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"Every man carries with him through life a mirror, as unique and impossible to get rid of as his shadow."

Wystan Hugh Auden (1907 – 1973)
UK poet

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Editorial

Improving Asthma Outcomes: Strategies for the Future

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Introduction

Despite accelerated research and major advances in the treatment of asthma in recent years, the disease burden remains high even in well resourced countries where up to 50% of patients may experience poor control of clinical disease. This is a global challenge which calls for a robust collective response.[1,2] Thus, establishing future strategies to improve asthma outcomes is an important responsibility for both physicians and policy makers.

Primary Prevention

During early life, priming of our immune system in response to microbes and allergens in the environment appears to be pivotal in the development of allergic diseases. Changes in the profile of this microbiota is probably the main cause of the dramatic rise in asthma prevalence associated with the transition from rural to urban lifestyles. Exposure to complex traditional farm dust protects children from developing asthma.[3] This protective effect appears to be mediated by a negative feedback loop following the activation of innate immunity.[4] Thus, manipulation of microbiota and allergen compositions in the environment which prime the immune system during early life may be an effective strategy for the primary prevention of asthma in high-risk families. This prospect, however, remains in a more distant future.

Behaviour Change

The most prevalent yet preventable barrier to better asthma outcomes is poor adherence to current guideline-based best practice by both patients and their doctors. This is best seen in the study of a tip-of-the-iceberg situation like the UK National Review of Asthma Deaths which concluded that complacency with respect to asthma care was an important potentially preventable factor in asthma deaths.[5] We need to design and test more effective treatment adherence interventions based more firmly on the theory of behaviour change.[6,7] These will certainly need to be augmented by mobile information technology (IT) support tools.[8-11] IT support for behaviour change requires careful detailing in designs which encourage regular use and minimise burden to patients and physicians. They will also need to be adaptive in relation to local patient culture and practice settings. Improving basic adherence to current asthma treatment is an urgent priority and probably the most cost-effective strategy to improve overall asthma outcomes and reduce preventable asthma deaths.

Oral Immunotherapy

Until recently immunotherapy in asthma requires regular injections, has modest effects, is inconvenient, potentially risky and not popular with either patients or physicians. However, immunotherapy with sublingual house dust mite allergens is a notable advance.[12] It appears to reduce asthma exacerbations safely in adults.[13] This is a promising development but it requires further development and evaluation.

More Mileage for Old Strategies

The cornerstone of conventional treatment for persistent asthma is inhaled corticosteroids (ICS) followed by, in non-responding cases, adding on long-acting bronchodilators. Recent advances in this approach include potent ICS with minimal effects on the hypothalamic-pituitary axis, ultra-long active beta agonist (LABA), ultra-long acting muscarinic antagonist (LAMA) and more convenient, patient-preferred devices.[14] Some of these ultra-long acting bronchodilators may also possess rapid onset action and so they serve as quick relievers during asthma exacerbations.[15] Thus, in future, the basic maintenance inhalational therapy for asthma may consist of all 3 drugs in a single devise to be taken once per day for prevention and acute flare-ups.

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Targeted Treatment

The novel strategy of targeted or personalised treatment arose from research on asthma which is refractory to conventional treatment. The era of targeted treatment commenced with the discovery of a series of new drugs which inhibit different immunopathogenic pathways, or endotypes, in type 2 immunity (TH2).[16] Effective treatments which block TH2 pathways include omalizumab (anti-IgE) for severe persistent allergic IgE-mediated asthma and mepolizumab (anti-IL5) for severe eosinophilic asthma.[17,18] These treatment options are already recommended at step 5 of the practice guidelines promulgated by the Global Initiative for Asthma.[2] A large and growing number of similar drugs are currently under investigation. But all these new asthma treatments have been designed to target different aspects of TH2 inflammation. Thus, this targeted approach is not yet possible for the minority of patients with non-TH2-mediated asthma. However, other treatment options for these patients may also be effective. They include macrolides and bronchial thermoplasty.[19,20] Further research is needed on the most reliable diagnostic tests which will differentiate between asthma endotypes for appropriately customised treatment. We anticipate the advent of novel endotypes and new treatments in this rapidly expanding field.

Conclusion

The future appears propitious for patients with asthma. However, before patients can enjoy real benefits, the disparate advances in many different fields ranging from molecular biology to IT, delivery devices and the social sciences need to be coordinated and translated into comprehensive treatment strategies. Areas of potential improvement include primary prevention of asthma, enhanced convention treatment and targeted customised treatment according to precisely defined asthma endotypes. Improving asthma outcomes is a priority and an eminently attainable goal.

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Original Article

Characteristics and Risk Factors for Mortality in Paediatric In-Hospital Cardiac Events in Singapore: Retrospective Single Centre Experience

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Abstract

Introduction: There is limited data on paediatric resuscitation outcomes in Asia. We aimed to describe outcomes of paediatric in-hospital cardiac arrests (IHCA) and peri-resuscitation factors associated with mortality in our institution. Materials and Methods: Using data from our hospital's code registry from 2009 to 2014, we analysed all patients younger than 18 years of age with IHCA who required cardiopulmonary resuscitation (CPR). Exposure variables were obtained from clinical demographics, CPR and post-resuscitation data. Outcomes measured were: survival after initial CPR event and survival to hospital discharge. We analysed categorical and continuous variables with Fisher's exact and Wilcoxon rank-sum tests respectively. Statistical significance was taken as $P < 0.05$. Results: We identified 51 patients in the study period. Median age of patients was 1.9 (interquartile range [IQR]: 0.3, 5.5) years. Twenty-six (51%) patients had bradycardia as the first-recorded rhythm. The most common pre-existing medical condition was respiratory-related (n = 25, 48%). Thirty-eight (75%) achieved sustained return of spontaneous circulation, 24 (47%) survived to paediatric intensive care unit (PICU) discharge and 23 (45%) survived to hospital discharge. Risk factors for hospital mortality included: age, duration of CPR, adrenaline, calcium or bicarbonate administration during CPR, Paediatric Index of Mortality (PIM)-II scores, first recorded post-resuscitation pH and hyperglycaemia within 24 hours of resuscitation. Conclusion: We demonstrated an association between clinical demographics (age, PIM-II scores), CPR variables (duration of CPR and administration of adrenaline, calcium or bicarbonate) and post-resuscitation laboratory results (first recorded pH and hyperglycaemia within 24 hours) with PICU survival. The availability and quality of post-resuscitation care may have implications on survival after paediatric IHCA.

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Key words: Cardiopulmonary resuscitation, Child, Infant

Introduction

Despite advances in resuscitation, survival from paediatric in-hospital cardiac arrests (IHCA) remains poor. Reported peri-resuscitative factors associated with mortality include pre-existing haematological, oncological, immunologic, genetic or metabolic disorders; presence of endotracheal tube or use of vasoactive infusions before arrest; use of adrenaline, calcium or sodium bicarbonate during arrest; and duration of cardiopulmonary resuscitation (CPR).[1-3] Post-resuscitation factors associated with mortality include hypotension, hyperoxia or hypoxia, serum lactate levels, hypo- or hyperglycaemia, and partial pressure of carbon dioxide ($PaCO_2$) levels.[4-8] Recent data from large North American cardiac arrest databases suggest a survival-to-discharge rate of between 34.8% to 48.7%.[1,9] There is, however, limited paediatric data available from Asia.[10-12]

We aimed to describe the outcomes of IHCA and study peri-resuscitation factors associated with mortality in our institution. We hypothesised that both resuscitation and post-resuscitation factors were associated with survival. In addition, we aimed to compare our data with other published reports from Asia.

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Materials and Methods

KK Women's and Children's Hospital is a tertiary paediatric centre with 364 beds, an average of 170,000 paediatric emergency visits and 20,870 admissions per year. Our paediatric intensive care unit (PICU) and high dependency unit (HD) comprises 45 multidisciplinary beds. A specialised code team, established since 1997, provides 24-hour coverage for paediatric cardio-pulmonary arrests. A formal rapid response system comprising early warning scores and a rapid response team was not yet established during the study period.

Post-resuscitation care was at the discretion of managing intensivists. General principles included keeping oxygen saturation (SpO_2) targets at >95%, maintaining haemodynamic stability, avoiding hyperthermia and ensuring adequate sedation and analgesia. There was no established protocol for active cooling. Measures to control hyper-pyrexia (defined as >38°C) include the use of anti-pyretics and external cooling measures.

Since 2007, details of all paediatric codes were prospectively collected according to Utstein-style reporting guidelines.[13] For this study, we analysed data from January 2009 to December 2014. The study was approved by the Local Centralised Institutional Review Board. All patients aged 1 day to 18 years who required activation of the code team for an event requiring CPR were included. CPR was defined as any event that required initiation of chest compression for: 1) inability to palpate a pulse, unresponsive and apnoeic; 2) bradycardia <60 beats per minute with haemodynamic compromise; or 3) ventricular fibrillation or pulseless ventricular tachycardia.[3,13] Sustained return of spontaneous circulation (ROSC) was defined as persistence of palpable pulse or blood pressure for 20 consecutive minutes without the need for CPR. "Office hours" was defined as between the hours of 8.00 am and 5.30 pm on weekdays, while "after office hours" was defined as the hours from 5.31 pm to 7.59 am on weekdays and weekends. Events occurring in the emergency room, non-clinical area or neonatal unit were excluded. We also excluded patients who had a prior "do not resuscitate" order. In the event of multiple arrests, only data from the index event was used.

The dose and route of adrenaline for CPR was standardised according to our national resuscitation council's advanced paediatric life support guidelines.[14] Doses of calcium and sodium bicarbonate were standardised to our institutional guidelines for resuscitation (calcium chloride 0.14 mmol/kg and sodium bicarbonate 1 mmol/kg).

Outcomes measured were immediate survival (i.e. achieved ROSC) and survival to hospital discharge. Data collected included: 1) patient's baseline characteristics; 2) characteristics of CPR events; 3) PICU data (e.g. PIM-II scores, temperature, first recorded serum lactate levels, partial pressure of carbon dioxide [$PaCO_2$] and partial pressure of arterial oxygen [PaO_2]) in the first 6 hours, and

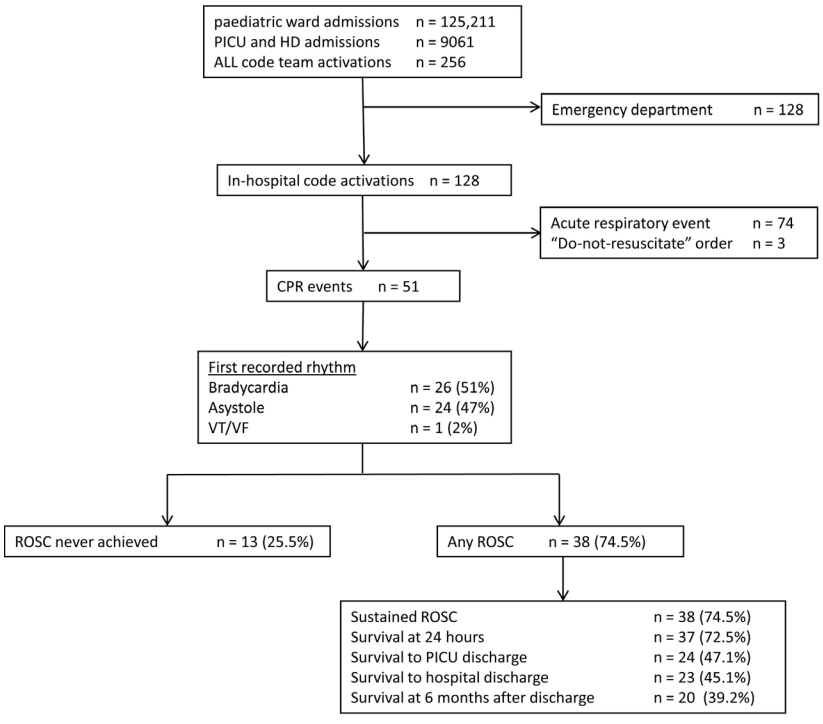

Fig. 1. Outcomes for in-hospital CPR events (n = 51). CPR: Cardio-pulmonary resuscitation; HD: High dependency; PICU: Paediatric intensive care unit; ROSC: Return of spontaneous circulation; VF: Ventricular fibrillation; VT: Ventricular tachycardia

highest recorded glucose concentrations in the first 24 hours post-event; and 4) survival to PICU and hospital discharge.

Statistical analysis was performed only for patients with complete data for the studied variables. Categorical variables were described using counts and percentages. We summarised continuous variables with medians and interquartile ranges (IQR). We analysed categorical and continuous variables with Fisher's exact and Wilcoxon rank-sum tests respectively. Statistical significance was taken as $P < 0.05$ for all tests. Analysis was performed with Stata v12 (College Station, Texas, USA).

Results

Over the study period, there were 125,211 admissions with 51 CPR events (Fig. 1). Thirty-eight patients (74.5%) achieved ROSC, 24 (47%) survived to PICU discharge and 23 (45%) survived to hospital discharge. Bradycardia (n = 26, 51%) was the most common first-recorded rhythm. The median age of patients was 1.9 (0.3, 5.5) years. The majority of events occurred after office hours (n = 39, 76.5%) and in PICU/HD (n = 33, 67.4%). Respiratory-related disease was the most common pre-existing medical condition [pneumonia, n = 17 (33.3%) and chronic respiratory disease, n = 14 (27.4%)]. Pre-existing oncological conditions were present in 4 patients (7.8%).

Peri-event factors associated with poorer immediate survival included a longer duration of CPR; any use of adrenaline (epinephrine), calcium or bicarbonate; and higher median doses of adrenaline and bicarbonate (Table 1).

