with hearing aid (HA), 13.6% ($n = 17$) were aided with cochlear implant (CI) and HA on different ears, and 11.2% ($n = 14$) were aided with CI only. The degree of hearing loss, social

Table 1. Demographic, Audiological and Functioning Profile of Caregivers and Their Children with Hearing Loss

	Type of Hearing Devices			
	No Aid, n = 12	HA, n = 82	CI + HA, n = 17	CI, n = 14
Children with hearing loss				
Male (%)	7 (58.3)	47 (57.3)	12 (70.6)	7 (50)
Age of hearing loss diagnosis (months)	49 (0 – 144)	33 (0 – 180)	29 (1 – 46)	15 (1 – 41)
Age at the time of study (months)	87 (14 – 192)	87 (3 – 226)	78 (26 – 133)	56 (27 – 97)
Degree of hearing loss (defined by hearing in the better ear)*				
None (unilateral hearing loss)	3 (25.0)	5 (6.1)	0 (0)	0 (0)
Mild	4 (33.3)	15 (18.3)	0 (0)	0 (0)
Moderate	2 (16.7)	22 (26.8)	1 (5.9)	0 (0)
Moderately severe	0 (0)	3 (3.6)	1 (5.9)	0 (0)
Severe	0 (0)	32 (39.0)	13 (76.5)	9 (64.3)
Profound	0 (0)	1 (1.2)	2 (11.7)	5 (35.7)
Usefulness of hearing device				
Not very	NA	10 (12.2)	1 (5.9)	2 (14.3)
Somewhat	NA	21 (25.6)	2 (11.8)	1 (7.1)
Very	NA	24 (29.3)	11 (64.7)	3 (21.4)
Extremely	NA	21 (25.6)	3 (17.6)	8 (57.1)
Social functioning*				
Poor	0 (0)	5 (6.1)	0 (0)	0 (0)
Fair	4 (33.3)	22 (26.8)	4 (23.5)	1 (7.1)
Good	4 (33.3)	26 (31.7)	6 (35.3)	4 (28.6)
Very good	2 (16.7)	17 (20.7)	4 (23.5)	3 (21.4)
Excellent	0 (0)	7 (8.5)	2 (11.8)	6 (42.9)
Academic functioning*				
Poor	2 (16.7)	17 (20.7)	0 (0)	0 (0)
Fair	3 (25.0)	20 (24.4)	6 (35.3)	3 (21.4)
Good	2 (16.7)	18 (22.0)	6 (35.3)	4 (28.6)
Very good	1 (8.3)	8 (9.8)	2 (11.8)	3 (21.4)
Excellent	0 (0)	3 (3.6)	0 (0)	2 (14.3)
Caregivers of children with hearing loss				
Male (%)	1 (8.3)	17 (20.7)	4 (23.5)	3 (21.4)
Age (years)*	35 (29 – 43)	39 (25 – 62)	39 (25 – 50)	33 (25 – 44)
Education level				
Primary or lower	1 (8.3)	7 (8.5)	1 (5.9)	0 (0)
Secondary	4 (33.3)	17 (20.7)	3 (17.6)	4 (28.6)
High school or college	4 (33.3)	38 (46.3)	9 (52.9)	7 (50.0)
Degree or higher	3 (25.0)	16 (19.5)	4 (23.5)	2 (14.3)
Involvement in child's rehabilitation				
None	3 (25.0)	7 (8.5)	0 (0)	0 (0)
Some	2 (16.7)	29 (35.4)	6 (35.3)	5 (35.7)
Mostly	7 (58.3)	43 (52.4)	11 (64.7)	8 (57.1)
Household income				
<\$10,000	0 (0)	13 (15.9)	1 (5.9)	2 (14.3)
\$10,000 – 80,000	9 (75.0)	55 (67.1)	12 (70.6)	10 (71.4)
>\$80,000	3 (25.0)	10 (12.2)	3 (17.6)	1 (7.1)
Other stress in past 6 months	1 (8.3)	17 (20.7)	5 (29.4)	6 (42.9)

CI: Cochlear implant; HA: Hearing aid; NA: Not applicable

*P <0.05 (2-tailed)

functioning and academic functioning differed significantly among children with different hearing devices ($P < 0.05$).

Expert Panel Review

After multiple rounds of review by the expert panel, 7 questions as shown in Table 2 were removed. These questions were removed primarily because of their focus on sign language. They are less relevant in Singapore compared to the United States, as only a small number of children with HI are attending a school in Singapore where the primary medium of instruction is sign language.

Data Analysis

Exploratory Factor Analysis

Exploratory factor analysis was conducted on the remaining 61 items after the imputation of missing data and item recoding. Each of the different non-graphical solution to the scree test yielded different number of factors to retain. The number of factors ranged from 1 to 14 (Fig. 1). The suggested factor solutions were studied but none of them yielded any interpretable solution. A more thorough search for an interpretable solution was conducted for a 3- to 14-factor structure. The 1-factor structure was not included in the search as adopting a 1-factor structure would imply that the construct of caregiving is essentially one-dimensional. Given the wide range of sources for caregiving stress, the authors decided to search for a solution that is more than 1 factor. A 6-factor solution was eventually adopted as the most interpretable factor solution yielding the factors, “Expectation”, “Policy”, “Healthcare”, “Education”, “Support”, and “Adaption”. The 22 items with high cross-loadings were removed (Table 3). This solution however had a factor, “Expectation”, with only 2 items (Question 42 and 40) left after the removal. A decision was then made to move these 2 items to the next factor on which it loaded heaviest on (to “Policy” and “Adaption” respectively). This was done as factors with small number of items would be hard to interpret.²² This resulted in a 5-factor solution.

Table 2. Questions Removed from Original 68-item PHICE Questionnaire due to Reduced Focus on Signing Requirements in Singapore

02	Child care provider/schools/teachers/out-of-home caregiver's lack of signing skills.
22	Lack of interpreters for child.
25	My lack of signing skills.
36	My child's lack of signing skills.
47	Healthcare provider's lack of signing skills.
58	Immediate family and relative's lack of signing skills.
67	Lack of a large deaf community.

PHICE: Paediatric hearing impairment caregiver experience

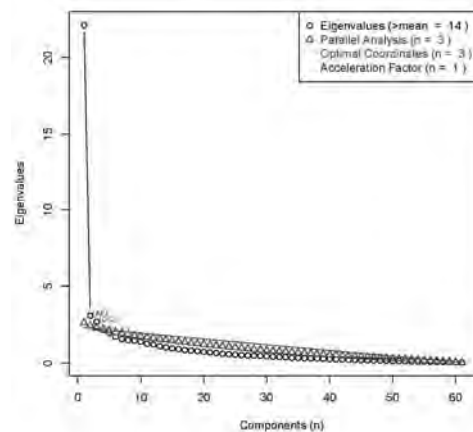


Fig. 1. Non-graphical solutions to the scree test. The number of factors suggested to retain is 14, 3, 3, and 1 by eigenvalues, parallel analysis, optimal coordinates, and acceleration factor respectively.

Table 3. Items in the Original PHICE with High Cross-Loadings

Items*		
50	(F)	Costly medical equipment and expenses.
37	(C)	Difficulty in communicating with my child.
57	(SO)	Problems discussing sexual issues with my child.
65	(H)	Worries about success of my child's therapy or rehabilitation.
60	(EQ)	Caring for the hearing aid or implant.
68	(SO)	Seeing my child frustrated because of his/her hearing loss.
34	(SU)	Lack of childcare or babysitters for child.
51	(EM)	Having no time for myself.
18	(EM)	Not being able to attend to the needs of other family members.
52	(EM)	Overwhelmed by information on caring for a child with hearing impairment.
63	(H)	Worries about risks associated with medical treatment (e.g., surgery, hearing equipment).
14	(C)	Distinguishing between behavior and communicating problems.
64	(H)	Knowing that my child was diagnosed with hearing impairment late.
21	(SU)	Worries about deaf community's perceptions of my decisions for my child.
55	(SU)	Inadequate support or understanding from spouse or partner.
17	(EM)	Worries about not doing enough for my child.
24	(SO)	Worries about my child's safety.
30	(EM)	Feeling uncertain about disciplining my child.
31	(H)	Traveling to medical appointments.
61	(F)	Costly daily aids like vibrating alarms and teletypewriter (TTY) services.
06	(EM)	Having difficulties accepting that my child is hearing impaired.
19	(H)	Worries if my child is getting good medical care.

PHICE: Paediatric hearing impairment caregiver experience

*The original factors in which the items below are denoted in parenthesis where C: Communication; ED: Education; EM: Emotional; EQ: Equipment; F: Finance; H: Health; SO: Social; SU: Support.

Adjustments of Factor Solution

Further changes were made to the 5-factor solution by the expert panel. Six questions assigned by the analysis software to certain factors were reassigned to other factors as shown in Table 4. This was done to ensure congruence between the meaning of the factors and the questions, and to improve interpretability of the factors. Three questions that were removed due to high cross-loadings were reintroduced by the expert panel as these questions were useful in identifying important factors that could negatively impact the rehabilitation outcome, and for which psychological counselling or financial help would be important (Table 4). They were grouped under existing factors based on their content after examining the change in model fit statistics as presented in the subsequent portions. Table 5 shows the actual 42 items of the modified PHICE, grouped under the 5 factors which represent the 5 categories of concerns contributing to caregiver stress for children with HI.