Location and timing of the CPR event were not associated with survival to hospital discharge. Variables available pre- and during the arrest that were associated with survival to hospital discharge included: age (0.6 [0.3, 3.5] vs 2.9 [1.0, 8.7] years, $P = 0.02$); CPR duration (2.5 [2, 6] vs 30 [12, 45] minutes, $P < 0.01$); any use of adrenaline, calcium or sodium bicarbonate; median doses of adrenaline administered (0 [0, 1] vs 5 [2.5, 8] doses, $P < 0.01$); and median doses of sodium bicarbonate administered (0 [0] vs 2 [0.5, 3], $P < 0.01$) in survivors and non-survivors, respectively (Table 2).

Among the 38 patients with ROSC, post-resuscitation factors that were associated with survival to hospital discharge were: median PIM-II scores (15.9 [6.7, 24.2] vs 34.0 [11, 87.6], $P = 0.03$), first measured pH (7.3 [7.2, 7.35] vs 7.08 [6.97, 7.27], $P = 0.01$), and median peak serum glucose levels (first 24 hours) (8.45 [7.0, 13.9] vs 15.2 [12.5, 23.5] mmol/L, $P = 0.01$) in survivors and non-survivors, respectively (Table 3).

Arterial blood gas data was available in 24 patients. There was no statistically significant difference in first recorded median lactates between survivors and non-survivors (1.6 [1.15, 3.73] mmol/L vs 7.29 [3.88, 10.19] mmol/L, $P =$

Table 1. Characteristics of Patients in Relation to Immediate Survival (n = 51)

	Any ROSC Achieved n = 38	ROSC Never Achieved n = 13	*P* Value
Demographics			
Age (years)	1.07 (0.29, 5.52)	2.34 (1.58, 4.19)	0.46
Male gender	20 (52.6%)	8 (61.5%)	0.41
Race			0.27
Chinese	25 (65.8%)	6 (46.1%)	
Malay	8 (21.1%)	3 (23.1%)	
Indian	1 (2.6%)	2 (15.4%)	
Others	4 (10.5%)	2 (15.4%)	
Time of event			0.35
Office hours	9 (23.7%)	2 (15.4%)	
After office hours/ weekends	29 (76.3%)	11 (84.6%)	
Location of event			0.33
General ward	11 (28.9%)	5 (38.5%)	
PICU or high dependency	26 (68.4%)	7 (53.8%)	
Others	2 (5.3%)	0 (0)	
Illness category			0.9
Medical non-cardiac	30 (78.9%)	11 (84.6%)	
Medical cardiac	2 (5.3%)	1 (7.7%)	
Surgical cardiac	3 (7.9%)	0 (0)	
Surgical non-cardiac	3 (7.9%)	1 (7.7%)	
Pre-existing medical conditions			
Pneumonia	13 (34.2%)	4 (3.1%)	0.55
Chronic respiratory disease	13 (34.2%)	1 (7.7%)	0.06
Baseline depression in central nervous system (non-stroke)	12 (31.6%)	3 (23.1%)	0.42
Congenital heart disease	10 (26.3%)	2 (15.4%)	0.35
Malignancy	2 (5.3%)	2 (15.4%)	0.27
Renal impairment	2 (5.3%)	1 (7.7%)	0.6
Hepatic impairment	0 (0)	3 (23.1%)	0.01
Interventions/monitoring present prior to event			
Non-invasive ventilation	13 (34.2%)	4 (30.8%)	0.55
Invasive ventilation	7 (18.4%)	1 (7.7%)	0.33
Invasive arterial blood pressure monitoring	7 (18.4%)	2 (15.4%)	0.59
Vasoactive infusions	3 (7.9%)	2 (15.4%)	0.29

CPR: Cardiopulmonary resuscitation; PICU: Paediatric intensive care unit; ROSC: Return of spontaneous circulation
Note: Values expressed as absolute counts (percentage) for categorical variables and median interquartile ranges (IQR) for continuous variables.

Table 1. Characteristics of Patients in Relation to Immediate Survival (n = 51) (Cont'd)

	Any ROSC Achieved (n = 38)	ROSC Never Achieved (n = 13)	*P* Value
First recorded rhythm			0.5
Bradycardia	21 (55.3%)	5 (38.5%)	
Asystole	16 (42.1%)	8 (61.5%)	
Ventricular fibrillation/ pulseless ventricular tachycardia	1 (2.6%)	0 (0)	
CPR characteristics and interventions			
Duration of CPR (minutes)	4.5 (2, 15)	45 (45, 50)	<0.01
Adrenaline administered during CPR	23 (60.5%)	13 (100%)	<0.01
Doses of adrenaline administered during CPR	1 (0, 3)	8 (7, 9)	<0.01
Calcium administered during CPR	5 (13.2%)	11 (84.6%)	<0.01
Bicarbonate administered during CPR	10 (26.3%)	13 (100%)	<0.01
Doses of bicarbonate during CPR	0 (0, 1)	3 (2, 4)	<0.01

CPR: Cardiopulmonary resuscitation; PICU: Paediatric intensive care unit; ROSC: Return of spontaneous circulation
Note: Values expressed as absolute counts (percentage) for categorical variables and median interquartile ranges (IQR) for continuous variables.

0.14). The highest median $PaCO_2$ recorded within 6 hours post-ROSC was 64.1 (49.9, 91.3) mmHg and 61.5 (38, 78.4) mmHg in survivors and non-survivors respectively ($P = 0.5$). The highest median PaO_2 recorded within 6 hours post-ROSC was 83 (66.9, 129.7) mmHg and 165.7 (94.3, 211.1) mmHg in survivors and non-survivors respectively ($P = 0.08$). Neither was significantly associated with survival to discharge.

Discussion

Our findings describe the incidence, clinical characteristics and outcomes of a cohort of paediatric patients who experienced an in-hospital CPR event requiring chest compressions.

Our survival-to-discharge rate for IHCA of 45% is comparable with published rates from North American[9] and European studies,[2] but there is significant heterogeneity of

Table 2. Characteristics of Survivors and Non-Survivors in Relation to Hospital Discharge (n = 51)

	Survivors (n = 23)	Non-Survivors (n = 28)	*P* Value
Demographics			
Age (years)	0.6 (0.3, 3.5)	2.9 (1.0, 8.7)	0.02
Male	12 (52%)	16 (57%)	0.47
Location of event			0.5
General ward	7 (30.4%)	9 (32.1%)	
PICU or high dependency	16 (69.6%)	17 (60.7%)	
Others	0 (0)	2 (7.1%)	
Illness category			0.6
Medical non-cardiac	18 (78.3%)	23 (82.1%)	
Medical cardiac	2 (8.7%)	1 (3.6%)	
Surgical cardiac	2 (8.7%)	1 (3.6%)	
Surgical non-cardiac	1 (4.3%)	3 (10.7%)	
Pre-existing medical conditions			
Pneumonia	8 (34.8%)	9 (32.1%)	0.5
Chronic lung disease	8 (34.8%)	6 (24.1%)	0.2
Baseline depression in central nervous system (non-stroke)	6 (26.1%)	9 (32.1%)	0.4
Congenital heart disease	9 (39.1%)	3 (10.7%)	0.02
Sepsis	2 (8.7%)	7 (25%)	0.12
Malignancy	1 (4.3%)	3 (10.7%)	0.4
Inborn errors of metabolism	2 (8.7%)	0 (0%)	0.2
Interventions present prior to event			
Non-invasive ventilation	9 (39.1%)	8 (28.6%)	0.3
Invasive ventilation	3 (13%)	5 (17.9%)	0.5
Vasoactive infusions	2 (8.7%)	2 (7.1%)	0.5
First documented rhythm			0.16
Asystole	8 (34.8%)	16 (57.1%)	
Bradycardia	14 (60.9%)	12 (42.9%)	
Ventricular fibrillation/ pulseless ventricular tachycardia	1 (4.3%)	0 (0%)	
CPR characteristics and interventions			
Duration of CPR (minutes)	2.5 (2, 6)	30 (12, 45)	<0.01
Adrenaline administered during CPR	11 (47.8%)	25 (89.3%)	0.02
Doses of adrenaline administered during CPR	0 (0, 1)	5 (2.5, 8)	<0.01
Calcium administered during CPR	1 (4.3%)	15 (53.4%)	<0.01
Bicarbonate administered during CPR	2 (8.7%)	21 (75%)	<0.01
Doses of bicarbonate during CPR	0 (0)	2 (0.5, 3)	<0.01

CPR: Cardiopulmonary resuscitation; PICU: Paediatric intensive care unit
Note: Values expressed as absolute counts (percentage) for categorical variables and median interquartile ranges (IQR) for continuous variables.

Table 3. Characteristics of Patients with Return of Spontaneous Circulation (n = 38) in Relation to Survival to Hospital Discharge

	Survivors (n = 23)	Non-Survivors (n = 15)	*P* Value
PIM II scores (%)	15.9 (6.7, 24.2)	34 (11, 87.6)	0.03
Use of ECMO within 24 hours after CPR	1 (4.3%)	1 (3.6%)	0.6
Peak glucose recorded within 24 hours post-ROSC (mmol/L)	8.45 (7, 13.9)	15.2 (12.5, 23.5)	0.01
Lowest temperature recorded within 24 hours post-ROSC (°C)	36 (35.1, 36.2)	35.3 (34.0, 36.0)	0.3
Highest temperature recorded within 24 hours post-ROSC (°C)	37.6 (37.2, 38.2)	37.4 (36.4, 38.0)	0.67
First measured pH after ROSC	7.3 (7.2, 7.35)	7.08 (6.97, 7.27)	0.01

CPR: Cardiopulmonary resuscitation; ECMO: Extra-corporeal membrane oxygenation; PICU: Paediatric intensive care unit; PIM: Paediatric Index of Mortality; ROSC: Return of spontaneous circulation
Note: Values expressed as absolute counts (percentage) for categorical variables and median (IQR) for continuous variables.

survival outcomes from paediatric IHCA across Asia (Table 4). We postulate that this may be secondary to differences in institutional responses and systems of care across Asia. The first report on our institution's IHCA outcomes was in 2001, with 10 CPR events out of 51,241 admissions (0.2 per 1000 admissions).[15] None of these patients survived to hospital discharge. This study provides an updated account of resuscitation outcomes in our institution demonstrating significant improvement over a decade despite a twice-fold increase in CPR events. We postulate that this improvement is related to institutional educational initiatives, regular deliberate practice to maintain competencies in paediatric basic and advanced life support, development of the paediatric intensive care service and standardised reporting of cardiac arrests for auditing purposes.

The majority of events in our cohort occurred after office hours. While adult and paediatric studies have reported lower survival rates at night and during weekends,[16,17] we observed no such differences. This may be related to the observation that the majority of our events occurred in the PICU and HD, which is a resource-rich environment, with less variability in staffing and a high level of monitoring. Berg et al analysed 5870 paediatric CPR events over a 10-year period, and demonstrated an increasing trend towards paediatric cardiopulmonary events occurring in the ICU compared to in-patient wards, with concomitant increases in ROSC.[9] The authors postulated that the improvement could be due to ICU environments being resource-intense, with higher staff-to-patient ratios, and more recent CPR training, experience and expertise in ICU personnel.

We also found that younger age was associated with improved survival from IHCA. This finding is in keeping with current literature,[10,18] and may be related to the increased chest wall compliance in younger patients, resulting in more effective blood flow during chest compressions.

Symptomatic bradycardia in children is associated with a low cardiac output, and can occur as a physiological consequence to hypoxia and acidosis in neonates. It is also typically a rhythm seen prior to the onset of asystole. There is evidence that paediatric patients requiring chest compressions for haemodynamically significant bradycardia are more likely to survive than those with asystole or pulseless electrical activity,[19,20] but this was not observed in our cohort. We postulate this may be due to inaccuracies in the reporting of the first observed rhythm. While the arrival of the code team is often preceded by resuscitative efforts of the primary in-patient care team, the first recorded rhythm is based on the rhythm present on arrival of the code team, and patients presenting with bradycardia may already have progressed to asystole by the time of the team's arrival.

We noted that longer durations of CPR; any use of adrenaline, calcium and bicarbonate and higher number of doses of adrenaline and bicarbonate were associated with inferior survival outcomes in our cohort. This is not surprising and may be a reflection of the prolonged resuscitation attempt in a sicker cohort of patients with higher PIM-II scores (PIM-II scores: 15.9% [6.7, 24.2] vs 34% [11, 87.6], $P = 0.03$, in survivors and non-survivors, respectively).

Patients who regain spontaneous circulation after cardiac arrest undergo a distinct pathophysiological process characterised by brain injury, myocardial dysfunction and a systemic ischaemia/reperfusion response.[21] The focus of post-resuscitation research in recent years has included the role of glucose control, therapeutic hypothermia, and optimal oxygenation and ventilation targets.