Confirmatory Factor Analysis

CFA was conducted on the original 8-factor model, the 5-factor model suggested in the exploratory factor analysis and the modified 5-factor model. Table 6 lists the various goodness-of-fit indices proposed by Hu et al.²³ From the various indices, we can see that the original 5-factor solution is a superior fit for the data. The changes made to the 5-factor model increased the levels of misfits as indicated by the

Table 4. Adjustment to Questions

Question	From	To
09 Feeling that healthcare providers do not listen to me.	Adaptation	Policy
35 Worries about my child's ability to make friends.	Education	Policy
62 Relocation to be near resources that meet my child's special needs.	Education	Policy
03 Working together with education professionals.	Healthcare	Policy
44 Understanding the laws related to hearing impairment.	Healthcare	Policy
42 Keeping large number of medical appointments.	Policy	Policy
06* Having difficulties accepting that my child is hearing impaired.	—	Policy
21* Worries about the deaf community's perceptions of my decisions for my child.	—	Policy
50* Costly medical equipment and expenses.	—	Policy

*Questions which were removed after exploratory factor analysis were reintroduced after reviews by the expert panel.

Table 5. Five-factor Solution Resulting in the Modified 42-item PHICE After Removal of Items with High Cross-loadings*

Factor	Question Number and Question in Original PHICE
Policy	10 Inadequate support or understanding from an employer.
	28 Inadequate insurance coverage for treatment of hearing impairment.
	33 Not able to take time off from work to tend to child's needs.
	39 Problems dealing with insurance company.
	44 Understanding the laws related to hearing impairment.
Healthcare	09 Feeling that healthcare providers do not listen to me.
	20 Working together with doctors.
	32 Feeling confused about medical information.
	42 Keeping large number of medical appointments.
	43 Working with the nursing or rehabilitation team.
	45 Difficulty getting information about hearing impairment or rehabilitation.
	50 Costly medical equipment and expenses.
Education	53 Difficulty getting medical and rehabilitation care.
	03 Working together with education professionals.
	27 Worries about decisions I have made for my child's education.
	38 Child's behavior in school.
	48 Child's academic achievement in school.
	49 Lack of educational opportunities for my child.
	59 Child's reading ability.
Support	15 Obtaining special learning materials for my child (e.g. books, captioned videos).
	21 Worries about the deaf community's perceptions of my decisions for my child.
	23 Worries about others taking advantage of my child.
	26 Worries about choosing the best form of communication for child (oral, sign, total).
	29 Feeling partly responsible for my child's hearing impairment.
	35 Worries about my child's ability to make friends.
	41 Changes in my relationship with my partner or spouse.
	46 Worries about how my child fits into the hearing community.
	54 Worries about whether my child should have a hearing aid, cochlear implant, or no aid.
	56 Lack of support network of parents facing similar problems.
	62 Relocation to be near resources that meet my child's special needs.
	66 Inadequate support or understanding from friends and relatives.

Table 5. Five-factor Solution Resulting in the Modified 42-item PHICE After Removal of Items with High Cross-loadings* (Con't)

Factor	Question Number and Question in Original PHICE
Adaption	01 Child has temper tantrums related to hearing loss.
	04 Worries about my child losing or damaging his/her equipment.
	05 Being unable to go to work.
	06 Having difficulties accepting that my child is hearing impaired.
	07 Hearing aids or cochlear implants not meeting expectations.
	08 Delayed cochlear implantation.
	11 Child uses hearing loss as an excuse to behave badly.
	12 Feeling uncertain about my child's future.
	13 Sound of child's voice is irritating, loud or shrill.
	16 Equipment interfering with child's activities.
	40 Tired due to caring for my child with hearing impairment.

PHICE: Paediatric hearing impairment caregiver experience

*In the shortened PHICE to be administered to caregivers, questions will not be grouped according to the 5-factor categories, so that caregivers would not know what issue is being assessed.

indices. Furthermore, the change between the original and the modified 5-factor model is deemed to be minimal. However, this is a trade-off that has to be made to improve the interpretability. The CFA suggests that after refactoring and reducing the number of items, the new factor structure is able to better explain the underlying phenomenon as expressed by the data.

Internal Consistency

Cronbach's α values for the original and the modified 5-factor solution are presented in Table 7. All subscales had an α value of more than 0.7 suggesting good internal consistency.²⁴ The change from the original 5-factor solution to the modified 5-factor solution is also minimal.

Questionnaire Results

The modified and shortened 42-item PHICE questionnaire results are shown in Table 8. While caregivers of children with no aids reported higher stress in the area of healthcare, caregivers whose children were aided with hearing devices reported higher stress in the areas of education and adaption. Caregivers of children aided with both CI and HA (bimodal aids in different ears) reported the highest levels of stress (low to moderate stress) over all 5 areas, followed by those of children aided with HA and children aided with CI (P

<0.05). Caregivers of children with no aids reported the lowest levels of stress (no to very low stress).

Discussion

A total of 26 items have been removed from the original PHICE questionnaire and the factor structure has been changed. The 8-factor structure comprising "Communication", "Emotional Well-Being", "Equipment", "Financial", "Social", "Education", "Healthcare" and "Support" has been reduced to a 5-factor structure comprising "Policy", "Adaptation", "Education", "Healthcare" and "Support". The shortened PHICE questionnaire for our Singapore context is a 42-item instrument that can be completed in about 15 minutes. It is structurally valid and internally consistent as suggested by the goodness-of-fit indices and Cronbach's α values.

Overlapping and Non-overlapping Factors

Given the adjustment of reassignment and reintroduction, some may worry that that the new structure could be an artefact of factor analysis and may not be meaningful in clinical usage. We thus discuss the overlapping and non-overlapping factors and explore the qualitative changes in the adjustment.

The 3 overlapping factors are shown in Table 9. The table was formulated after items were removed from the old factor structure and adjustments were made to the new factor structure. This allows for a fairer comparison of the changes made to the new factor structure. The number of shared items varies between 3 and 6 items suggesting that qualitatively, the factors share some similarity.

Both the healthcare and education subscales have more than half of the items in the new factors belonging to the old factor. This implies that these 2 subscales have changed little qualitatively. The items removed from and new items added to these 2 subscales were most likely due to the probable attribution to 1 or more of the subscales at the inception of the questionnaire. Factor analysis in this instance has helped to clarify under which subscale the items would more appropriately belong to. Furthermore, the new items are coherent with the implied meaning of the subscale.

The support subscale expanded from the original 6 items to the current 12 items. The original support subscale consisted of items that suggest the need of support for caregivers such as "Q56: Lack of support network of parents facing similar problems." The new support subscale contains items that pertain to the need of support for the child with HI such as "Q15: Obtaining special learning materials for my child (e.g. books, captioned videos)." A closer look at the various items under the new subscale reveals this difference. This

suggests that support in the context of caregiver stress may be homogenous, whether they are pertaining to the needs of caregiver or to the needs of the child with HI.

The other 5 non-overlapping subscales from the old factor structure have been regrouped into 2 subscales. The reassignments of the subscales have helped to better define the meaning of each subscale by the new composition of the items, and are supported by the confirmatory analysis.

Modified PHICE Questionnaire for Singapore

Results from the current study indicate that caregivers of children aided with different hearing devices experience different areas and levels of stress. Caregivers of children with no hearing aids worried more about “Healthcare” issues while caregivers of children with HA or CI had more concerns about “Education” and “Adaption” issues. Caregivers of children with HI with hearing devices reported significantly higher stress (stress score range, 3.39 to 4.14) than those of children with no hearing devices (score of 2.45).

This likely results from children with more severe HI naturally needing hearing devices more, as shown in Table 1. With more severe HI, the impact on education and academic achievements is more significant, even with hearing devices. Caregivers worry about their child’s educational options, progress in school, and working with the teachers (Table 5). With more severe HI, the impact on the child’s adaption is also more significant. For example, there would be more concerns regarding the child’s future options, worries that the hearing devices may interfere with the child’s activities and issues on regulating expectations about the hearing devices. The caregiver themselves have adaption concerns, like feeling tired while caring for the child, unsure of how to discipline the child, and being unable to go to work.

As children with HI without HA usually have less severe HI, the caregiver stress in the areas of “Education” and “Adaption” would correspondingly be reduced. This would allow other concerns like “Healthcare” to surface. They may feel that healthcare workers are not paying as much attention to them, as they do not need as many clinic visits

Table 6. Goodness-of-fit Indices

	8-factor Solution	5-factor Solution I*	5-factor Solution II†
Root mean square error of approximation (RMSEA)	0.087	0.068	0.074
Root mean square residual (RMR)	0.353	0.331	0.343
Standardised RMR (SRMR)	0.081	0.076	0.081
Normed fit index (NFI)	0.883	0.893	0.885
Incremental fit index (IFI)	0.937	0.949	0.944
Comparative fit index (CFI)	0.937	0.948	0.943

*Refers to the factor solution before reassignment and reintroduction of items.

†Refers to after modifications to 5-factor solution I.

Table 7. Internal Consistency of PHICE (Cronbach’s α)

Factor	5-factor Solution I*	5-factor Solution II†
Policy	0.770	0.737
Healthcare	0.862	0.854
Education	0.877	0.841
Support	0.875	0.890
Adaptation	0.875	0.873

PHICE: Paediatric hearing impairment caregiver experience

*Refers to the factor solution before reassignment and reintroduction of items.