Hyperglycaemia has been associated with poorer outcomes in critically ill children.[22-25] Dysregulation in glucose homeostasis is not uncommon after cardiac arrest, and hyperglycaemia post-arrest may also be a reflection of the degree of stress response as well as the cumulative amount of adrenaline required during resuscitation. In a retrospective trial on therapeutic hypothermia in 181 infants and children after cardiac arrest, initial hypo- or hyperglycaemia was independently associated with mortality.[26] Twenty-four (63.2%) of our patients had

Table 4. Summary of Studies on Paediatric In-Hospital Cardiac Arrest in Asia

Author/Country/ Year	Type of Institution	Incidence	Most Common First-Recorded Rhythm	Study Population	Sustained ROSC	Survival to Hospital Discharge	Risk Factors for Mortality/Comments
Mok YH et al; Singapore; 2016[#]	Single centre: 20,870 admissions per annum	0.4 per 1000 admissions (n = 51)	Bradycardia	1 day to 18 years	37 (72.5%)	23 (45%)	Older age; longer CPR duration; any use of adrenaline, calcium or bicarbonate during CPR; increasing doses of adrenaline during CPR; higher PIM II scores on admission to ICU; hyperglycaemia in the first 24 hours post-ROSC; lower pH recorded immediately after ROSC.
Wu E et al;Taiwan; 2009[*]	Single centre: 8874 admissions per annum	8.9 per 1000 admissions (n = 316). Conventional CPR: 252/316. ECPR: 64/316.	Bradycardia or asystole	7 days to 18 years	Conventional CPR: 153 (60.7%)	Overall: 66 (20.9%). Conventional CPR: 50 (19.8%). ECPR: 16 (25%).	Vasoactive infusions prior to CPR; haematologic or oncologic diseases and longer CPR durations. High percentage of patients who underwent ECPR (20.2%).
Zeng J et al;China; 2013[†]	Multicentre	1.6 per 1000 admissions (n = 174)	Bradycardia	1 month to18 years	108 (62.1%)	49 (28.2%)	Older age, longer CPR duration, and presence of endotracheal tube before arrest.
Haque A; Pakistan; 2011[‡]	Single centre: 4424 admissions per annum	4 per 1000 admissions (n = 106)	Bradycardia	1 month to 14 years	58 (54.7%)	12 (11.3%)	Prolonged CPR duration (>20 minutes), ≥2 doses of adrenaline during CPR and any bicarbonate use during CPR.
Singh SK et al;India; 2013[§]	Single centre	427 patients. Number of admissions not defined.	Not described	1 month to 14 years	26%	1.9%	CPR during night hours, prolonged CPR duration (>10 minutes) and older age (>1 year).

CPR: Cardiopulmonary resuscitation; ECPR: Initiation of ECMO during active chest compressions; ICU: Intensive care unit; PIM: Paediatric Index of Mortality; ROSC: Return of spontaneous circulation

[#]Mok YH, Loke APT, Loh TF, Lee JH. Characteristics and risk factors for mortality in paediatric in-hospital cardiac events in Singapore: A retrospective single centre experience. Annals Acad Med Singapore 2016;45:534-41.

[*]Wu ET, Li MJ, Huang SC, Wang CC, Liu YP, Lu FL, et al. Survey of outcome of CPR in pediatric in-hospital cardiac arrest in a medical center in Taiwan. Resuscitation 2009;80:443-8.

[†]Zeng J, Qian S, Zheng M, Wang Y, Zhou G, Wang H. The epidemiology and resuscitation effects of cardiopulmonary arrest among hospitalized children and adolescents in Beijing: an observational study. Resuscitation 2013;84:1685-90.

[‡]Haque A, Rizvi A, Bano S. Outcome of in-hospital pediatric cardiopulmonary arrest from a single center in Pakistan. Indian J Pediatr 2011;78:1356-60.

[§]Singh SK, Kumar R, Koonwar S. Epidemiology and outcome of pediatric in-hospital cardiopulmonary resuscitation in Northern India. J Pediatr Intensive Care 2013;2:55-61.

hyperglycaemia (glucose levels >8.3 mmol/L) within the first 24 hours after ROSC, and we found that peak blood sugar levels within the first 24 hours post-event was associated with overall mortality. Despite the association between hyperglycaemia and poor outcomes, paediatric intensivists continue to maintain clinical equipoise on glycaemic control.[27] This is understandable, given the risks of hypoglycaemia associated with tight glycaemic control, the lack of randomised studies of glycaemic control in paediatric IHCA survivors, as well as the recent multicentre trial on tight glycaemic control which demonstrated lack of effect on clinical outcomes in critically ill children.[28]

Current guidelines recommend using the minimum fraction of inspired oxygen (FiO_2) concentration to maintain SpO_2 ≥94%, in an attempt to ensure adequate oxygen delivery while preventing oxidative injury.[29] However, the ideal therapeutic range of oxygenation and FiO_2 concentrations after paediatric cardiac arrest remains unclear. In a cohort of 1875 patients, Ferguson et al reported an association between both hyperoxia and hypoxia at 1 hour post-ROSC and PICU mortality.[5] However, other studies have not demonstrated such associations. In a prospective multicentre study of 223 children after IHCA, neither hyperoxia nor hypoxia immediately or at 24 hours post-ROSC was associated with hospital mortality.[8] Bennett et al similarly found no association between hyperoxia within 6 hours post-ROSC and hospital survival with good neurological outcomes.[30] Given the differences in PaO_2 thresholds, time periods and outcomes measured, it is difficult to analyse these studies collectively. In our study, there was no difference in the proportion of survivors in PICU patients with PaO_2 >200 and <200 mmHg (14/22 vs 1/4, $P = 0.19$). Because of the uncertainty surrounding ideal oxygenation targets in paediatric resuscitation and risks associated with hyperoxia, future studies are needed to examine the impact of low FiO_2 concentrations for paediatric resuscitation.

Post-arrest serum lactate levels, a global biomarker of tissue hypoxia, has been explored as a means of stratifying injury severity and outcome prognostication to better titrate therapeutic interventions to improve survival. A retrospective cohort study of 264 patients (1 day to 18 years old) post-cardiac arrest demonstrated that elevated lactate levels in the first 12 hours after successful resuscitation from cardiac arrest was associated with increased hospital mortality (maximum serum lactate at 0-6 hours: 5.3 mmol/L [2.2, 10] vs 11.9 mmol/L [6.4, 18.1], P <0.001; maximum serum lactate at 7 to 12 hours: 2.7 mmol/L [1.6, 5.70] vs 8.8 mmol/L [3.8, 15.9], P <0.001, in survivors and non-survivors, respectively), and lactate levels in the first 6 hours post-arrest were significantly higher in patients who received more doses of adrenaline.[6] While the serum lactate levels between survivors and non-survivors in our cohort were clearly different (first recorded median lactate 1.6 mmol/L vs 7.29 mmol/L), this was not statistically significant. This likely arises from our small sample size, which may be inadequately powered to demonstrate statistical significance.

We acknowledge certain limitations in our study. The small sample size precluded multivariate analysis to determine independent factors for mortality in our cohort. Not all PICU and HD patients who require CPR had a code activation; this may have contributed to the low incidence of IHCA in our study. It would have been ideal to report functional outcomes of our survivors, however, not all patients had documented paediatric cerebral performance category scores prior to and after cardiac arrest. Given the low incidence of paediatric IHCA, and the current lack of adequate assessment of neurologic outcomes in our survivors, the authors propose establishment of a regional paediatric cardiac arrest registry, as well as proper attention to functional outcome assessment in paediatric IHCA survivors at our centre.

Conclusion

We found an association between age, duration of CPR, use of adrenaline, calcium or bicarbonate during CPR, PIM-II scores, first recorded post-resuscitation pH and hyperglycaemia within 24 hours post-resuscitation and hospital survival. There is a marked difference in resuscitation outcomes for paediatric IHCA across Asia. Future regional collaboration and development of a paediatric cardiac arrest registry will be helpful to identify factors that can potentially improve outcomes of paediatric cardiac arrest within Asia.

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Original Article

Anaphylaxis in Children: Experience of 485 Episodes in 1,272,482 Patient Attendances at a Tertiary Paediatric Emergency Department from 2007 to 2014

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Abstract

Introduction: Anaphylaxis is a predominantly childhood disease. Most of the literature on anaphylaxis has emerged from Western countries. This study aimed to describe the incidence, triggers and clinical presentation of anaphylaxis among children in Singapore, look for predictors for anaphylaxis with severe outcomes, and study the incidence of biphasic reactions. Materials and Methods: We retrospectively reviewed records of children presenting with anaphylaxis to our paediatric emergency department from 1 January 2007 to 31 December 2014. Results: We identified 485 cases of anaphylaxis in 445 patients. Cutaneous symptoms (urticaria/angio-oedema) were the most common across all age groups (481 cases, 99%), followed by respiratory (412, 85%), gastrointestinal (118, 24%) and cardiovascular (35, 7.2%) symptoms. Central nervous system symptoms (drowsiness/irritability) were rare across all age groups (11, 2.2%). Food was identified as the most common trigger across all age groups (45% to 63%). Seafood was the most common food trigger (57, 25%). A total of 420 (86.6%) children were treated with adrenaline, 451 (93%) received steroids and 411 (85%) received antihistamines. Sixty-three (13%) children fulfilled the criteria of severe anaphylaxis. There was no statistically significant association between severe anaphylaxis and the type of trigger ($P = 0.851$), nor an overall past history of atopy ($P = 0.428$). The only independent predictor for severe anaphylaxis was a previous drug allergy ($P = 0.016$). A very low prevalence of biphasic reactions (0.6% of study population) was noted in our study. Conclusion: We described the presentation and management of anaphylaxis in the Singapore population. A history of drug allergy is associated with severe presentation. Biphasic reactions are rare in our population.

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Key words: Allergy, Angioedema, Hypotension, Paediatrics

Introduction

Anaphylaxis is a severe and potentially fatal allergic reaction that occurs rapidly after exposure to an allergen.[1] There have been reports that the incidence of paediatric anaphylaxis is on the rise in the industrialised world.[2-4] There is, however, limited data confirming these trends in the Asian population.

Anaphylaxis is a predominantly childhood disease.[5,6] Young children with anaphylaxis present differently from adults. They have difficulty describing symptoms such as pruritus, throat tightness, or feelings of impending doom. Potential signs of anaphylaxis often occur in young children for a variety of other reasons. These include behavioural changes, irritability, drooling, regurgitation, and incontinence of urine and stool.

Because of the variable and non-specific nature of presentation, there are often delays between the child's arrival in the emergency department (ED) and the institution of definitive management.[4,7,8] A recent study concluded that the paediatric ED treatment and management of patients with anaphylaxis fell short of standard recommendations. Only 54% of patients who met the diagnostic criteria were treated with epinephrine despite current clear guidelines.[9]

In an earlier Singapore study, it was reported that hypotensive episodes are more likely to be due to drug triggers than food triggers. Among the food triggers causing

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anaphylaxis, there is an increasing number of peanut-related anaphylaxis episodes as compared to the previous decade.[10] The diet of Asian children differ from their counterparts in Western countries. Unique allergens such as bird's nest are not commonly consumed in the West and they have been reported to be significant allergens.[10]

Moving beyond the initial presentation, others have studied the incidence of biphasic reactions among children with anaphylaxis. The reported incidences are highly variable, ranging from 1% to 20% of all anaphylactic reactions.[11]

In view of the above, we set out to: i) describe the incidence, triggers and clinical presentation of anaphylaxis among children in Singapore, primarily an Asian population; ii) look for discriminatory predictors for anaphylaxis with severe outcomes; and iii) study the incidence of biphasic reactions in this population of children.

Materials and Methods

This was a retrospective chart review. We reviewed electronic records of children presenting with anaphylaxis to the KK Women's and Children's Hospital (KKWCH) paediatric ED from 1 January 2007 to 31 December 2014. This is 1 of the 2 tertiary hospitals in Singapore with a dedicated paediatric ED, and sees an annual attendance of about 170,000 children. Records of all children with a free text discharge diagnosis containing the words "anaphylaxis", "anaphylactic shock", "anaphylactic reaction", "anaphylactoid reaction" as well as International Classification of Diseases, 9th Revision (ICD-9) coding of "anaphylaxis" (995.0), "anaphylactic reaction" (995.0), "anaphylactic shock" (995.0) and "anaphylactic shock or reaction to adverse food reaction" (995.6) were obtained and reviewed.

We included all patients younger than 16 years old who met the definition of anaphylaxis.[12] This is defined as: i) acute onset of illness with involvement of skin, mucosal tissue, or both, and at least 1 other system involved (respiratory compromise, or cardiovascular compromise/associated end organ dysfunction); ii) two or more of skin-mucosal, respiratory, reduced blood pressure/associated end organ dysfunction, gastrointestinal symptoms, and occurring rapidly after exposure to a likely allergen for that patient; and iii) reduced blood pressure minutes to hours after exposure to a known allergen for that patient.

We evaluated the severity of anaphylaxis with a 3-grade scale according to the criteria proposed by Huang et al.[13] Mild anaphylaxis was defined as those with skin involvement (flushing, urticarial and angio-oedema), mild respiratory (minimal dyspnoea, wheeze and upper respiratory tract symptoms) and gastrointestinal symptoms (mild abdominal pain and/or emesis). Moderate anaphylaxis included those who had mild symptoms and features suggesting moderate respiratory (dysphagia, shortness of breath, hoarseness, and/or stridor, wheezing and retractions), cardiovascular or gastrointestinal (recurrent vomiting and/or diarrhoea, crampy abdominal pain) symptoms. The definition of severe anaphylaxis included patients with severe respiratory compromise resulting in cyanosis or hypoxia (SpO_2 <92%), hypotension or neurological compromise (confusion, collapse, loss of consciousness or incontinence).[13]

Each record was hand searched and patients who did not fulfill the above criteria were excluded from the study.

We recorded information on the demographics, presenting complaints, suspected triggers, risk factors, vital signs, and physical examination findings. The risk factors that we studied for an overall history of atopy included: a history of asthma, eczema, allergic rhinitis, food or drug allergies. We divided the symptoms and signs based on systems involved: cutaneous (urticarial, angio-oedema), respiratory (wheeze, stridor), cardiovascular (hypotension), gastrointestinal (abdominal pain, vomiting, diarrhoea) and central nervous system (drowsiness, irritability), but these were not mutually exclusive. We reviewed the ED management—specifically the use of adrenaline, antihistamines and steroids—and followed up all admitted patients for biphasic reactions by reviewing their inpatient notes, re-attendances to the ED and clinic notes.

The study was approved by the Singhealth Institutional Review Board (E, Paediatrics), with a waiver of informed consent.

Data Analysis

Categorical variables were described in frequencies and percentages while continuous variables were described with means and standard deviations (SD). Univariable logistic regression was performed to search for discriminatory predictors for severe outcomes, consistent with previous reported definitions for severe anaphylaxis.[13] Statistical significance was established at P <0.05. The data was analysed using IBM SPSS statistics 19.

Results

There were a total of 1,272,482 attendances in our ED from 2007 to 2014. Our initial search identified 639 cases with ICD codes related to anaphylaxis. Nineteen patients (3%) were aged 16 years and older, and 135 patients (21%) were excluded because they did not meet the criteria for anaphylaxis on a detailed chart review (Fig. 1). The total number of patients excluded were 154 (24%). We identified 485 cases of anaphylaxis in 445 patients. The number of

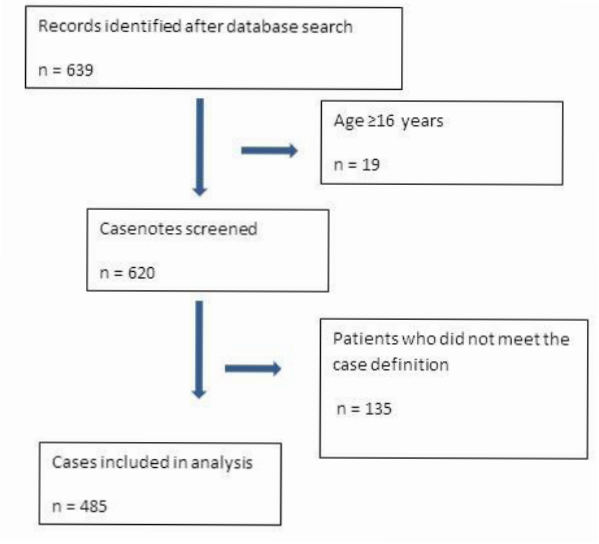

Fig. 1. Flowchart of patients included for the analysis in the study.

Table 1. Patient Demographics

Characteristics	n (%)
Age, mean (SD)	8.2 (4.3)
Males (%)	297 (61.2)
Patients receiving adrenaline (%)	420 (86.6)
Patients receiving prehospital adrenaline (%)	31 (6.4)
Patients receiving repeat adrenaline (%)	4 (0.8)
Patients receiving antihistamines (%)	411 (84.7)
Patients receiving steroids (%)	451 (93.0)
Patients with biphasic reactions (%)	3 (0.6)
Disposition	
Admitted to GW (%)	434 (89.5)
Admitted to HD/ICU (%)	29 (6.0)
Discharged (%)	10 (2.1)
Discharged against medical advice (%)	11 (2.3)

GW: General ward; HD/ICU: High dependency/Intensive care unit

patients diagnosed with anaphylaxis increased from 23 cases in 2007 to 84 in 2014. Over these 8 years, there was an average increase in 7.6 patients (or 33.0%) per year. The frequency of anaphylaxis in our ED appears to be 1 event in 2624 attendances, equivalent to a risk level of 38 events in 100,000 emergency visits.

The mean age of the children was 8.4 years (SD: 4.3). Of the 485 presentations, 297 (61.2%) were males (Table 1). A total of 284 patients (58.6%) in our cohort had a past history of atopy, specifically asthma (105, 21.6%), food allergy (139, 28.7%), drug allergy (46, 9.4%), eczema (39, 8.0%) and allergic rhinitis (33, 6.8%).

Based on the system of involvement (Table 2), cutaneous symptoms (urticaria/angio-oedema) were the most common across all age groups (97.8% to 100%) followed by respiratory symptoms (65.2% to 93.7%), gastrointestinal symptoms (19.4% to 47.8%) and cardiovascular symptoms (3.1% to 12.6%). Central nervous system symptoms

Table 2. System(s) of Involvement

Systems Affected*	0 to <2 Years n = 46	2 to <5 Years n = 89	5 to <10 Years n = 159	10 to <16 Years n = 191
Respiratory, n (%)	30 (65.2)	78 (87.6)	149 (93.7)	155 (81.2)
Wheeeze‡	28 (60.9)	74 (83.1)	144 (90.6)	147 (77.0)
Stridor‡	2 (4.3)	5 (5.6)	15 (9.4)	18 (9.4)
Cardiovascular†, n (%)	2 (4.3)	4 (4.5)	5 (3.1)	24 (12.6)
Cutaneous, n (%)	45 (97.8)	89 (100.0)	156 (98.1)	191 (100.0)
Urticaria	25 (54.3)	37 (41.6)	49 (30.8)	59 (30.9)
Angioedema	3 (6.5)	14 (15.7)	52 (32.7)	52 (27.2)
Both	17 (37.0)	38 (42.7)	55 (34.6)	80 (41.9)
Gastrointestinal, n (%)	22 (47.8)	23 (25.8)	36 (22.6)	37 (19.4)
Vomiting‡	20 (43.5)	16 (18.0)	17 (10.7)	16 (8.4)
Diarrhoea‡	2 (4.3)	1 (1.1)	0 (0.0)	4 (2.1)
Abdominal pain‡	0 (0.0)	6 (6.7)	20 (12.5)	19 (9.9)
Central nervous system§, n (%)	1 (2.2)	2 (2.2)	1 (0.6)	7 (3.7)

*Not mutually exclusive, as per anaphylaxis definition.
†Evidenced by hypotension.
‡Not mutually exclusive.
§Evidenced by drowsiness and irritability.

Table 3. Identifiable Trigger, by Age

	0 to <2 years n = 46	2 to <5 years n = 89	5 to <10 years n = 159	10 to <16 years n = 191
Food, n (%)	29 (63.0)	46 (51.7)	72 (45.3)	87 (45.5)
Seafood	4 (13.7)	5 (10.9)	13 (18.0)	35 (40.2)
Peanut	3 (10.3)	10 (21.7)	10 (13.8)	10 (11.5)
Tree nut	0 (0.0)	9 (19.6)	9 (12.5)	9 (10.3)
Egg	18 (62.0)	1 (2.1)	1 (0.1)	2 (2.2)
Cow's milk	3 (10.3)	6 (13.0)	3 (4.1)	0 (0.0)
Drugs, n (%)	5 (10.9)	11 (12.4)	28 (17.6)	38 (19.9)
Insects, n (%)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.5)
Others, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.6)
Unknown, n (%)	12 (26.1)	32 (36.0)	58 (36.5)	62 (32.5)

(drowsiness/irritability) were rare across all age groups (0.6% to 3.7%). Gastrointestinal symptoms predominated in the younger age groups (47.8% in children aged 0 to 2 years old as compared to 19.4% in children aged 10 to 16 years old). Cardiovascular symptoms predominated in the older age group (10 to 16 years old), affecting 12.6% of patients in this age group.

Identifiable triggers divided by age strata are described in Table 3. Food was identified as the most common trigger across all age groups (45.3% to 63.0%). Among those with food triggers (Table 4), seafood was the most common food trigger, causing 25% of all food triggered anaphylaxis presenting to the ED. This was followed by peanuts (14.5%), tree nuts (11.9%), egg (9.6%) and bird's nest (6.6%). Drugs were the second most common trigger (10.9% to 19.9%) and were noted to be more common among older children aged 10 to 16 years,involving 38 (19.9%) patients. Ibuprofen was the most common trigger (47.6%) among anaphylaxis cases triggered by medication and it was followed by paracetamol (13.4%) and antibiotics (11.9%) (Table 5). We had 2 cases of insect bite-induced anaphylaxis and 2 cases of exercise induced anaphylaxis (both in the 10- to 16-year-old range). No specific triggers were identified in 164 (33.8%) of all patients.

A total of 420 patients (86.6%) were treated with adrenaline. Thirty-one (6.4%) patients received pre-hospital adrenaline, the majority of which was administered by a caregiver. Among those given steroids (n = 451), 447 (99.1%) were given in the hospital and 4 (0.9%) were given at home. Among those with antihistamines (n = 411), 356 (86.7%) of them were given in the hospital while 55 (13.4%) were given at home.

Sixty-three (13%) of all anaphylaxis cases fulfilled the criteria of severe anaphylaxis. The mean age of severe cases was slightly higher at 9.6 years with similar male predominance as compared with non-severe cases. A higher percentage of severe cases (56, 89%) received adrenaline

Table 4. Details of Specific Food Triggers

Food Trigger*	Number	Percentage
Seafood	57	25.0%
Peanuts	33	14.5%
Tree nuts	27	11.9%
Egg	22	9.6%
Bird's nest	15	6.6%
Commercially packed food	14	6.1%
Cow's milk	12	5.3%
Fruits/vegetables	10	4.4%
Herbal drink	9	4.0%
Wheat	7	3.0%
Honey	7	3.0%
Meat/poultry	6	2.6%
Baked goods	6	2.6%
Chocolate	4	1.8%
Goat's milk	3	1.3%

*More than 1 food trigger may be involved in a case of anaphylaxis.

Table 5. Details of Specific Drug Triggers

Drug Trigger	Number	Percentage
Ibuprofen	39	47.6%
Antibiotics*	27	11.9%
Paracetamol	11	13.4%
Traditional Chinese medicine	4	4.8%
Cough syrup	3	3.6%

*Antibiotics refer to the following: amoxicillin, cephalexin, bactrim, erythromicin, clarithromicin.

Table 6. A Detailed Description of the 3 Biphasic Reactions

Reaction	Age	Trigger	System	ED Management	Time of Reaction	Ward Management
1	6.3	Food: crab	Respiratory and skin – wheeze, periorbital and lip swelling.	IM adrenaline, IV dyphenhydramine and hydrocortisone.	Wheeze, pruritus and periorbital swelling 12 hours after first reaction.	Continued on steroids and antihistamine.
2	3.6	Unknown	Respiratory and skin – hoarse voice, urticaria and periorbital swelling.	IM adrenaline, IV dyphenhydramine and hydrocortisone, and ventolin puffs.	Developed worsening urticaria and periorbital oedema 18 hours after first symptoms.	Repeat IM adrenaline and IV dyphenhydramine.
3	12.8	Food: egg	Respiratory and skin – chest tightness, periorbital swelling and urticaria.	IM promethazine and prednisolone.	Developed wheeze, stridor, worsening pruritus, abdominal pain and vomiting 14 hours after first symptoms.	Treated with IM adrenaline, IV hydrocortisone and IV dyphenhydramine.

ED: Emergency department; IM: Intramuscular; IV: Intravenous

and steroids (59, 95%) compared to the non-severe cases. A significantly higher number of severe cases were also admitted to the high dependency or intensive care unit (ICU) (18 out of 63 patients, 28.5%) as compared to non-severe cases (11 out of 422 patients, 2.6%). There was no statistically significant association between the severity of cases and types of triggers ($P = 0.851$), nor an overall past history of atopy ($P = 0.428$). Specifically, a previous drug allergy was found to be the only predictor of a severe episode of anaphylaxis.($P = 0.016$)

Only 3 cases of biphasic reaction were recorded, representing a very low proportion (0.6%) of all cases of anaphylaxis. Table 6 describes these 3 patients in detail.

Forty (8.9%) patients had repeat attendances for anaphylaxis, of which 4 patients were seen 3 times and 2 other patients were seen 4 and 5 times each. Of these 6 patients who were seen 3 times or more, 3 of them had a positive history of atopy and 3 had multiple known food allergies. The severity of their anaphylactic reactions were all mild.

Discussion

To our knowledge, this is the largest report of the incidence, clinical presentation, triggers and management of anaphylaxis presenting to an Asian paediatric ED.

There had been an increasing trend of anaphylaxis cases presenting to our ED over the duration of our study. This trend is consistent with other studies worldwide.[11,12,14,15] Apart from a possible true increase in the incidence of anaphylaxis, we postulate that this trend may be contributed by increased awareness and recognition of anaphylaxis amongst ED physicians. Others have suggested that a change in physician practices may have resulted in increased hospitalisations.[16]

We observed certain age-related patterns in our cohort of patients with anaphylaxis. Gastrointestinal symptoms were more prevalent in the younger age groups whereas cardiovascular symptoms were primarily seen in the older age groups. Our results mirrors the results of Rudders et al from Boston. In this study, cardiovascular symptoms, while noted among adolescents, were rarely reported among the younger children.[17] In another study performed among children with anaphylaxis presenting to the Mount Sinai pediatric ED between 2004 and 2008, the authors identified that infants are less likely to have a blood pressure measurement obtained in the ED compared with older children.[13] This could potentially confound the true numbers of hypotension seen in younger age groups.