†Refers to after modifications to 5-factor solution I.

Table 8. Modified PHICE Scores of Caregivers of Children Aided with Different Hearing Devices

Subscale (factor)	Type of Hearing Devices				Average
	No Aid	HA	CI + HA	CI	
Policy	2.35	3.08	3.72	2.79	3.06
Healthcare*	2.71	3.63	4.10	3.00	3.54
Education*	2.40	4.34	4.35	3.95	4.11
Support*	2.53	3.86	3.89	3.50	3.70
Adaption*	2.25	3.86	4.62	3.70	3.79
PHICE*	2.45	3.76	4.14	3.39	3.64

CI: Cochlear implant; HA: Hearing aid; PHICE: Paediatric hearing impairment caregiver experience

*P < 0.05

Interpretation of questionnaire scores: 0 = Not applicable, 1 = No stress, 2 = Very low stress, 3 = Low stress, 4 = Moderate stress, 5 = High stress, 6 = Very high stress, 7 = Extremely high stress.

Table 9. Overlapping Factors and Number of Shared Items

Factors	No. of Items		No. of Shared Items
	Old	New	
Support	7	12	3
Healthcare	9	8	6
Education	7	6	6

without use of the hearing devices. They may not be given as much medical information and support indirectly. For example, those with significant HI in one ear and normal hearing in the other ear may be deemed by many healthcare professionals to not need any help. However, they may have difficulty hearing in background noise situations like in classrooms; or if they are seated with the poorer hearing ear directed towards their teachers. Increasingly, the scientific literature supports the rehabilitation of even unilateral HI.

The degree of HI, social functioning and academic functioning differed significantly among children without and with different hearing devices ($P < 0.05$). Interestingly, the group of caregivers who reported the highest levels of stress was not those with children who had the most severe/profound HI in both ears requiring CI, but it was the group of caregivers with children aided with both a HA and CI due to less severe HI in one of the ears. A closer look at Table 1 revealed that the second group of children also had a longer duration before diagnosis of HI was made (average age of 29 months, compared to the average age of 15 months for children with CI). The later diagnosis will result in poorer social functioning and poorer academic functioning for the child, which in turn will contribute to increased caregiver stress (Table 1).

Utility of the Modified PHICE Questionnaire

The modified PHICE questionnaire has increased relevance and will improve uptake of use in our Singapore population. It is a validated instrument which can be quickly administered with ease to caregivers who visit the clinics with their children. Identifying the factors and specific issues that cause the greatest stress to caregivers allows the healthcare team, teachers, other family members, caregivers, counsellors and social workers to help to mitigate the stressors for the caregiver. Reducing the stress for the caregivers can improve the downstream functioning outcomes for the child across audiological, educational and social function domains. The instrument can also be applied to longitudinal research studies to determine the impact of and effectiveness of reduction of various areas of stress for specific caregiver groups. We hope to have other healthcare groups adopt this questionnaire if it is relevant to their population, so that the modified questionnaire can

be validated in different populations of patients in other countries. It is very possible too that caregivers in Asia have concerns and stressors that are significantly differently from caregivers in the West, and this tool can be used to compare across different regions in Asia. Details of the various steps involved in validating the instrument have been documented to allow a conduct of a similar study to provide evidence for the validity of the instrument in the context of other populations where this could be relevant.

Limitations

Seven questions from the original PHICE were removed primarily because of their focus on sign language. They are less relevant in Singapore compared to the United States, as only a small number of children with HI are attending schools in Singapore where the primary medium of instruction is sign language. With the Singapore Universal Hearing Screening Programme having been established in restructured hospitals in Singapore since 2001, and with good uptake in the private hospitals all over Singapore too, diagnosis of newborn HI within 3 to 6 months of birth is the norm here, and hearing rehabilitation is started early with HA, CI, and speech and language therapy where appropriate. With increasing awareness of the importance of good hearing amongst the public, education and healthcare teams (teachers, paediatricians, child development specialists, speech and language therapists, audiologists and otolaryngologists), there is also now less delay in the diagnosis of HI in children, allowing good hearing and learning outcomes with early intervention.

As a result, sign language use as the sole or main form of communication for children with HI is decreasing in Singapore. Most of our children with HI are able to join mainstream schools, or schools with combined aural and oral communication, complemented by some signing only if needed. There will be a small subset of children with HI who still sign—mainly those with concomitant health issues like other cognitive, neurological, major system disorders, or the minority of families who prefer that the child only signs. For populations that do have extensive use of sign language, the results from the use of our modified instrument should be interpreted with caution as we are unsure of the dynamics of interaction of sign language with the various domains of caregiving.

Conclusion

The original 68-item PHICE questionnaire has been shortened to a 42-item PHICE and reorganised in 5 subscales from the original 8 subscales. The resulting instrument is structurally valid and internally consistent, and is a useful tool to identify factors that can negatively impact rehabilitation outcome for HI in Singapore.

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Hearing Loss in Newborns with Cleft Lip and/or Palate

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Abstract

Introduction: This study aims to review the results of hearing screens in newborns with cleft deformities. **Materials and Methods:** A retrospective audit of 123 newborns with cleft deformities, born between 1 April 2002 and 1 December 2008, was conducted. Data on the results of universal newborn hearing screens (UNHS) and high-risk hearing screens, age at diagnosis, severity/type of hearing loss and mode of intervention were obtained from a prospectively maintained hearing database. **Results:** Thirty-one of 123 newborns (25.2%) failed the first automated auditory brainstem response (AABR). Seventy percent of infants (56 out of 80) who passed the UNHS failed the high-risk hearing screens which was conducted at 3 to 6 months of age. Otolaryngology referral rate was 67.5% (83/123); 90.3% of 31 newborns who failed the first AABR eventually required otolaryngology referrals. Incidence of hearing loss was 24.4% (30/123; 25 conductive, 2 mixed and 3 sensorineural), significantly higher than the hospital incidence of 0.3% (OR: 124.9, 95% CI, 81.1 to 192.4, $P < 0.01$). In terms of severity, 8 were mild, 15 moderate, 5 severe, 2 profound. Eighteen out of 30 infants (60%) were detected from the high-risk hearing screens after passing the first AABR. **Conclusion:** These newborns had a higher risk of failing the UNHS and high-risk hearing screen. There was a higher incidence of hearing loss which was mainly conductive. Failure of the first AABR was an accurate predictor of an eventual otolaryngology referral, suggesting that a second AABR may be unnecessary. High-risk hearing screens helped to identify hearing loss which might have been missed out early on in life or which might have evolved later in infancy.

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Key words: Malformation, Screening

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Introduction

Cleft lip and/or palate (CL/P) is one of the commonest congenital malformations.¹⁻³ A recent update collating data from international organisations for the years 2002 to 2006 reported an overall international rate of 7.94 in 10,000 live births with the highest prevalence of 10.2 occurring in the Asian continent.⁴ In Singapore, the incidence of cleft cases was reported to be 1.87 to 2.07 per 1000 live births.⁵⁻⁶

Hearing impairment has been reported in 20% to 60% of affected infants.⁷⁻¹² In a child with cleft palate, there is poor tensor veli palatini function with velopharyngeal insufficiency and increased Eustachian tube compliance.

This is postulated to result in persistent fluid collection in the middle ear, predisposing the young child to otitis media with effusion (OME) and thus, conductive hearing loss.¹³⁻¹⁷ The association of OME with CL/P has been clearly demonstrated in many studies across different racial groups.¹⁷⁻²⁰ A previous study in Singapore²¹ reported an incidence of middle ear disease to be 23% in Chinese patients with cleft palate, whereas a recent study in China²² reported a higher incidence of 64% amongst 42 Chinese infants with non-syndromic CL/P and a consequently higher incidence of hearing loss of 86%. This should be given due concern

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as studies have shown that hearing loss due to persistent middle ear effusions can have long-term effects on speech, language, and cognitive development.²³⁻²⁵ In view of this, it is vital to detect hearing loss early and to institute timely intervention if it is present. Although the Joint Committee for Infant Hearing (JCIH) from the American Academy of Pediatrics has recommended that these high-risk infants should be referred for audiological assessment at least once by 24 to 30 months of age, an earlier high-risk hearing screen may be advantageous for them.

Universal newborn hearing screening (UNHS) is currently practised in many countries worldwide. This has led to early detection of hearing loss, leading to early intervention which in turn, facilitates improvement of speech and language outcomes.²⁶⁻²⁹ The UNHS programme in KK Women's and Children's Hospital (KKH), which was implemented in 2002, uses a 2-step automated auditory brainstem response (AABR) protocol (Fig. 1). The AABR measurements are obtained non-invasively via surface electrodes that record neural activity generated in the cochlea, auditory nerve, and brainstem in response to acoustic stimuli delivered. Results of the AABR reflect the status of the peripheral auditory system, the eighth cranial nerve, and the brainstem auditory pathway. Hence, it has the advantage of detecting peripheral (conductive and sensory) hearing loss as well as neural auditory disorders.³⁰⁻³¹

The first screen is typically performed before hospital discharge for all newborns on day 1 of life or after 34 weeks of gestation in premature infants. A "refer" result is conferred on patients who do not pass the AABR. They

then undergo the second screen at 3 to 6 weeks of life at the outpatient setting. The high-risk hearing screen is performed at 3 to 6 months of life for those who have passed the UNHS but have been identified with high-risk for hearing impairment. The high-risk hearing screen is performed by the audiologist at the otolaryngology centre with the otoacoustic emission (OAE) test. Selected risk factors for hearing impairment include: craniofacial anomalies, positive family history of hearing impairment, intrauterine infections, neonatal intensive care unit stay with use of ototoxic drugs or mechanical ventilation etc.³² Infants who do not pass the high-risk hearing screen or UNHS are referred to the otolaryngologist for further evaluation. This practice recognises the fact that hearing impairment can occur later in life and will be missed by the UNHS. The UNHS office staff track the progress of the infant and record the outcome of audiological assessment.

Having implemented UNHS and high-risk hearing screen in our hospital since 2002, this paper is the result of a systematic audit performed on hearing screening in high-risk infants to identify service gaps and to streamline the screening process. It reviews the results of the newborn and high-risk hearing screens in infants with CL/P born in KKH. There is little current literature on the outcome of the UNHS and early postnatal hearing screening in these infants.

Materials and Methods

The results of UNHS and high-risk hearing screen performed for newborns delivered in KKH, including newborns with CL/P, had been prospectively downloaded to a computerised database (HITRACK). Risk factors for hearing loss, the results of high-risk hearing screens, referrals to the otolaryngology department, audiological investigations and subsequent hearing outcomes had been entered manually by the UNHS staff. Hearing loss was confirmed by evoked response audiometry (ERA) with steady state evoked potential (SSEP) done in the outpatient clinic under conscious sedation or under the same general anaesthesia setting as the cleft repair. The following data on newborns with CL/P born between 1 April 2002 and 31 December 2008 were obtained from the HITRACK database and audited: results of UNHS and high-risk hearing screen, age at diagnosis, severity and type of hearing loss and the mode of intervention. Comparisons were made with the KKH cohort data involving 87,882 newborn infants.³³ Interventions include: 1) medical treatment (oral or aural antibiotics and treatment for cerumen), 2) surgical treatment (myringotomy and tympanostomy), 3) amplification and auditory verbal therapy, and 4) speech and language intervention. Missing information was obtained from reviews of case records. The study was approved by the institutional review board.

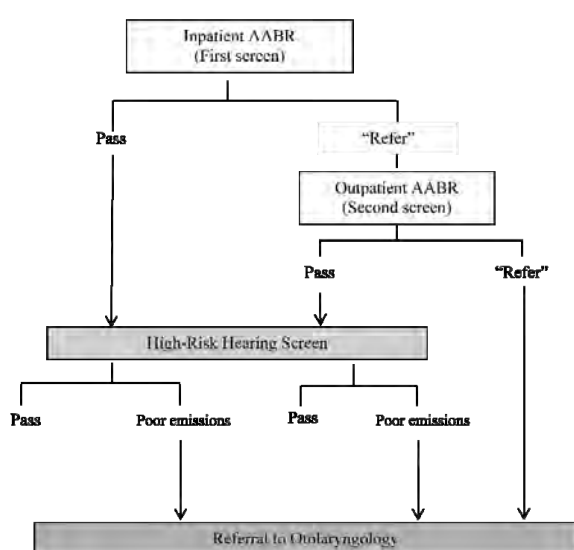


Fig. 1. The UNHS and high-risk hearing screen protocol in KKH.

Results

There were 123 newborns with CL/P during the audit period from 1 April 2002 to 31 December 2008, from a total of 87,882 births (0.14%). This incidence of 1.4 per 1000 births is comparable to the past reported incidence of cleft cases in Singapore.^{5,6}

Results of Universal Newborn Hearing Screening (UNHS)

A total of 96.7% underwent hearing screen prior to hospital discharge. Figure 2 shows the outcomes of the UNHS in these patients. Out of the 4 newborns who missed the inpatient AABR, one had been discharged shortly after birth and did not return for the outpatient AABR. At 1.5 months of life, she was re-admitted for sepsis and right otorrhea, and was referred to otolaryngology, where a unilateral moderate conductive hearing loss was detected. Two of these 4 newborns were transferred to the Paediatric Intensive Care Unit (PICU) after cardiac surgery for coarctation repair and abdominal surgery for necrotising enterocolitis. They were not screened before discharge from the paediatric department but both returned for outpatient screening.

Results of High-Risk Hearing Screening

A total of 94 cleft infants were eligible for high-risk hearing screen (Fig. 3). These included the 88 infants who passed the inpatient AABR, 3 who passed after a first “refer” result, 1 who missed the repeat screen after a first “refer” result, and 2 who passed as outpatients after missing the inpatient screen. Despite sending reminder letters following failure to attend the high-risk hearing screen visit, 14 (14.9%) did not attend. Out of the 80 who underwent high-risk hearing screen, 56 (70%) had poor emissions and were referred to otolaryngology.

Referrals to Otolaryngology

In total, 83 were referred to the otolaryngology department for further evaluation, giving rise to an otolaryngology referral rate of 67.5% (Fig. 4). Out of these 83 infants, 30 were found to have hearing loss: one was directly referred from birth, 8 were referred from the UNHS, 3 were directly referred after the first AABR, and 18 were referred from the high-risk hearing screen (Fig. 5).

Hearing Loss

Thirty (24.4%) of the 123 infants with cleft deformities were diagnosed to have hearing loss at a median age of 39.9 weeks of life (range, 7.9 to 126.9 weeks). The age of diagnosis in each individual referral category is shown in Figure 5. The number needed to screen to pick up one case of hearing loss is 5. In the 30 cases of hearing loss,

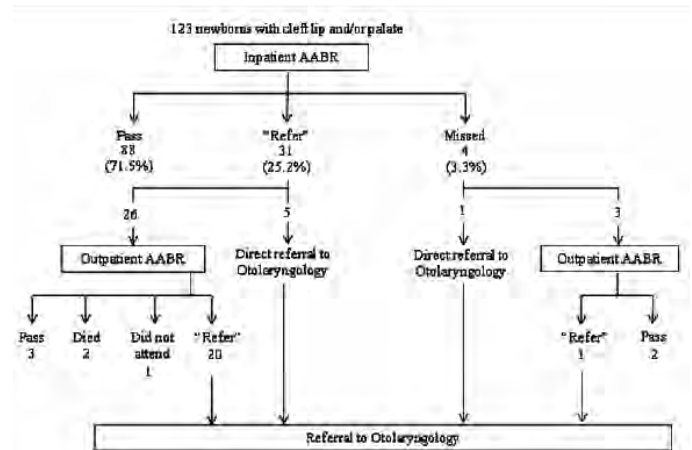


Fig. 2. Outcome of the UNHS for newborns with cleft lip and/or palate.

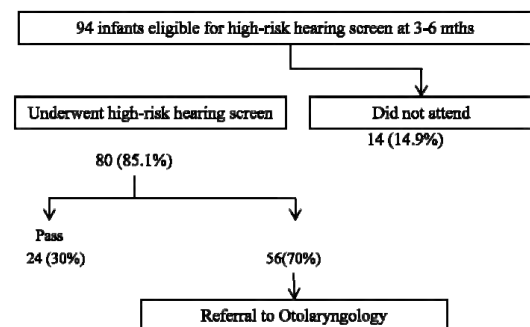


Fig. 3. Outcome of the high-risk hearing screen for newborns with CL/P.

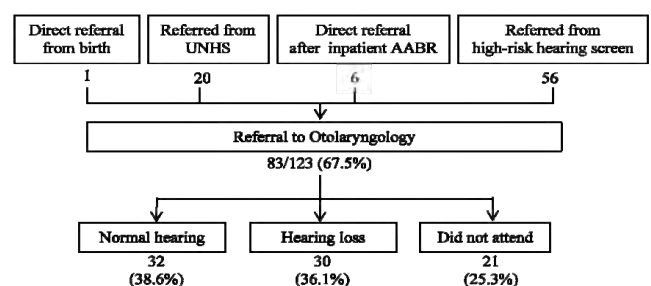


Fig. 4. Outcome of infants referred to otolaryngology for audiological evaluation.

23 (76.6%) were conductive, 2 (6.7%) were permanent conductive hearing loss, 2 (6.7%) were mixed and 3 (10%) were sensorineural; 12 had unilateral involvement (6 of mild severity, 3 of moderate severity, 2 of severe severity, 1 of profound severity); 18 had bilateral involvement (2 of mild severity, 12 of moderate severity, 3 of severe severity, 1 of

profound severity). Twenty-seven (90%) of the 30 affected infants underwent intervention; 22 underwent both surgical and medical treatment, 3 underwent medical therapy alone, 1 underwent surgical intervention and audiovisual therapy (AVT), and 1 underwent speech and language intervention.

Table 1 shows that much larger percentages of infants with CL/P do not pass the newborn AABR either at birth or at 3 to 6 weeks, and are referred to otolaryngology for audiological assessment and have hearing loss compared to the general population of non-cleft newborns born in KKH during the same period of time (unpublished data from HITRACK database of UNHS in KKH, 1 April 2002 to 31 December 2008).