This highlights the need to consider the age group of the patient when identifying the symptoms and signs of anaphylaxis in the ED. A low prevalence of central nervous system symptoms in this study is consistent with the findings of other studies.[18,19]

From the 1990s to 2000s, peanut allergy has increased in prominence.[10,20] In our current study, seafood (25.0%) emerged as the most common overall trigger, followed by peanuts (14.5%) and tree nuts (11.9%). The reason for this overall change in food-triggered anaphylaxis remains largely unknown. Firstly, we postulate that our largely cosmopolitan society with changing demographics may have contributed to this evolving landscape of food allergies. Singapore's population demographics has changed significantly in the past 2 decades, with a significant increase of non-residents from 10.2% in 1990 to 18.7% in 2000, and 25.7% in 2010 to 30% in 2015.[21] Secondly, in this study, we obtained the information surrounding the triggers from a detailed clinical history. Seafood consumption is usually obvious and easily reported while peanuts could well be hidden as part of baked products or combined food components. However, the specific food triggers for each age group remains comparable with Liew et al, with egg being the

predominant food trigger for children less than 1 year old, peanut being the predominant food trigger for children between 1 to 5 years old, and seafood in the older children. While milk products have been reported to be the most common cause of food-triggered anaphylaxis among young children aged <2 years old,[17] egg was the most common in our population for this age group. This could be related to different feeding and weaning patterns in different cultures. In our population, it is common to introduce eggs early to weaning infants. We also noted that bird's nest allergy spans most age groups.[10]

Medication-triggered anaphylaxis was less common in the younger age group (10.9%) but gradually rose to 19.9% among the older children. This was similarly reported in 2 previous studies in Singapore.[10,14] This was likely due to increasing medication exposure with age. Ibuprofen-induced anaphylaxis was indeed the most common cause of drug-induced anaphylaxis in our population, comprising up to half of our drug-induced anaphylaxis (39 patients, 47.6%). We also report an increasing trend of antibiotics-induced anaphylaxis (11.9%) as compared to 6% in a previously published series in our population.[10]

One important finding is the very low prevalence of biphasic reactions in our study population. There was no cardiovascular instability noted during the biphasic phase of reactions in all 3 patients. Although biphasic reactions are not as common in the paediatric population when compared to adults, there has been varying reports of its occurrence of between 1% to 20%.[2,11,22] The low rate of occurrence of biphasic reactions in our population is potentially practice changing. Our instititution currently admits all patients presenting with anaphylaxis. However, most paediatric patients with anaphylaxis may not require prolonged monitoring or admission. Our low rates of biphasic reaction could potentially be due to our high use of adrenaline and glucocorticoids in the emergency setting.[23,24] Ellis and Day found that early treatment of the initial anaphylactic reactions with adrenaline was associated with a lower risk of developing biphasic reactions.[25] Due to the geographic proximity of our population to the hospital, most patients present to the ED quite quickly after the onset of symptoms, thus reducing the time delay between the onset of symptoms to the first dose of adrenaline. This may also have contributed to a low rate of biphasic reactions.[24] The findings in this study has the potential to guide a more careful selection of patients who require admission, thus reducing the burden of unnecessary admissions among this group of patients.

The strength of our study lies in our large number of patients seen and treated for anaphylaxis. We have approached our study from the point of view of the initial presentation, highlighting findings that would help ED physicians to understand age-specific triggers and the variable presentations among children presenting with anaphylaxis.

Limitations

We recognise the following limitations of our study. As this was a retrospective chart review, there was potential for incomplete or inadequate documentation in case notes, which may lead to missing data. Secondly, this retrospective work spanned a long period in which the institution's protocols on anaphylaxis and physician practices may have undergone changes. Thirdly, we searched using ICD codes and keywords linked to anaphylaxis, and patients who had wrongly coded in other ICD codes of allergic reactions might have been missed or omitted. Finally, we found only a small number of patients with severe anaphylaxis or biphasic reactions. This could explain why we did not establish statistically significant associations when describing triggers and an overall previous history of atopy.

Conclusion

In this study, we described the paediatric anaphylaxis population presenting to a large tertiary paediatric hospital in Singapore. The estimated frequency of anaphylaxis is 1 event in 2624 attendances, equivalent to a risk level of 38 events in 100,000 emergency visits. Clinical presentations vary depending on the age of the child. Severe anaphylaxis and biphasic reactions appear to be rare in our population, possibly because of relatively rapid treatment with adrenaline and corticosteroid. Further studies focusing on the predictors for severe anaphylaxis and biphasic reactions would guide firstline physicians on risk stratification and resource allocation.

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Original Article

Relationship between Sleep Habits and Nighttime Sleep among Healthy Preschool Children in Taiwan

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Abstract

Introduction: We examined the nighttime sleep habits associated with insufficient sleep quantity and poor sleep quality among healthy preschool-aged Taiwanese children. Materials and Methods: The study population of this cross-sectional survey was a stratified random sample of 3 to 6-year-old preschool children from 19 cities and counties in Taiwan. A caregiver-administered questionnaire was used to collect information on preschooler sleep quantity (sleep duration and sleep latency) and sleep quality (sleep disturbances and disruption) and potentially related sleep habits. Results: Of the 1253 children for whom analysable survey data were collected (children's mean age: 5.03 ± 1.27 years), more than half (53.07%) engaged in bedtime television (TV)-viewing, 88.95% required a sleep reminder, 43.85% exhibited bedtime resistance, 93.6% engaged in co-sleeping (bed-sharing or room-sharing), and only 33.72% slept in a well darkened bedroom. Bedtime TV-viewing, co-sleeping, bedroom light exposure, and bedtime resistance were the primary predictors, without a bedtime TV-viewing habit was the strongest predictor analysed; it explained 15.2% and 19.9% of the variance in adequate sleep quantity and improved sleep quality in preschool children. Conclusion: Sleep loss and poor sleep quality in preschool children could be alleviated, at least partly, by curtailing bedtime TV-viewing, limiting light exposure during sleeping, and reducing bed-sharing habit.

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Key words: Bedtime TV-viewing, Co-sleeping, Bedroom light exposure, Sleep quantity

Introduction

Both the quantity and quality of sleep affect the normal development of preschool children. Insufficient sleep quantity and poor sleep quality—defined as short sleep duration, long sleep latency, and low sleep efficiency—are common among schoolchildren and also preschool children.[1,2] Studies from Asia have shown that delayed bedtimes, reduced nighttime sleep duration, or increased sleep disturbances are common among preschoolers in China,[3-4] Japan,[5] Singapore,[6] and Taiwan.[7] The sleeping habits of children from distinct geographic locations, such as the habits of children from China and the United States, differ considerably.[2] However, little information is available regarding the association between the sleeping habits and the sleep quantity and quality of Taiwanese preschool children. Delayed bedtimes, difficulty in sleep initiation, and short sleep durations might be particularly acute in Taiwan preschool children because of their primary caregivers' demographic characteristics, including age, education, and monthly family income.[7]

Evening television (TV) viewers had significantly worse sleep quality (higher sleep disturbance including sleep terrors, nightmares, sleep talking, and tired when waking up) compared with preschool children who watched TV earlier during the day.[8] Melatonin is a hormone secreted by the pineal gland that helps maintain the body's circadian rhythm, and melatonin levels are drastically affected by light exposure to the eyes.[9,10] A previous study showed that as

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compared with exposure to dim light (<3 lux), exposure to room light (<200 lux) before bedtime more potently inhibited melatonin secretion, which resulted in a shortening of the melatonin duration by roughly 90 minutes and a delayed melatonin onset in 99% of healthy volunteers enrolled in the study.[11] A cross-cultural comparison revealed that in young children, sleep disruption and diminished total sleep duration associated with bed-sharing and room-sharing resulted from parental presence at bedtime; the behaviour of co-sleeping is more common in predominantly Asian regions than in predominantly Caucasian regions.[12]

Numerous factors might reduce sleep duration, increase sleep latency, increase sleep disturbances, and disrupt sleep among preschool-aged and school-aged children; some of these factors are increased TV-viewing,[8,13-14] light exposure of the sleeping environment,[9-11] sleep resistance,[4] and co-sleeping.[12] Previous studies addressing these factors have focused on children in Western and various Asian countries, but no study has evaluated the association between sleep habits and nighttime sleep in Taiwanese preschool children. The purpose of this study was to ascertain and investigate whether sleep habits predicted sleep quantity and quality among 3- to 6-year-old preschool children in Taiwan and to compare the results to those from existing studies.

Materials and Methods

Participants and Sampling

A cross-sectional study design was used, and 3- to 6-year-old children were recruited from certified public or private preschools in Taiwan.[15] We employed stratified random sampling and used the proportions of preschool children of 19 cities and counties in the northern, central, southern, and eastern regions of Taiwan in order to calculate the required sample number. The written informed consent for participation in the study was obtained from children's parents or guardians. Questionnaires were returned by the primary caregivers of 1450 (85.29%) out of 1700 preschool children enrolled in the study. After excluding incomplete or inconsistent questionnaires, 1253 (73.7%) preschool children were available for the final analyses.

Sleep Habits and Measures of Sleep Quantity and Quality

Based on relevant literature,[7,16,17] a researcher developed a self-administered questionnaire entitled 'Self-Designed Preschool Children's Sleep Habits and Quantity and Quality of Sleep'. The primary components of the questionnaire items were the preschool children's demographic characteristics, sleep habits, and sleep quantity and quality scale. The primary caregivers of the preschool children completed the multiple-choice questions in the following 3 categories:

1. Demographic characteristics of preschool children: this included gender, age, and area of residence.

2. Sleep habits of preschool children: these were defined as the sleep habits observed 7 nights per week. The questions were specifically related to the children's bedtime (after 7 pm) TV-viewing habit (yes or no), requirement of a bedtime sleep reminder (yes or no), bedtime resistance manifested in the form of calling out, crying, or leaving their room after bedtime (yes or no), co-sleeping (bed sharing: sleeping in the same bed with a caregiver or other family members [reasons:], room sharing: sleeping in the same room with a caregiver or other family members [reasons:], or sleeping alone [reasons:]), and bedroom lights (light switched off and no instructive light; night light [reasons:]; or room light [reasons:]).

3. Items of sleep quantity and quality scale: this scale included 13 items that were categorised into 2 subscales: a) Sleep Quantity, and b) Sleep Quality. The Sleep Quantity subscale included 4 items that asked about the likelihood of the preschool children's weekly sleep duration ("My child generally sleeps 10 to 11 hours every night on weekdays," "My child generally sleeps 10 to 11 hours every night on weekends") and sleep latency ("My child falls asleep within 15 minutes after going to bed," "My child needs at least 30 minutes to fall asleep after going to bed [negatively worded item]"). The Sleep Quality subscale included 9 items that enquired about the likelihood of the preschool children's sleep disturbances ("My child does not have 'sleep talking', 'primary snoring', 'enuresis', 'bruxism', 'sleep terrors [i.e., screaming, crying, and/or increased pulse rate and breathing during sleep but not remembering any detail of the dream after waking up]', 'nightmares [waking up from a bad dream and remembering details of the dream]', 'respiratory pause [i.e., snoring because of airway obstruction; in some instances, the apnoea lasts for at least 10 seconds]', and 'sleep walking')" and sleep disruption ("My child does not wake up in the middle of the night"). The scales of sleep quantity and quality were rated on a 4-point Likert scale. Primary caregivers of the preschool children answered each question by selecting one of 4 answer choices (1 = never, 2 = sometimes, 3 = usually, and 4 = always). Of the 13 questions listed in the scale, only 1 question was negatively worded; all other 12 questions were positively worded. For these 12 questions, answers "never," "sometimes," "usually," and "always" were given a score of 1, 2, 3, and 4, respectively. By contrast, for Question 4, the same answers were given a reverse score of 4, 3, 2, and 1, respectively. A high total score indicated having adequate sleep quantity and better sleep quality in the preschool children.

Reliability and Validity of Sleep Quantity and Quality Scale

Five experts (2 sleep medicine, 2 early childhood education and 1 preschool educator) were first invited

to examine the content validity of the first draft of the questionnaires. Each question was rated as "appropriate," "to be modified," or "to be deleted." The experts were then asked to offer their recommendations regarding the questionnaire content. After collecting the questionnaires, questions that were rated by 3 or more experts as "to be deleted" were removed, whereas those that were rated as "to be modified" were revised according to the reviewer's suggestion and related literature to make the questions easier to understand and answer. The revised questionnaire then served as the pretest questionnaire. Fifty pretest questionnaires were each distributed in northern, central, southern, and eastern Taiwan for a total of 200 pretest questionnaires. A total of 178 questionnaires were returned, of which 166 were valid. The reliability and construct validity of the scale were assessed using item and factor analyses and Cronbach's alpha (α). A stepwise item selection procedure was performed on the basis of item quality, taking into account the results of the internal consistency analysis as a measure of reliability.[18] The significance level was $\alpha < 0.05$. A threshold of >0.3 for corrected item-total correlation and *t* value >3.0 for critical ratio were considered sufficient. Items were eliminated if their elimination caused an increase in the Cronbach's α value.

The theoretical basis of the scale was tested by applying a principal component analysis with orthogonal rotation (VARIMAX). The Kaiser-Meyer-Olkin (KMO) criterion was used to assess the requirements for a factor analysis.[18] Items not clearly loading on any factor were excluded. For the factor analysis, all requirements were fulfilled. The KMO criterion was fair (0.916). The Bartlett test was significant ($\chi^2 = 5075.70$; $P < 0.000$). Two factors were extracted according to the KMO criterion. On the VARIMAX rotation method, all items showed clear loadings (>0.30) on 1 of the 2 factors. The principal component analysis with VARIMAX was performed for the remaining 13 items (9 items for sleep quality, and 4 items for sleep quantity), resulting in a two-factor solution: Factor 1 (sleep quality, Items 5-13, eigenvalue = 5.54), Factor 2 (sleep quantity, Items 1-4, eigenvalue = 1.38).

The 2 dimensions of quantity of sleep and quality of sleep yielded Cronbach's α values of 0.87 and 0.89, respectively. The scale of sleep quantity and quality among preschool children exhibited acceptable internal consistency reliability values, and 50.02% of the total variance of the 2 dimensions was explained.

Statistical Analysis

All data were coded, entered, and analysed using Statistical Package for Social Sciences (SPSS Chinese Version 12.0). The descriptive results were expressed as numbers (n), percentages (%), and means (M) ± standard deviation (SD). Continuous variables were analysed using an independent t test or a one-way analysis of variance (ANOVA). The Scheffe test (homogeneity of variance) or the Games-Howell test (heterogeneity of variance) was performed as a posthoc test. Stepwise regression included regression models in which the predictive variables were selected using an automatic procedure. All results were considered statistically significant at $P < 0.05$.

Results

Sample Characteristics

Questionnaires were completed for 1253 preschool children: 633 girls (50.52%) and 620 boys (49.48%). The age distribution of these 3- to 6-year-old children is as follows: 36 to 47 months, 10.03% (n = 126); 48 to 59 months, 28.73% (n = 360); 60 to 71 months, 49.12% (n = 615); and 72 to 75 months, 12.12% (n = 152). The mean age was 5.03 years (SD = 1.27 years). Of these, 39.03% (n = 489), 27.93% (n = 350), 24.34% (n = 305), and 8.7% (n = 109) resided in northern, central, southern, and eastern Taiwan, respectively. The urban-rural distribution of preschool children is as follows: approximately 58% (n = 726) of the preschool children lived in urban areas and 42.06% (n = 527) lived in rural areas.

Sleep Habits Prevalent among Preschool Children

The results of the caregiver survey revealed the following sleep habits of the preschool children (Table 1): More than half (53.07%) of the children engaged in bedtime TV-viewing, 88.95% required a sleep reminder, and 43.85% exhibited bedtime resistance. In terms of co-sleeping, the prevalence rates measured for bed-sharing, room-sharing, and sleeping alone were 65.94%, 27.66%, and 6.40%, respectively; thus, 93.6% of the children slept in their caregiver's or other family member's bed or room. The reasons of bed-sharing and room-sharing were obtained from 129 and 146 caregiver as follows: children unwilling to sleep alone, insufficient bedroom, convenient child care or enhance parent-children relationship. In 80 sleeping-alone children, only 5 caregivers cited the reason as "training children to be independent". Lastly, 66.28% of the children slept in an environment that was poorly darkened (i.e., they were exposed to nightlight or room light). Caregivers explained that fear of sleeping in the dark was a major cause for children sleeping in nightlight or room light.

Bedtime TV-Viewing and Sleep Quantity and Quality

Sleep quantity and quality were significantly different between preschool children who did and did not engage in bedtime TV-viewing (Table 2). Children who engaged in bedtime TV-viewing exhibited reduced quantity of

Table 1. Sleep Habits Prevalent among Preschool Children (n = 1253)

Sleep Habits	Item	n	%
Bedtime TV-viewing	1. Yes	665	53.07
	2. No	588	46.93
Sleep reminder requirement	1. Yes	1115	88.95
	2. No	138	11.05
Bedtime resistance	1. Yes	549	43.85
	2. No	704	56.15
Co-sleeping	1. Bed-sharing	826	65.94
	a) No explanation	697	55.63
	b) Children unwilling to sleep alone	87	6.95
	c) Room insufficient	38	3.04
	d) Convenient child care	4	0.32
	2. Room-sharing	347	27.66
	a) No explanation	201	16.04
	b) Children unwilling to sleep alone	94	7.46
	c) Room insufficient	30	2.40
	d) Convenient child care	22	1.76
	3. Sleeping alone	80	6.40
	a) No explanation	75	5.99
	b) Training children to be independent	5	0.41
Bedroom lighting	1. Nightlight switched on	770	61.46
	a) No explanation	687	54.83
	b) Fear of sleeping in the dark	79	6.31
	c) Convenient child care	4	0.32
	2. Well darkened*	423	33.72
	a) No explanation	387	30.86
	b) Easily fall asleep	36	2.86
	3. Ordinary room lighting	60	4.82
	a) No explanation	31	2.48
	b) Fear of sleeping in the dark	28	2.34

*Defined as bedroom light switched off and no instructive light.

sleep (P <0.001) and lower quality of sleep (P <0.001) as compared with children who did not engage in bedtime TV-viewing.

Sleep Reminder Requirement and Sleep Quantity and Quality

The results in Table 2 indicate that sleep quality and quantity were not significantly different (P >0.05) in children who did and did not require a bedtime sleep reminder.

Bedtime Resistance Habit and Sleep Quantity and Quality

Preschool children who displayed bedtime resistance exhibited significantly reduced quantity of sleep (P <0.01) and lower quality of sleep (P <0.001) as compared with children who did not display bedtime resistance (Table 2).

Co-Sleeping Habit and Sleep Quantity and Quality

The results of one-way ANOVA indicated that the co-sleeping habit of preschool children was associated with sleep quantity and quality. Children who slept alone or who room-shared exhibited significantly enhanced quantity of sleep (P <0.001) and higher quality of sleep (P <0.001) as compared with children who slept in their caregiver's or other family member's bed (Table 3).

Bedroom Lighting and Sleep Quantity and Quality

Bedroom lighting was significantly associated with the sleep quantity and quality of preschool children (Table 3). Children who slept in well darkened bedrooms exhibited significantly increased quantity of sleep (P <0.001) and higher quality of sleep (P <0.001) as compared with children who slept in either nightlight bedrooms or bedrooms in which room lights were switched on. Moreover, preschool children who slept in nightlight bedrooms exhibited significantly enhanced quantity of sleep (P <0.001), and improved sleep quality (P <0.001) as compared with children who slept in a bedroom under room lighting.

Sleep Habits as Predictors of Both Sleep Quantity and Quality

Stepwise multiple regression analyses revealed that sufficient sleep duration in preschool children was predicted by without a bedtime TV-viewing habit (β = 0.23), sleeping alone (β = 0.15), a well darkened bedroom (β = 0.13), a nightlight bedroom (β = 0.09), and absence of bedtime resistance (β = 0.07). Bedtime TV-viewing, co-sleeping, bedroom light exposure, and bedtime resistance were the primary predictors, with the strongest being bedtime TV-viewing, which explained 15.2% of the variance of sleep quantity in preschool children (Table 4).

The results of stepwise multiple regression analysis indicate that those preschool children, without a bedtime TV-viewing habit (β = 0.45), a well darkened bedroom (β = 0.23), a nightlight bedroom (β = 0.14), sleeping alone (β = 0.07), and absence of bedtime resistance (β = 0.05) have better sleep quality and explained 29.5% of the variance. A

Table 2. Associations between Nighttime Sleep Habits (Bedtime TV-Viewing, Sleep Reminder Requirement, or Bedtime Resistance) and Sleep Quantity and Quality (n = 1253)

Sleep Habits	Aspects	Association	n	M	SD	T	Analysis
Bedtime TV-viewing	Sleep quantity	a) Positive	665	11.67	2.15	-4.56†	b) > a)
		b) No	588	12.94	1.99		
	Sleep quality	a) Positive	665	27.03	4.83	-5.81†	b) > a)
		b) No	588	29.57	4.47		
Sleep reminder requirement	Sleep quantity	a) Positive	1115	12.17	2.14	-1.02	NS
		b) No	138	12.46	2.45		
	Sleep quality	a) Positive	1115	27.37	4.80	-1.26	NS
		b) No	138	28.05	5.50		
Bedtime resistance	Sleep quantity	a) Positive	549	11.89	1.98	-3.02*	b) > a)
		b) No	704	12.47	2.02		
	Sleep quality	a) Positive	549	26.41	4.80	-4.87†	b) > a)
		b) No	704	28.01	3.86		

M: Mean; n: Number; NS: Not significant; SD: Standard deviation
*P <0.01.
†P <0.001.

habit of bedtime TV-viewing was the strongest predictor: it explained 19.9% of the variance in improved sleep quality in preschool children (Table 4).

Discussion

Bedtime TV-viewing has been associated with delayed bedtimes, difficulty in falling asleep, sleep disturbances, and reduced overall sleep among children.[8,13,19,20] Bedtime TV-viewing refers to TV-viewing after 7 pm (evening), given that the median bedtimes of 3 to 5-year-old children fall between 8 and 10 pm.[17] According to primary caregivers' ratings, the bedtime for 16.69% of Taiwanese preschool children is before 9 pm, and it is between 9.01 and 10 pm for 57.31% of the children.[7] This finding indicates that as compared with preschool children who did not engage in bedtime TV-viewing (after 7 pm), children who engaged in bedtime TV-viewing exhibited reduced quantity of sleep (shortened sleep duration and prolonged sleep latency), and lower quality of sleep (increased frequency of sleep disturbances and sleep disruption). Several potential mechanisms

Table 3. Associations between Nighttime Sleep Habits (Bedroom Lighting and Co-Sleeping) and Sleep Quantity and Quality (n = 1253)

Sleep Habits	Aspects	Item	n	M	SD	F	Posthoc Analysis*
Co-sleeping	Sleep quantity	a) Sleep alone	80	12.64	1.84	6.99	a) > c)
		b) Room sharing	347	12.34	1.61	P <0.001	b) > c)
		c) Bed-sharing	826	11.21	1.77		
	Sleep quality	a) Sleep alone	80	28.79	4.14	5.83	a) > c)
		b) Room-sharing	347	27.87	4.29	P <0.001	b) > c)
		c) Bed-sharing	826	26.64	3.97		
Bedroom lighting	Sleep quantity	a) Well darkened	423	12.68	2.11	6.12	a) > b)
		b) Nightlight	770	11.95	2.25	P <0.001	a) > c)
		c) Ordinary room light	60	10.85	1.91		b) > c)
	Sleep quality	a) Well darkened	423	28.03	4.71	8.08	a) > b)
		b) Nightlight	770	26.46	4.93	P <0.001	a) > c)
		c) Ordinary room light	60	25.92	4.04		b) > c)

M: Mean; n: Number; SD: Standard deviation
*Scheffe Test.

Table 4. Nighttime Sleep Habits as a Significant Predictor of Both Quantity and Quality of Sleep in Stepwise Multiple Regression Analyses (n = 1253)

Aspects	Variables	R	R^2	ΔR^2	F	B	β
Sleep quantity	Without bedtime TV-viewing†	0.390	0.152	0.152	141.35*	2.67	0.23
	Sleeping alone‡	0.435	0.189	0.037	91.65*	2.25	0.15
	Well darkened bedroom§	0.453	0.205	0.016	67.43*	2.12	0.13
	Nightlight bedroom§	0.464	0.215	0.010	53.65*	1.93	0.09
	Without bedtime resistance‖	0.470	0.221	0.006	44.34*	1.07	0.07
Sleep quality	Without bedtime TV-viewing†	0.450	0.199	0.199	195.42*	3.96	0.45
	Well darkened bedroom§	0.520	0.270	0.070	144.82*	2.88	0.23
	Nightlight bedroom§	0.530	0.281	0.012	102.36*	1.56	0.14
	Sleeping alone‡	0.540	0.289	0.008	85.73*	1.22	0.07
	Without bedtime resistance‖	0.540	0.295	0.006	75.02*	0.98	0.05

β: Regression coefficient R: Multiple correlation coefficient; R^2: Coefficient of determination; ΔR^2: Adjusted R^2

*P <0.001.

†Reference group: with bedtime TV-viewing.

‡Reference group: bed-sharing.

§Reference group: ordinary room lighting.

‖Reference group: with bedtime resistance.

underscore the link between bedtime TV-viewing and sleep quantity and quality: TV-viewing at bedtime is associated with exposure to artificial light (from brightly lit screens), which might result in increased sympathetic activation due to hyperarousal,[21] disrupted melatonin secretion,[22-24] or latent sleep onset and effects on the endogenous circadian timing system;[25] thus, bedtime TV-viewing appears to be a major driver of sleep timing. Overall, this study indicates that a bedtime TV-viewing habit is highly predictive of nighttime sleep quantity and quality outcomes in preschool children, and further to that, to promote optimal sleep, TV-viewing after 7 pm must be limited.

Acquiring the ability to transition from being awake to asleep is a critical step in sleep development in preschool children.[26] "Should parents be required to remind their children that it is time to go to bed?" was used as the question to find out whether the young children followed their "bedtime routine" (i.e., the young children went to bed on their own at the designated bed time). Here, we estimated that 88.95% of the children included in the study required a sleep reminder and that this habit was not associated with sleep quantity or quality in a statistically significant manner. Bedtime resistance was previously defined as calling out, crying, or leaving the room after bedtime,[27] and the problem of sleep resistance was reported to be prevalent in 23.4% of Chinese preschool children.[4] Moreover, bed-sharing and room-sharing were suggested to be associated with increased probability of bedtime resistance and sleep disturbances (night waking, parasomnia, and sleep-disordered breathing).[28] In this study, 43.85% of the preschool children exhibited bedtime resistance, which potentially exerted a negative influence on both sleep quantity and quality. Data analysis showed that of the 549 young children who experienced bedtime sleep resistance, 88% (n = 487) had the habit of watching TV before going to bed. The high percentage of overlap between bedtime sleep resistance and the habit of bedtime TV-viewing may indicate a correctable risk factor.