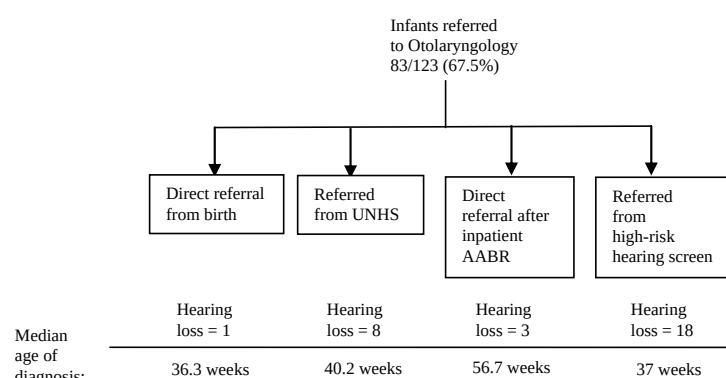


Fig. 5. Referral sources for infants with hearing loss.

Confounders

Univariate analyses were carried out with the other known risk factors such as positive family history of hearing loss, low birth weight less than 1.5 kg, meningitis, use of ototoxic drugs, associated syndromes, hyperbilirubinaemia, intrauterine infections, craniofacial anomalies, use of mechanical ventilation, asphyxia, gestation less than 32 weeks and neonatal intensive care unit stay for more than 48 hours. They showed no significant confounding effect on the outcome of hearing screening ($P > 0.05$).

Discussion

Diagnosis of Hearing Loss

More than 95% of affected infants were screened before hospital discharge, as recommended by JCIH.³² The percentage of infants with CL/P who did not pass the UNHS is comparable with other studies.³³⁻³⁵ The percentage of infants with hearing loss was at the lower end of reported ranges in other studies (20% to 60%).^{7-11,20} There are several possible reasons that could explain this. First, the confirmatory audiometric test done in the otolaryngology clinic or in the operating theatre with the cleft surgery may have been performed after some medical treatment had been instituted by the otolaryngologist as deemed appropriate during the initial reviews. Second, it could also be due to the fact that we had an unfortunately high default rate (14.9% at the high-risk hearing screen and 25.3% at the otolaryngology evaluation).

Table 1. Comparison of Screening Results in Infants with Cleft Lip and/or Palate with the General KKH Non-Cleft Cohort

Born Between 1 April 2002 and 31 December 2008				
	KKH Cohort Excluding Cleft Infants (n = 87,759)	Infants With Cleft Lip and/or Palate (n = 123)	Odds Ratio (95% CI)	P Value
Did not pass inpatient AABR	3.3% (2857/87,759)	25.2% (31/123)	10.0 (6.6 – 15.1)	<0.01
Did not pass outpatient AABR*	13.8% (407/2940†)	72.4% (21/29‡)	16.3 (7.2 – 37.1)	<0.01
Referral to otolaryngology	0.5% (395/87,759)	67.5% (83/123)	458.9 (310.7 – 677.8)	<0.01
Diagnosed with hearing loss	0.3% (226/87,759)	24.4% (30/123)	124.9 (81.1 – 192.4)	<0.01

AABR: Automated auditory brainstem response; KKH: KK Women's and Children's Hospital

*In infants who were scheduled for outpatient AABR as they did not pass or had missed the inpatient newborn AABR.

†The denominator of 2940 includes the 2857 infants who did not pass and 127 who missed their inpatient AABR and excludes 44 infants who were referred directly to otolaryngology for other reasons. Of the 2940, 407 infants did not pass, 2345 passed and 188 did not attend.

‡The denominator of 29 includes the 31 infants who did not pass and 4 infants who missed the inpatient AABR and excludes 6 infants who were referred directly to otolaryngology for other reasons. Of the 29, 2 infants died prior to assessment, 5 passed and only 1 did not attend.

High-Risk Hearing Screen

The majority of infants with hearing loss in this audit were identified by the high-risk hearing screen. This further reinforces the importance of this high-risk hearing screen at 3 to 6 months of age for these newborns as hearing impairment may evolve later in their infancy and thus may not be apparent during the first AABR. JCIH 2007 recommended a referral for audiological assessment at least once by 24 to 30 months of age.³² Our current protocol reassesses the child at risk at an earlier age with the high-risk hearing screen. It is effective for the detection of late-onset hearing loss even when done at an age earlier than the recommended age stipulated by JCIH. It allowed intervention before the age of spoken language.

Age of Diagnosis

The age of diagnosis was at a median age of 39.9 weeks of life (range, 7.9 to 126.9 weeks). It is preferable to diagnose hearing impairment under 1 year of age, before the onset of speech. This is crucial for early intervention and the possibility of normal speech.³⁶

The cases which were diagnosed (i.e. underwent the confirmatory audiometric test) beyond the age of 1 year were usually already identified earlier through a failed hearing screen and seen by the otolaryngologist before 6 months of age for initial assessment and perhaps a trial of treatment. Only 1 infant defaulted multiple otolaryngology visits due to medical illnesses and was first seen by the otolaryngologist at 8 months of age. At times, when it is difficult or inappropriate to sedate the young infant for the outpatient audiometric test, the otolaryngologist may defer the confirmatory audiometric test to the date of the cleft palate surgery so that it can be done under the same general anaesthetic setting.

The age of diagnosis is only slightly earlier for the group which was referred from the UNHS compared to that referred from the later high-risk hearing screen (Fig. 5). This should not be misinterpreted to mean that there is no significant advantage in early screening for hearing loss. An earlier otolaryngology referral prompted by a failure to pass the UNHS widens the window period for intervention whilst awaiting the confirmatory audiometric test. As mentioned above, the confirmatory audiometric test may only be done at the otolaryngology clinic after some initial assessment and trial of medical treatment, and may at times be deferred to coincide with the date of the cleft surgery.

As per JCIH 2007 guidelines for congenital permanent bilateral or unilateral hearing loss, permanent conductive hearing loss and neural loss, it would have been preferable for these infants to have undergone comprehensive audiological evaluation at no later than 3 months of age and receive

appropriate intervention at no later than 6 months of age if they were confirmed to have hearing loss. In our audit, there were 2 infants diagnosed with permanent conductive hearing loss and 3 infants with sensorineural hearing loss, with the age of diagnosis ranging from 3 to 22 months (median age of 8 months). Two of these 5 infants were diagnosed before the age of 3 months. The remaining 3 infants who were diagnosed after 3 months of age were all reviewed by the otolaryngologist before 3 months of age – one was an ex-premature 26-weeker neonatal intensive care unit graduate who had a stormy neonatal period and required surgical treatment for bilateral OME; another had Goldenhar syndrome with left microtia and normal hearing on the right ear; the last infant had recurrent OME requiring multiple surgical interventions.

Nature of the Hearing Loss

Similar to other studies, hearing loss was mainly conductive in this study.^{8,18} This is not surprising as OME has been found to be almost universally present in infants with cleft palate.^{17-18,37-38} Conductive hearing loss due to OME is potentially treatable by intervention with antibiotics or grommet insertion. Hence, it is beneficial and imperative to initiate otolaryngology referral upon failure of the hearing screens done in the first 6 months of life.

Default Rate

Fourteen out of 94 infants (14.9%) defaulted the high-risk hearing screen. Out of the 80 infants who attended the high-risk hearing screen, 56 (70%) did not pass. Using this same percentage, it is postulated that at least 9 infants out of the 14 defaulters would have not passed the high-risk hearing screen. Twenty-one infants out of 83 (25.3%) did not attend the otolaryngology referral. Out of the 62 infants who attend the otolaryngology referral, 30 of them (48.4%) were documented to have hearing loss. Using this same percentage, it is postulated that at least 10 of the otolaryngology defaulters and 4 of the high-risk hearing screen defaulters would have hearing loss. Assuming the worst case scenario, if all 14 high-risk hearing screen defaulters and all 21 otolaryngology defaulters had hearing loss, the proportion of infants with cleft abnormalities who have hearing loss will be increased to 52.8%.

While it is heartening to know that all of the infants did undergo at least one hearing screen, the increasing rate of defaulting at the later stages of the screening process, when the risk of hearing loss is rising, is alarming. This high default rate is similarly seen in other centres, and in infants with other risk factors for hearing impairment.²⁸ It would be useful to review the characteristics of the infants who default and to explore the reasons for defaulting. One

possible reason could be that parents of these infants with cleft deformities may be more focused on the surgical management and feeding issues related to the cleft deformities. Not realising the associated high incidence of hearing loss, they may overlook the need for hearing screens in early infancy. This highlights the importance of parental education. It has been shown that speech and language development is more dependent on hearing ability than the severity of cleft or surgical repair.³⁹

Recommendations for Improvement

Direct Referral for Otolaryngology Assessment After a First Failed Automated Auditory Brainstem Response (AABR)

Out of 31 infants who did not pass the first AABR, 5 were referred to otolaryngology, 2 passed away and 1 did not attend. The majority (87.0%) of the remaining 23 had the same result on the outpatient screen and were referred to otolaryngology. All 3 infants who passed the repeat outpatient AABR subsequently failed the high-risk hearing screen and were also referred to otolaryngology. In total, 28 out of the 31 infants (90.3%) who did not pass the first AABR required an eventual otolaryngology referral. Thus, we recommend a direct referral to otolaryngology if the infant does not pass the first AABR. This will be discussed with the Department of Otolaryngology and the birth defect team of the Department of Neonatology.

Reduction of the Default Rate

Infants with CL/P are followed up in the neonatal birth defect clinic and in the craniofacial unit, both by a plastic surgeon and a speech and language therapist. These visits can serve as an excellent platform to reiterate advice to parents regarding the high incidence of hearing loss and recurrent otitis media. Both teams of staff can be prompted to reinforce compliance with hearing screens.