The prevalence of a co-sleeping habit decreases with an increase in age; whereas 70.5% of Chinese preschool children (mean age: 5.72 years) were reported to be unwilling to sleep alone,[4] the proportion dropped to 37.6% (23.0%, routine bed-sharing; 14.6%, room-sharing) in Chinese urban school-aged children (mean age: 9.00 years).[28] Co-sleeping was prevalent in Singaporean children aged 2 to 6 years (mean age: 4.1 years) with 80.9% of room-sharing and 42.2% of bed-sharing.[6] This finding revealed that the habit of co-sleeping was highly common (93.6%) among Taiwanese preschool children (mean age: 5.03 years): 65.94% of the children slept in their caregiver's or other family member's bed, 27.66% in their caregiver's or other family member's room. The prevalence of co-sleeping among Taiwanese preschool children is close to or higher than in China, Singapore, and Japan,[3] Asian and culturally similar countries.[4,6,28,29] The results show that the high prevalence of co-sleeping in Taiwan was partly due to children unwilling to sleep alone, insufficient bedroom, convenient child care or to enhance parent-children relationship. But most caregivers did not fill out reasons for co-sleeping. However, experts have thus far failed to reach a consensus on the distinct views on parent-child co-sleeping in various cultures. Co-sleeping habit was suggested to be

associated with increased probability of sleep disturbances and bedtime resistance.[6,28] Sleep quantity and quality were markedly diminished in preschool children who engaged in bed-sharing or room-sharing as compared with the sleep quantity and quality in children who slept alone; moreover, children who engaged in bed-sharing exhibited significantly shorter sleep times and a lower sleep quality than did children who engaged in room-sharing. This finding indicates that bed-sharing can potentially adversely affect children's sleep quantity and quality. Because the sleep quantity and quality of children whose parents co-sleep with them in the same room but on different beds is superior compared with that of those who co-sleep with their parents in the same bed, we recommend that parents who are incapable of training their children to sleep independently to at least sleep in the same room with their children.

The circadian rhythm is an internal 24-hour "clock" that plays a critical role in controlling the time at which humans fall asleep and wake up.[30] The suprachiasmatic nucleus (SCN) of the hypothalamus serves as the master biological clock in humans, and the timing and strength of SCN rhythmic signals are affected by light exposure. A cross-sectional survey indicated that the common sleep problems observed in children from China and the United States were a difficulty in falling asleep and a fear of sleeping in the dark.[2] An experimental study determined that melatonin was considerably more sensitive to light suppression in children than in adults, because children possess large pupils and pure crystal lenses; melatonin secretion was markedly suppressed by regular room lighting at home in children but not in adults.[9] This study has demonstrated that exposure to light (nightlight or room light) during sleep in preschool children markedly reduced sleep quantity and worsened sleep quality as compared with the sleep quantity and quality in children who slept in well darkened bedrooms. Furthermore, preschool children who slept in bedrooms under nightlight exhibited considerably longer nighttime sleep durations and higher sleep quality than did children who slept in bedrooms under room lighting. Therefore, if preschool children display a fear of sleeping in the dark, nightlight exposure could be maintained. These could be suggestive of allowing preschool children to control the amount of bedroom light before bedtime and gradually decreasing brightness after falling asleep.

This is the first study in Taiwan to assess the association between sleep habits and sleep quantity and quality in preschool children. However, this study has certain limitations that require careful consideration when interpreting its findings. Firstly, because this was a cross-sectional study, our findings should be interpreted as correlational and not causal. Secondly, as most caregivers did not fill out reasons of co-sleeping, sleeping in the nightlight or room light, and did not evaluate the amount of bedroom light, therefore we do not really know the level of illumination of nightlight and room light. Thirdly, although TV has been quickly replaced by computer, communication, and consumer electronics products, this study only questioned young children if they had the habit of watching TV before going to bed and did not question them about the amount of time that they spent on computers, smartphones, and/or tablet computers before going to bed. Researchers may wish to include these items in the future to elevate the value of the research. Finally, in addition to demographic factors[7] and sleep habits, other factors (positive reinforcement of bedtime activities such as reading books or bedtime routines) are associated with sleep quantity and quality among preschool children in Taiwan.

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Extended-Spectrum Beta-Lactamase-Producing *Enterobacteriaceae* in Retail Chicken Meat in Singapore

Dear Editor,

Extended-spectrum beta-lactamases (ESBLs) are rapidly expanding groups of enzymes that can hydrolyse the majority of beta-lactam antibiotics with the exception of carbapenems, and are inhibited by clavulanic acid.[1] They are commonly found on plasmids, which are extra-chromosomal deoxyribonucleic acid (DNA) that can transfer between bacteria. ESBL-producing *Enterobacteriaeceae* (ESBL-E) frequently cause infections in Singapore hospitals, and have increased rapidly since the 1990s to approximately 20% and 35% of all *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* (*K. pneumoniae*) clinical isolates respectively.[2]

ESBL-E carriage and infection rates in the community setting have increased globally since the 1990s.[3] In Singapore, 6.3% of emergency department attendees in 2006 with no previous healthcare contact were ESBL-E carriers—unfortunately, there has been no follow-up study.[4] It is postulated that the rise in community-associated ESBL-E carriage and infection rates is due to cross-species transmission from food-producing animals, particularly poultry.[3,5,6] Numerous studies have shown high rates of ESBL-E in chickens around the world.[3,6-8] Citing the Agri-Food and Veterinary Authority of Singapore (AVA), a 2013 news report stated that Singapore imported approximately 500 tons of chicken a day, of which 78.8% came from Brazil (205 tons) and Malaysia (189 tons).[9]

We performed a cross-sectional survey on 26 chicken breast samples over a period of 4 months (May 2015 to August 2015) in an attempt to determine the prevalence of ESBL-E in chicken meat in Singapore, and to determine if there was a difference in ESBL-E carriage between raw and commercially cooked chicken.

Raw chilled and frozen meat were obtained from various wet markets, supermarkets, and online shops (n = 19), whereas cooked samples were obtained from fast food restaurants and hawker centres (n = 7). Samples were labelled as "antibiotic-free" if this was indicated on the packaging. The country of origin was obtained from the packaging label, or from the seller in the case of wet market samples.

Samples were processed under aseptic conditions within 4 hours of collection. Approximately 25 grams of breast meat was macerated in a stomacher with 225 mL buffered peptone water at 260 rpm for 1 minute, and incubated for 18 to 24 hours at 35°C. Subsequently, the homogenate was diluted 1:100 in peptone water and 10 μL of the resulting mix was plated on selective ChromID ESBL agar (Biomerieux, France). After incubation overnight, several colonies with distinct morphologic appearances per plate were randomly selected for further testing and identified using MALDI-TOF (Bruker Daltonics, Germany), with confirmation of *E. coli* identification via standard microbiology testing.[10]

Phenotypic confirmation of ESBL production was made according to Clinical and Laboratory Standards Institute (CLSI) guidelines.[11] ESBL-E were screened for the presence of genes expressing the CTX-M subclass of beta-lactamase enzymes (CTX-M) using previously described multiplex polymerase chain reaction (PCR) methods.[12,13] Confirmation of the CTX-M group was performed via Sanger sequencing (performed commercially by AITbiotech, Singapore), with consensus sequences compared to existing sequences within the National Center for Biotechnology Information (NCBI) databases.

The majority of the raw samples were fresh chilled chicken from Malaysia (n = 11, 57.9%), with the rest being frozen chicken from France (21.1%), Brazil (10.5%), and the United States of America (USA) (10.5%). Seven samples of "antibiotic-free" chicken originated from Malaysia (n = 3, 42.9%), France (28.6%) and USA (28.6%). The countries of origin of the cooked samples were presumably from either Malaysia or Brazil.

The ChromID ESBL screening plates detected ESBL-E in 15 (78.9%) raw samples and none of the cooked samples. Eleven of 12 (91.7%) samples from conventionally raised chickens harboured ESBL-E, compared to 4 of 7 (57.1%) "antibiotic-free" samples. Fifty-six of the colonies tested were confirmed to be ESBL-E phenotypically (Table 1). The majority was *E. coli* (82.1%), followed by *Proteus mirabilis* (10.7%) and *K. pneumoniae* (7.1%).

Multiplex PCR revealed that 54 ESBL-E (96.4%) harboured CTX-M genes. CTX-M-1 group genes were found in the most isolates (n = 28, 51.9%), followed by the CTX-M-9 group genes (n = 17, 31.5%), CTX-M-2 group genes (n = 9, 16.7%), and CTX-M-8 group genes

Table 1. Distribution of CTX-M Genes and *Enterobacteriaceae* Isolates from 15 Chicken Samples According to Type of Chicken and Country of Origin

Country of Origin	Type of Chicken	Poultry Farming	*Enterobacteriaceae* (Number of Isolates)	CTX-M Group (Number of Isolates)
Malaysia	Black (ayam cemani[†])	Conventional	*Escherichia coli* (2)	1 (2)
Malaysia	Ordinary	Conventional	*E. coli* (2)	1 (1)
				9 (1)
Malaysia	Ordinary	Conventional	*E. coli* (2)	9 (2)
Malaysia	Ordinary	Conventional	*E. coli* (4)	9 (3)
				2 and 9 (1)
Malaysia	Ordinary (ayam kampong[‡])	Conventional	*E. coli* (2)	1 (1)
				9 (1)
Malaysia (France)[*]	Yellow chicken	Conventional	*E. coli* (2)	1 (2)
Malaysia	Ordinary	Antibiotic-free (probiotic)	*E. coli* (3)	1 (3)
Malaysia	Ordinary	Antibiotic-free (probiotic)	*E. coli* (3)	2 and 9 (2)
				9 (1)
Malaysia	Ordinary	Antibiotic-free (probiotic)	*E. coli* (1)	1 (1)
			Proteus mirabilis (1)	9 (1)
			Klebsiella pneumoniae (2)	CTX-M negative
Malaysia	Ordinary	Antibiotic-free (probiotic)	*E. coli* (2)	1 (2)
			P. mirabilis (5)	9 (5)
			K. pneumoniae (2)	1 (2)
Brazil	Ordinary	Conventional	*E. coli* (5)	2 (2)
				8 (3)
Brazil	Ordinary	Conventional	*E. coli* (4)	2 (4)
France	Ordinary	Conventional	*E. coli* (4)	1 (4)
France	Yellow chicken	Conventional	*E. coli* (5)	1 (5)
France	Yellow chicken	Antibiotic-free	*E. coli* (5)	1 (5)

[*]A French chicken breed but raised on Malaysian farms.
[†]Black chicken.
[‡]Chickens raised using traditional free range production techniques.

(n = 3, 5.5%). Three (5.6%) isolates had both CTX-M-2 and CTX-M-9 group genes, while the CTX-M genes of 2 isolates could not be grouped.

Our study, even with its limited sample size, showed very high percentages of ESBL-E carriage in retail chicken in Singapore, comparable if not higher than most other reports from around the world.[5,7-9] Even in chicken that were ostensibly raised antibiotic-free, many samples were found to be positive for ESBL-E. The vast majority of chicken samples from Malaysia (90.9%) and Brazil (100%) tested positive for ESBL-E.

The vast majority of ESBL-E carried CTX-M genes, which is unsurprising given the success of this group of ESBL genes in *Enterobacteriaceae* of both animal and human origin.[3,5,6] It is likely that at least 2 isolates carried the older TEM and SHV-ESBL genes, but these were not tested. It is noteworthy that CTX-M-positive *Enterobacteriaceae* were first noted in human clinical isolates in Singapore in the 1990s,[2] and gradually became the predominant ESBL in Singapore hospitals by the mid-2000s,[2,14] with an increasing number of sporadic community-associated ESBL-E carrying CTX-M genes seen in the past several years.[14] A small but significant percentage of the community had already been found to be colonised by ESBL-E in 2006, with the majority (74.4%) of the isolates testing positive for CTX-M genes, primarily CTX-M-1 and CTX-M-9 groups.[4]

One silver lining of this study is that none of the cooked samples tested positive for ESBL-E, suggesting that thorough cooking may minimise the transmission of ESBL-E. However, given the presence of community human carriage of ESBL-E with CTX-M groups similar to those found in ESBL-E from chicken,[4] it is plausible that cross-transmission has occurred and continues to occur. How cross-transmission takes place locally is speculative

at best, but perhaps transpires during food preparation, or via ingestion of large amounts of less well cooked chicken. Food sources other than meat have also been found to be positive for ESBL-E, including vegetables,[15] and this may contribute to the overall colonising pressure of ESBL-E on humans in Singapore.

Our study is primarily limited by the small sample size, although the results are striking enough that a larger sample size would not necessarily yield more significant results. Further molecular work could be performed to determine whether the ESBL-E from the chicken samples corresponded to human pathogenic clones of *Enterobacteriaceae*. However, such work has already been performed elsewhere,[6] and in any case, the issue is not primarily whether the bacteria from chicken are pathogenic to humans, but that these antibiotic resistance determinants can easily be transferred between animal and human (pathogenic) bacterial strains. Because our methodology specifically required bacterial cultures, it may not identify ESBL-E at low concentrations or other ESBL-producing bacteria that are unculturable using these methods, and alternative direct PCR-based techniques may be complementary.

What can be done concretely with regard to the overall issue of antimicrobial resistance in food products is less clear. Singapore imports the majority of its food,[10] and has limited ability to influence agricultural producers with regard to antibiotic and farming practices. Perhaps heightened awareness of the issue of antimicrobial resistance, framed as a food safety or health issue, may result in local consumers exerting greater economic selection pressure in terms of antibiotic-free (or better yet, antibiotic resistance-free) food products.

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View towards Rehabilitation in the Home – A Survey of Patient's Mindset towards a Home Rehabilitation Programme

Dear Editor,

Due to an ageing population, the need for acute hospital beds has been increasing exponentially in the past years. Stroke rehabilitation has been traditionally carried out in the inpatient setting, day rehabilitation or hospital outpatient setting and often, there is a wait list. Rehabilitation in the home is a relatively new idea in our country. In countries like the United Kingdom,[1] Australia and some Asian countries, early supported discharge (ESD) services have been implemented to accelerate the discharge of stroke patients. Studies have shown that appropriately resourced ESD services provided for a selected group of patients can reduce long-term dependency, reduce admission to institutionalised care and reduce the hospital length of stay. There was better patient satisfaction and activities of daily living (ADL) score.[2,3] Another study demonstrated improved 5-year survival in the ESD group.[4] In Singapore, ESD is usually a bridge to outpatient or day rehabilitation services and consists of few sessions in all.