Future Follow-Up

Other studies have reported that the median resolution of conductive hearing loss in infants with cleft palate was 5 years^{9,40} and persisted in 24.8%.⁹ Follow-up of this study cohort would be beneficial to determine if early diagnosis and intervention of hearing loss facilitated by systematic screening will lead to its earlier resolution and reduction in the percentage that persist. The results will be reviewed in 2 to 3 years after the appropriate amendments to the screening programme have been instituted.

Conclusion

Newborns with CL/P are at a higher risk of failing to pass both their newborn and high-risk hearing screens,

thus requiring otolaryngology referrals. The incidence of hearing loss in these newborns with cleft deformities is significantly higher than the general population. Failure of the first AABR was an accurate predictor of an eventual otolaryngology referral, suggesting that a second AABR may be unnecessary. The high-risk hearing screen is beneficial for those who may have missed earlier screens, or whose hearing problems evolve later in their infancy. The high default rate should be addressed by reinforcing compliance to hearing screens and otolaryngology assessments.

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Internet Addiction in Young People

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Abstract

In our technology-savvy population, mental health professionals are seeing an increasing trend of excessive Internet use or Internet addiction. Researchers in China, Taiwan and Korea have done extensive research in the field of Internet addiction. Screening instruments are available to identify the presence of Internet addiction and its extent. Internet addiction is frequently associated with mental illnesses such as anxiety, depression, conduct disorder and attention deficit hyperactivity disorder (ADHD). Treatment modalities include individual and group therapies, cognitive behavioural therapy (CBT), family therapy and psychotropic medications. A significant proportion of Singapore adolescents engaging in excessive Internet use are also diagnosed to have concomitant Internet addiction. Despite the presence of a variety of treatment options, future research in this area is needed to address its growing trend and to minimise its negative psychological and social impact on the individuals and their families.

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Key words: Aetiology, Pathophysiology, Treatment

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Introduction

The Internet has in recent years become ubiquitous in the lives of young persons and children due to rapid information technology (IT) development, high speed wire connection, easy accessibility and increasing affordability. Its growth has also been fuelled by a huge customer demand created by social and print media, advertisements and peer influences. Singapore has been ranked as one of the top three Asian countries to have a high proportion of its population accessing and using the Internet.¹ In our technology-savvy population, mental health professionals are seeing an increasing trend of excessive Internet use or Internet addiction. Much is not known about its presentation or treatment options. This paper intends to summarise the phenomenology and pathogenesis of Internet addiction and its available treatment modalities.

Definition and Prevalence of Internet Addiction

According to Young,²⁻⁴ Internet addiction closely resembles an impulse control disorder. She described 8

common signs⁵ of Internet addiction which are based largely on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for pathological gambling. The common features include preoccupation with the target activity, development of tolerance and withdrawal symptoms, compulsive need to engage in activity or a sense of loss of control, unsuccessful attempts to stop or cut down, and neglect of social, academic and occupational obligations with functional impairment. Based on these, she developed the Internet Addiction Test (IAT), which is the first validated instrument to assess Internet addiction. The psychometric properties of the IAT show that it is a reliable and valid measure of the degree and extent of Internet addiction, which can be used in both outpatient and inpatient settings.⁶

The prevalence of Internet addiction varies across countries: 2.4% of high school students⁷ and 19.8% of adolescents in Taiwan⁸ were found to be addicted to the Internet. In Korea, Ha et al⁹ reported in their study that

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14% of 455 children and 20% of 836 adolescents were screened positive for excessive Internet use, quite similar to the Singapore study in which Mythily et al¹⁰ reported that 17.1% of 2735 adolescents (mean age of 13.9 years) used more than 5 hours of Internet everyday. However, as the Singapore study only asked participants to self-report the number of hours they spent on the Internet rather than using any diagnostic tool, the results can only be interpreted as excessive Internet use instead of Internet addiction. In another local study on gaming addiction, 8.7% in 3034 children and adolescents were found to be addicted to online gaming.¹¹

Negative Effects of Internet Addiction

When Internet use becomes excessive and pathological, there could be ill-health effects on the adolescents such as impaired psychological well-being, less peer and family interaction, poor academic performance, and impediment to achievement of psychosocial developmental tasks.^{3,12} A study on the adversities of Internet overuse by the Korean National Youth Commission¹³ in school-going children indicated that as many as 27.6% children and 28.1% adolescents suffered deterioration in their grades. Up to 23.7% of them experienced disruptions in their lives, 10.6% experienced social isolation and as high as 13.4% of adolescents presented with school refusal. Violence at home occurred in 7.1% of the adolescents who overused the Internet. Typically affecting more boys than girls, sufferers tend to have behavioural problems such as hyperactivity, conduct disorder and worse overall psychosocial adjustments than their peers.¹⁴ Correlations between Internet use (including online gaming) and negative outcomes such as obesity, aggression and poor school outcomes have also been investigated.^{15,16}

Furthermore, excessive use of Internet can also impede one's physical health such as causing back pain, eye strain and carpal tunnel syndrome.³ Cardiopulmonary-related deaths were also reported in the most severe cases.¹³

Aetiology and Pathophysiology

Similar to many psychiatric illnesses, the interplay of neurobiological influences and psychosocial factors has been hypothesised as the main factor in producing addictive behaviour including Internet addiction.

In the past decade, there has been an increasing number of research studies that investigate Internet addiction using neuroscientific methods. Two most commonly utilised techniques are electroencephalogram (EEG) and functional magnetic resonance imaging (fMRI). Specifically, individuals with Internet addiction exhibit poorer executive control as illustrated by lower medial frontal negativity

(measured using EEG) during the incongruent Stroop test.¹⁷ Furthermore, altered neurophysiological condition^{18,19} as demonstrated by decreased absolute delta and beta powers, and increased gamma power at resting state could serve as potential neurobiological markers for Internet addiction due to the brainwaves' association with impaired inhibitory control and trait impulsivity.

On the other hand, using fMRI technique, Internet addiction was found to be associated with increased orbitofrontal cortex activation in money-gain trials during a card playing game and decreased anterior cingulate cortex activation in loss trials.²⁰ This implies that individuals with Internet addiction have enhanced reward sensitivity and decreased loss sensitivity than normal controls. A more recent fMRI study showed that individuals with Internet addiction necessitate greater cognitive efforts during decision-making tasks as illustrated by differential activation levels on certain brain regions involved in decision-making such as inferior frontal cortex, insula, posterior and anterior cingulate cortex.²¹ Lastly, brain activations similar to individuals with substance addiction were also observed in a study using cue-induced online gaming,²² thus suggesting common neurobiological pathways in both addictions.

Comparable with other addictions, the “addictive” components embedded within Internet use have a tendency to appeal to the users' brain reward system, which results in an increase in levels of the naturally-occurring neurotransmitter dopamine.²³ This modulates the brain's ability to perceive reward reinforcement and keeps the person coming back to re-experience these good feelings. After multiple reinforcements, the person might become “addicted” and requires higher level of stimulation to reach the same “good feeling”.

Apart from the neurobiological factors, prior research have found that psychological factors such as attention deficit hyperactivity disorder (ADHD), autism, anxiety and depression,^{24,25} and social factors like poor family support and adult supervision, parental unemployment, poor interpersonal relationships, and social isolation²⁶⁻²⁸ are linked to Internet addiction.

One of the important psychosocial developments in adolescence is to strive for autonomy and independence.²⁹ By engaging in activities that otherwise would be prohibited by parents, adolescents could have a free rein online without being regulated by adults. Their search for self-identity, need to be close to and be a part of a peer group also render them vulnerable to peer influence and they tend to gravitate toward shared interests.³⁰ Certain personality and temperament profiles, such as a high degree of impulsivity, anger expression, novelty seeking and neuroticism, but with low agreeableness and self-esteem, could predispose adolescents and young adults to develop Internet addiction.³¹⁻³⁴ Harm avoidance, initially believed to be low for individuals with addictions,

was on the contrary found to be high in those suffering from Internet addiction.³² Choi et al theorised that anxiety could be the mediating factor in these individuals who used the Internet as a means of avoiding uncomfortable feelings such as stress, anxiety and loneliness. The interplay of mediating factors such as anxiety, depression and impulsivity in a specific motivation and personality construct (Behavioural Inhibition/Approach System, BIS/BAS) seems to also confer certain vulnerabilities to the development of Internet addiction.³⁵

Severe competition in school, stress from studies, parent-child problems and peer conflicts are all highly stressful situations which could generate negative emotions, such as low self-esteem, feelings of inferiority and repressed anger, in adolescents. Since the Internet provides a ready channel for individuals to gain social support and cultivate relationships which otherwise would be unavailable, the adolescents could redirect their energy and focus on the Internet, using cyberspace as an escape from unpleasant events or memories, or to manage negative emotions.²³ Cyberspace thus provides a temporary respite from their troubles and worries in the real world.

Management of Internet Addiction

Cognitive behavioural therapy (CBT), family therapy and psychoeducation are the mainstays of treatment for Internet addiction. Individual psychotherapy with CBT and group therapy with CBT in the clinical setting have shown good outcomes mainly with individuals with mild Internet addiction.^{36,37} For example, a randomised controlled study in adolescents aged 12 to 17 years with Internet addiction using either school-based CBT or no treatment,³⁸ reported an improvement for both groups, but the active treatment group improved more in terms of time management as well as reduction of emotional, cognitive and behavioural symptoms.

Family therapy, communication and parenting skills training are important adjunctive treatment modalities for Internet addiction.^{39,40} Besides educating the whole family on the disorder, emphasis should be made to reduce blame on the adolescents and to improve parenting and discipline skills. Assisting adolescents to find alternative hobbies and activities including family outings are relevant in order to distance them from the Internet and enhance parent-child relationships.

Though there have been no double-blind, placebo-controlled studies on the pharmacotherapy for Internet addiction, pharmacological management of Internet addiction predominantly targets the core mental health problems driving the behaviour. Comorbid ADHD, anxiety, depression or autism disorders should be treated. Stimulants and antidepressant medications are frequently used together

with behavioural modification or cognitive therapy.^{41,42}

In Singapore, treatment for Internet addiction is available at National Addictions Management Service (NAMS) sited in the Institute of Mental Health (IMH), and in the community. Some community and welfare agencies such as TOUCH Community Services conduct regular school workshops and cyber wellness enrichment programmes for families and adolescents suffering from Internet addiction or Internet-related problems. The enrichment programme focuses on promoting self-awareness through structured and adventure learning processes, and connecting the adolescents back to healthier Internet use habits. Counselling, mentoring and supervision, and behavioural modification methods to improve self-regulation in Internet use are also provided. School counsellors are equipped with counselling skills to help students overcome their Internet addiction. Should there be a mental health condition contributing to the development of the addiction, school counsellors could obtain professional assistance from the Response, Early Intervention and Assessment in Community Mental Health (REACH) programme. This programme, first developed under the National Mental Health Blueprint in 2007,⁴³ comprises 4 teams of multidisciplinary allied health staff who perform assessments, provide support and manage students in their own schools and when necessary, link the affected students to child psychiatric services, NAMS and other community cyber wellness resources.

Prevention in Internet Addiction

With most behavioural and addiction problems, prevention is key to reducing incidence and morbidity associated with them. Public awareness of Internet addiction, parent education on Internet use and advocacy for proper parental supervision of Internet use are pertinent factors in prevention efforts. Simple measures, such as implementing house rules on Internet usage at a young age, placing the computer in the common living area and making available alternative social activities, are some of the practical tips parents could start doing easily. Improved parent-child relationship and family functioning, effective communication and positive social support further lay the foundation for the family and the children to become resilient and competent in problem solving.

Conclusion

Internet addiction is a complex behavioural syndrome, resulting from multiple biological and psychosocial factors. It tends to be persistent and resistant to treatment with high relapse rates. While it has yet to be included in the DSM-V as a distinct diagnostic entity, Internet addiction has been perceived by many mental health professionals as a very real

psychosocial problem likened to that of substance misuse. Its true prevalence is difficult to establish due to different instruments used to define and measure the problem. Regardless of whether Internet addiction is considered a clinical disorder, we know that its severity is highly correlated with that of comorbid psychiatric disorders. A multidisciplinary team approach involving collaboration among education, social and mental health agencies are necessary to provide a holistic and comprehensive management of Internet addiction. Preventive measures remain critical in curbing Internet-related problems early and effectively.

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Imaging Cardiac Sarcoidosis by Cardiac Positron Emission Tomography (PET): A Local Experience Using a High-Fat, Low-to-No Carbohydrate Protocol

Dear Editor,

A 40-year-old female presented acutely with syncope and recurrent ventricular tachycardia (VT) requiring repeated cardioversion. Transthoracic echocardiogram (TTE) revealed mildly depressed systolic function of 40% to 45% with normal right ventricular size and function. Coronary angiogram revealed insignificant coronary artery disease (CAD). Biopsy of enlarged mediastinal lymph nodes revealed evidence of non-necrotising granulomatous inflammation, with no evidence of tuberculosis or fungi.

To ascertain a diagnosis of cardiac sarcoidosis, an 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) study was performed under strict, non-fasting, high-fat, low-carbohydrate dietary modifications. The patient was instructed to consume 2 consecutive meals containing high fat and low-to-no-carbohydrate diet the evening prior to FDG PET/CT imaging, and on the morning of the scan. She was advised to have fatty unsweetened foods such as fried chicken, fried eggs or fried bacon, without bread or rice because these are sources of carbohydrates. She was also advised not to have beverages that contain milk or sugar. On the day of the scan, the patient was injected with 10-millicuries of 18F-FDG intravenously, followed by cardiac 18F-PET/CT imaging 60 minutes later.

18F-FDG PET/CT images were compared to myocardial perfusion imaging (MPI) study by single-photon emission computed tomography (SPECT). The cardiac 18F-FDG PET/CT study revealed markedly increased myocardial FDG uptake involving the mid to basal anterior and distal to basal anteroseptal walls that corresponded to segmental perfusion defects on MPI SPECT study, as well as focal FDG uptake in the right ventricle and distal to basal inferoseptum (Figs. 1a-c). The intense areas of diffuse uptake corresponded to near-transmural enhancement in the septum and anterior myocardium on cardiac magnetic resonance imaging (MRI) (Fig. 1d). The patient was treated with steroids and given an implantable cardio-defibrillator (ICD). Repeat 18F-FDG PET/CT study performed 6 months later demonstrated reductions in FDG uptake in the anterior, anteroseptal, right ventricle and inferoseptal walls, suggesting reduction in active disease activity in the myocardium (Fig. 1e).

On the other hand, a 54-year-old woman with biopsy-proven pulmonary sarcoidosis was evaluated for sarcoid involvement of the heart by the same 18F-FDG PET/CT imaging protocol and dietary instructions. While the whole body 18F-FDG PET/CT revealed multiple hypermetabolic mediastinal and bilateral hilar lymph nodes consistent with systemic sarcoidosis, there was absent myocardial FDG uptake on the 18F-FDG PET/CT scan, suggestive of the absence of cardiac sarcoid involvement (Fig. 2).

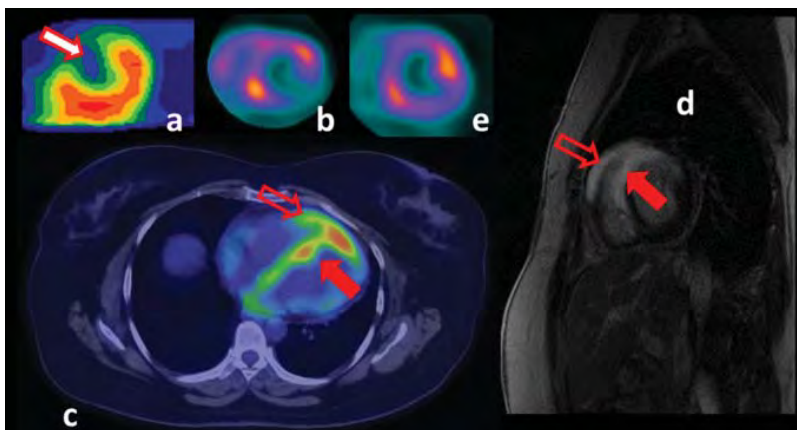


Fig. 1. 18F-FDG PET/CT scan images of 40-year-old patient. (A) Representative short-axis image of technetium-99m SPECT showing resting perfusion defect in the basal anteroseptum (arrow), with a corresponding mismatch on the (B) short-axis 18F-FDG PET/CT images, demonstrating FDG uptake in the anteroseptum, together with an area of abnormal uptake in the anterior and inferoseptum. Regions of the myocardium with normal perfusion in (A) (lateral and inferior walls) show no 18F-FDG uptake consistent with excellent suppression of myocardial glucose utilisation by the normal myocardium. (C) Axial fused 18F-FDG PET/CT image demonstrates intense focal FDG uptake in the interventricular septum (solid arrow) and right ventricle (empty arrow). (D) Late post gadolinium enhancement cardiac MRI image in short-axis acquisition showing myocardial thickening and near transmural enhancement in basal right (empty arrow) and left ventricular anterior walls as well as in septum (solid arrow). (E) Repeat short-axis 18F-FDG PET/CT study performed 6 months later demonstrating reductions in FDG uptake in the anterior, anteroseptal, right ventricle and inferoseptal walls, suggesting reduction in active disease activity in the myocardium.

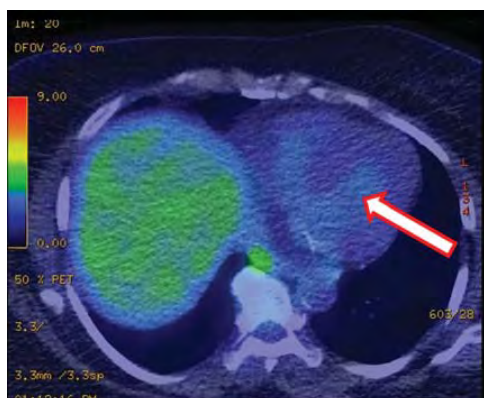


Fig. 2. Representative axial fused 18F-FDG PET/CT scan image of a 54-year-old patient, demonstrating no myocardial FDG uptake (only blood pool activity, indicated by the arrow), consistent with excellent suppression of myocardial glucose utilisation by the normal myocardium with no evidence of cardiac sarcoidosis.

Discussion

At present, there is no standardised approach for the diagnosis of cardiac sarcoidosis. The diagnosis of cardiac sarcoidosis is often difficult to make with precision, and is largely corroborated by a host of several, sometimes non-specific findings, including cardiac conduction abnormalities and abnormal ventricular function or motion.^{1,2} While endomyocardial biopsy may provide added specificity, the technique is invasive and has poor sensitivity with limited clinical utility due to the patterns of patchy involvement. 18F-FDG PET/CT and cardiac MRI are currently used to aid in the diagnosis of cardiac sarcoidosis;^{3,4} both techniques have been shown to have improved sensitivity and specificity compared to other traditional nuclear imaging techniques such as Gallium-67 scintigraphy or technetium-99m pyrophosphate.⁵

Adoption of a non-fasting, high-fat, low-to-no carbohydrate diet protocol prior to 18F-FDG PET/CT in our local population appears feasible.⁶ Cardiac sarcoidosis clinical manifestations relate primarily to the location and inflammatory effects of the granulomas. Since normal myocytes utilise glucose as one of their main energy sources, techniques are required to suppress physiological 18F-FDG uptake in the myocardium. By shifting myocardial metabolism to fatty acid and suppressing glucose utilisation by normal myocardium, dietary modifications with a high-fat, low-carbohydrate diet have been shown to reduce glucose uptake by normal myocardium.⁷ In abnormal myocardium with inflammatory cell infiltrates as it is in the case of cardiac sarcoidosis, 18F-FDG accumulates in lesions where inflammatory cells utilise glucose as an energy source. These active inflammatory cardiac sarcoid lesions are identified by abnormal, focal-to-diffuse 18F-FDG uptake on PET/CT imaging, depending on different stages of the disease.⁴

The revised Japanese Ministry Guidelines are currently the official published diagnostic guide used by many practitioners as an aid to identify patients with cardiac sarcoid involvement.⁸ While neither 18F-FDG PET/CT nor cardiac MRI has been included in international guidelines, there is growing data to support the role of 18F-FDG PET/CT as a sensitive technique for the diagnosis of cardiac sarcoidosis.^{3,4,9} As shown in our first case, 18F-FDG PET/CT can both identify disease and demonstrate response to therapy through serial temporal changes.¹⁰

In this era of multimodality cardiovascular imaging, imaging cardiac sarcoidosis by 18F-FDG PET/CT adds to the armamentarium of tools, apart from echocardiography, traditional nuclear imaging techniques and cardiac MRI.^{11,12} Apart from accumulating data that support the role of 18F-FDG PET/CT as an accurate technique, 18F-FDG PET/CT has been shown to be equally, if not more sensitive, than delayed enhancement (DE) cardiac MRI in detecting cardiac sarcoidosis.³ Practically, 18F-FDG PET/CT can be used in patients in whom cardiac MRI is contraindicated, such as in patients with renal dysfunction or implanted metallic devices. The ability of 18F-FDG PET/CT to assess disease activity based on quantitative information and standardised uptake value (SUV) is also an advantage over cardiac MRI.⁵ Furthermore, in the early diagnostic phase, whole-body 18F-FDG PET/CT imaging enables clinicians to evaluate the extent of systemic disease beyond the myocardium thus improving overall diagnostic confidence.¹³ Besides, the combined use of FDG PET/CT with cardiac MRI may provide detection of active granulomatous inflammation (both FDG PET/CT and MRI DE positive) from purely fibrotic disease (FDG PET/CT negative, MRI DE positive),^{14,15} with resulting improvements in diagnostic accuracy and confidence.¹⁶

Conclusion

18F-FDG PET/CT appears to be a useful, non-invasive diagnostic imaging test for cardiac sarcoidosis. We were able to institute a dietary and imaging protocol that was instituted on ambulatory outpatients, with satisfactory clinical results.

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A Case of Diarrhoea

A 68-year-old male presented with history of loose stools and lower abdominal pain and cramps of 10 days duration. He had multiple comorbidities which included systemic arterial hypertension, diabetes mellitus and coronary artery disease. He was recently hospitalised for ischaemic stroke and had suffered from hospital-acquired pneumonia (HAP) as well. On examination, he had low-grade fever and minimal lower abdominal tenderness. Haemogram revealed mild anaemia and polymorphonuclear predominant leukocytosis. Biochemical parameters were within normal limits. Sigmoidoscopy revealed multiple yellowish adherent plaques (Figs. 1A and 1B).

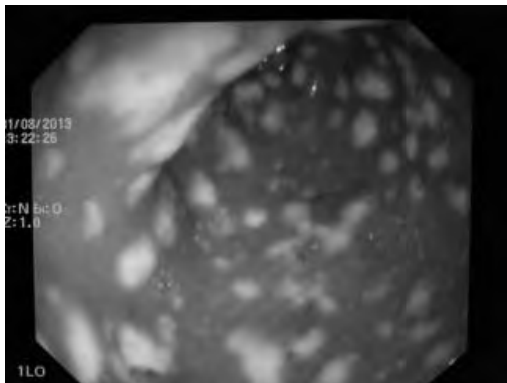


Fig. 1A. Multiple yellowish adherent plaques in the colon.

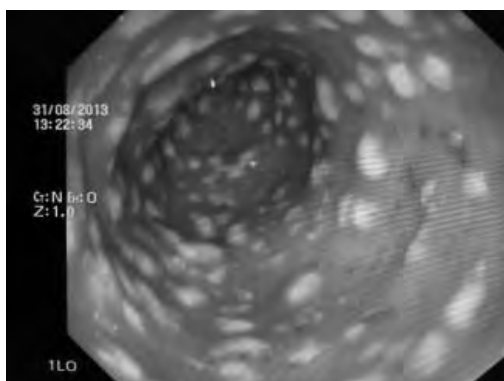


Fig. 1B. Multiple yellowish adherent plaques in the colon.

What is the diagnosis?

- A. Ulcerative colitis
- B. Lymphocytic colitis
- C. Amoebic colitis
- D. Pseudomembranous colitis
- E. Collagenous colitis

Discussion

Pseudomembranous enterocolitis, first reported in 1893, used to be a rare disorder but ever since the widespread use of antibiotics, it is fast becoming a major complication of antibiotic therapy. Caused by anaerobic gram-positive spore-forming toxigenic bacilli called *Clostridium difficile* (*C. difficile*), pseudomembranous enterocolitis is rapidly emerging as a major threat to antibiotic users. Osion et al has reported that symptomatic *C. difficile* infection (CDI) follows antibiotic use; 96% within previous 14 days and 100% within previous 3 months of onset of diarrhoea.¹ The vast majority of CDI patients remain asymptomatic but symptomatic patients typically present with loose stools. Other less common manifestations include fever and abdominal pain and cramps.^{1,2} Overt gastrointestinal (GI) bleeding is exceedingly rare in CDI. When severe, patients may present with ileus or toxic megacolon without diarrhoea.

At sigmoidoscopy, presence of pseudomembranes is virtually pathognomonic of *C. difficile* colitis. Pseudomembranes typically appear as yellowish plaques measuring between 2 mm to 5 mm in diameter. It may coalesce to cover larger areas of mucosa. Histopathology may reveal focal ulceration capped by pseudomembrane — the so-called “volcano” or “summit” lesion. Faecal assays for bacterial toxin remains the mainstay of diagnosis with tissue culture cytotoxicity assay remaining the gold standard for diagnosis.³ Stool cultures for *C. difficile* or polymerase chain reaction for detection of toxins are also accurate methods for diagnosis.³

Treatment options include metronidazole (500 mg thrice daily) or vancomycin (125 mg 4 times daily) administered orally for a duration of between 10 to 14 days. Metronidazole is inexpensive compared to vancomycin and it is mostly

Answer: D

used in treatment of mild to moderate CDI. However, in severe cases, vancomycin remains the drug of choice. Other potential treatment options especially in the setting of recurrent CDI include fidaxomicin, rifaximin, nitazoxanide, cholestyramine, intravenous immunoglobulin and fecal microbiota transplantation.⁴

Our patient was an elderly male with multiple comorbidities. He was recently hospitalised and was on antibiotics for pneumonia. Considering this background and the current presentation, the diagnosis of pseudomembranous colitis was suspected and endoscopy suggested a similar diagnosis. The sigmoidoscopy revealed multiple yellowish plaques typical of pseudomembranous colitis; virtually ruling out all other options mentioned earlier. At endoscopy, the mucosa often appears normal in patients with lymphocytic as well as collagenous colitis and the diagnosis is based on histology.

Ulcerative colitis (UC) is a chronic, often relapsing and remitting, inflammatory colon disorder characterised by bloody diarrhoea. At endoscopy, there will be loss of normal mucosal vascular pattern, mucosal friability, ulcerations and pseudopolyps.

Amoebic colitis presents classically with dysentery, and colonoscopy reveals multiple punctate ulcerations most commonly involving the caecum and ascending colon. Again, stool examination in amoebic colitis may reveal the presence of ova and trophozoites.

Our patient subsequently underwent enzyme immunoassay for *C. difficile* toxins A and B which were reported reactive, confirming the diagnosis. He was treated with oral vancomycin 500 mg 4 times a day for 10 days with which he had symptomatic response.

Conclusion

Pseudomembranous colitis is rapidly emerging as a common complication of antibiotic use; hence a high index of suspicion and low threshold for evaluation will help to clinch the diagnosis and initiate early treatment. With this paper, we intend to introduce all readers to the endoscopic appearance of pseudomembranous colitis.

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