In Australia, rehabilitation in the home programme is of the same intensity, frequency and duration as inpatient rehabilitation, which is 5 days a week with input from various allied healthcare workers lasting up to 6 weeks or more. This is not available in Singapore yet. This study was done to assess if Singaporean patients are open to a home rehabilitation programme (HRP).

In this study, we aimed to describe the demographics, clinical characteristics and entry functional status of stroke patients who were recruited into this study. We assessed the patient's attitudes and acceptance towards HRP and identified potential barriers to patients choosing HRP.

Consecutive patients who were admitted to our inpatient rehabilitation ward with the rehabilitation diagnosis of stroke were screened for eligibility between March 2013 and January 2015. Patients aged 21 and above, with Mini-Mental State Examination (MMSE) score of 25 or more were recruited. Patients with dysphasia, cognitive impairment and those admitted from nursing homes were excluded. A questionnaire was administered by a nurse or doctor, covering areas including demographics, premorbid functional status, premorbid activities of daily living, perception towards HRP and the patient's expectations towards recovery. MMSE was administered and information on the type of stroke and the functional independence measure (FIM) were retrieved from the medical records. Statistical analysis was performed with SPSS statistical software, version 19.0. This study was approved by the SingHealth Centralised Institutional Review Board.

The average age of the 100 recruited patients was 58.9 years. Majority of the patients were male and of Chinese ethnicity (Table 1). A quarter suffered intracerebral bleed and the rest cerebral infarct. Sixty-five of the 80 married patients stayed with their children. Only 14% of all patients stayed alone. There was lift access to the homes in 97 of the patients. Ninety-three of the patients could identify a caregiver at the time of the interview. All patients were ADL-independent prior to stroke except one. Ninety-three of patients were in the community for social activities at least weekly. More than 93 did some form of instrumental ADLs. The mean admission FIM was 72.6 and the median was 72. Majority of the stroke patients were of moderate disability and minority in the mild or severe disability category (Table 2).

Majority of the patients were keen for a HRP (Table 1). Of those who were not keen, reasons cited included cost, unsupportive family members, privacy issues and preferring a hospital-based rehabilitation. Currently, home physiotherapy or occupational therapy would require cash payment. Eighty-nine patients expressed that they would be more likely to opt for a HRP if it is Medisave deductible. Most patients (81) were willing to pay up to $30 per therapy session. There were higher perceived needs for physiotherapy and occupational therapy than nursing, speech therapist or the physician.

All but 2 patients desired to be as independent as possible. Ninety-nine patients felt strongly that they do take charge of their own health. The chief concern of 59 patients was in getting well, whereas 23 and 16 were most concerned about their finances and inconvenience to the family. From the results, it seems that being female, Malay, 60 years or younger, married, having moderate stroke, not having a family car, and being a worker not in the professional field would be factors leaning towards a HRP. However, these factors are not statistically significant, except for younger age (Table 1).

Cobley et al demonstrated in a small qualitative study exploring patients' and carers' experiences of ESD that there was a consensus of preference among participants

Table 1. Patients' Demographics

Demographic	Number of Patients (n = 100)
Gender	
Male	71
Female	29
Race	
Chinese	69
Malay	27
Indians	4
Mean age (range)	58.9 (25-90) years
Type of stroke	
Ischaemic	75
Haemorrhagic	25
Mean admission FIM (range)	72.6 (26 –126)
Stroke severity	
Severe (FIM = 18 to 53)	15
Moderate (FIM = 54 to 90)	66
Mild (FIM >90)	19
Marital status	
Single	9
Married	80
Separated/divorced	8
Widowed	3
Domestic helper at home	
Yes	16
No	84
Has a family car	
Yes	32
No	68
Proposed caregiver after discharge	
Nil	3
Domestic helper	13
Children	18
Spouse	43
Other relatives	20
Friend	3
Employment status	
Unemployed/retired	34
Non-professional	40
Professional	26
Education	(1 missing)
Less than 10 years	79
10 years or more	20

FIM: Functional independence measure

Table 2. Univariate Analysis of Patients' Factors and Their Keenness towards a HRP

	Very Keen to Keen for HRP n = 72	Neutral to Against for HRP n = 28	Unadjusted	
			OR (95% CI)	*P* Value
Gender				
Male	53 (74.6%)	18 (25.4%)	1.0	
Female	19 (65.6%)	10 (34.5%)	1.2 (0.393 – 4.106)	0.689
Race				
Chinese	48 (69.6%)	21 (30.4%)	1.0	
Malay	21 (77.8%)	6 (22.2%)	2.9 (0.609 – 13.831)	0.181
Age				
>60 years	26 (56.5%)	20 (43.5%)	1.0	
≤60 years	46 (85.2%)	8 (14.8%)	4.4 (1.7 – 11.4)	0.001
Stroke severity				
Severe (FIM = 18 to 53)	11 (73.3%)	4 (26.7%)	1.0	
Moderate (FIM = 54 to 90)	46 (69.7%)	20 (30.3%)	1.2 (0.3 – 4.2)	0.781
Mild (FIM >90)	15 (78.9%)	4 (21.1%)	0.7 (0.2 – 3.6)	0.702
Marital status				
Single	7 (77.8%)	2 (22.2%)	1.0	
Married	56 (70%)	24 (30%)	1.6 (0.179 – 13.487)	0.690
Separated/ divorced	6 (75%)	2 (25%)	1.1 (0.060 – 21.870)	0.929
Has domestic helper				
Yes	12 (75%)	4 (25%)	1.0	
No	60 (71.4%)	24 (28.6%)	1.3 (0.260 – 6.318)	0.760
Has a car in the family				
Yes	27 (84.4%)	5 (15.6%)	1.0	
No	45 (66.2%)	23 (33.8%)	1.35 (0.395 – 4.624)	0.632
Years of education				
<10 years	53 (67.1%)	26 (32.9%)	1.0	
≥10 years	19 (95%)	1 (5%)	0.3 (0.033 – 2.175)	0.217
Occupation				
Unemployed/ retired	24 (70.6%)	10 (29.4%)	1.0	
Non-professional	26 (65%)	14 (35%)	1.9 (0.51-6.876)	0.527
Professional	22 (84.6%)	4 (15.4%)	0.9 (0.199 – 4.809)	0.978

FIM: Functional independence measure; HRP: Home rehabilitation programme

for returning to their home soonest possible and almost all reported satisfaction with the rehabilitation exercises.[5] Some problems encountered in Cobley's study were disjointed transition between ESD and future services, limited support in dealing with carer strain, lack of education and training of carers and inadequate provision and delivery of information.

In our study, the majority of patients were keen for a HRP with the same intensity that an inpatient rehabilitation programme would provide, lasting up to 6 weeks. Cost could be a major barrier to the uptake of HRP in our study population. Given the evidence of its benefits,[2-4] a HRP is worth implementing. It appears that younger patients would prefer to be at home than in an institution. The therapy is in the real world setting when performed at home. We also perceive that the patient would be challenged more in the home environment than in the hospital environment. As for avoiding the issues faced by Cobley's population as well as addressing the obstacle of unsupportive family members, we have much more carer support than in the western world.[5] In Singapore, one can hire a domestic helper to relieve long-term carer stress. As for the acute to subacute period, interim carer service is available, especially when there is no carer available in the day. Such services provide carers who are trained to do transfers and look after the disabled in the short term, for up to 3 months. They can also check on the family member's caregiving skills. Stroke coordinators in our institution educate stroke patients in the ward and also call them to follow-up. This is a way to provide education and support. It is recommended that the teams providing care are acute hospital-based to facilitate collaborative decision-making between HRPs and acute services. It should be overseen by a rehabilitation physician who would then seamlessly transit the patient to outpatient rehabilitation or a day rehabilitation programme, if required. This would also provide confidence in patients that they are looked after by the acute hospital teams and the only difference is in the location of treatment. That may overcome the barrier of wanting a hospital-based treatment, especially when patients are medically stable to be discharged. In conclusion, HRP is worth implementing in Singapore, given its benefits and patients' enthusiasm. Making it Medisave deductible and having staff that is hospital-based and led by a rehabilitation physician would ensure its success.

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Milder Form of Urea Cycle Defect Revisited: Report and Review of Hyperornithinaemia-Hyperammonaemia-Homocitrullinuria (HHH) Syndrome Diagnosed in a Teenage Girl Presenting with Recurrent Encephalopathy

Dear Editor,

Hyperornithinaemia-hyperammonaemia-homocitrullinuria (HHH) syndrome (OMIM #238970) is a rare autosomal recessive disorder associated with mutations of the *SLC25A15* gene which encodes the mitochondrial ornithine transporter 1 (ORNT1).[1] ORNT1 is responsible for the transport of cytosolic ornithine into the mitochondria in exchange for citrulline in the urea cycle and ornithine degradation pathway. A defect in this transporter results in accumulation of ornithine in the cytosol (resulting in hyperornithinaemia), disruption of the urea cycle (resulting in hyperammmonaemia) and increased secretion of homocitrulline in urine (a product of transcarbamoylation of lysine). This biochemical reaction cascade is affected by protein load in the diet.[2]

It is challenging to diagnose HHH syndrome as it is not detected on newborn metabolic screening.[3] Hyperornithinaemia develops beyond infancy and hyperammonaemia tends to be milder compared to other urea cycle disorders. However, it is a preventable cause of intellectual disability, and prompt diagnosis with appropriate management can improve long-term outcome and quality of life for patients. HHH syndrome was first described in 1969 by Shih and colleagues[4] and it constitutes only 1% to 3% of all urea cycle disorders.[5] HHH syndrome has the highest prevalence among French-Canadians, followed by Italians and Japanese.[6] HHH syndrome has not been reported locally and only been reported once previously in an individual of Indian descent.[7] We describe an additional case of a girl of Indian descent, who presented with recurrent episodes of altered mental state in association with febrile illnesses and was subsequently diagnosed with HHH syndrome.

Clinical Report

An 11-year-old Indian girl presented to our hospital with altered mental state in association with acute upper respiratory tract illness. She was feeding less due to poor appetite and had vomiting prior to admission. She had no fever. She took oral dexamethasone, clarithromycin and dextromethorphan for 2 days before admission. She was found to be confused and unable to recognise her family or surroundings. Physical examination revealed a well-thrived child. She had spontaneous eye opening and was able to move her limbs voluntarily. However, she was disoriented to time, place and person. She was afebrile. She was mildly tachypnoeic but the respiratory examination did not reveal any abnormality. Neurological evaluation revealed symmetrical hyperreflexia over bilateral knee and ankle joints with bilateral abnormal Babinski sign. She did not have ankle clonus and her strength was full. Her sensory examination was normal and she did not exhibit neck stiffness or any signs of cerebellar involvement (nystagmus, dysmetria, dysdiadokinesia, ataxia or pendular reflexes). She had no hepatosplenomegaly.

She is the second child of non-consanguineous parents of Indian descent. She had a maternal uncle who passed away in infancy of unknown cause. She had a personal preference for a protein restricted vegetarian diet because she felt unwell after consuming meat. Besides asthma, she had a previous admission at 5 years of age where she had experienced a brief period of altered mental state. It occurred during an episode of acute asthma exacerbation and had resolved spontaneously. She did not require intravenous hydration during that admission. No further workup was done at that point of time in view of the spontaneous remission of symptoms. She was developmentally appropriate and was coping in mainstream school, albeit with poor performance in Mathematics.

Brain magnetic resonance imaging (MRI), electroencephalogram and cerebrospinal fluid (CSF) biochemical analysis were normal. Blood investigations were significant for mild respiratory alkalosis (pH 7.466, pCO_2 34.4 mmHg, pO_2 68 mmHg, BE 1, HCO_3 24.8 mmol/L) and mildly elevated alanine transaminase at 44 U/L, (normal range 9 to 25 U/L). Her coagulation profile was normal. Ammonia levels revealed mild hyperammonaemia (84 μmol/L, reference range 9 to 33 μmol/L). In view of her encephalopathy, hyperammonaemia, respiratory alkalosis and a history of protein aversion, a possible diagnosis of a urea cycle disorder was suspected. Plasma amino acid analysis showed elevations of glutamine (881 μmol/L; normal range 400 to 750 μmol/L) and ornithine (197 μmol/L; normal range 35 to 155 μmol/L) with citrulline and arginine levels within their respective normal reference ranges. No argininosuccinic acid was detected. Orotic acid was present and abnormally raised in the urine [orotic acid to creatinine

ratio 14.6 µmol/mmol (normal range 0.0-3.5 µmol/mmol)]. Urine amino acid analysis showed a small but distinguishable peak corresponding to the retention time of homocitrulline. This finding in combination with hyperornithinaemia and hyperammonaemia suggested a possible diagnosis of HHH syndrome. Due to the presence of mild orotic aciduria in the biochemical workup, as well as family history of male neonatal death, the differential diagnosis considered for our patient was that of a heterozygous female presenting with partial ornithine transcarbamylase (OTC) deficiency, a more well known metabolic cause of recurrent encephalopathy in females. Sanger sequencing of *OTC* gene was negative. Sanger sequencing of *SLC25A15* gene revealed that she was compound heterozygous for 2 variants (*c.88T>G; p.F30V* and *c.113A>C; p.Q38P*). One of the variants *c.113A>C*; *p.Q38P* is known to be a pathogenic mutation, while the second is a novel variant *c.88T>G; p.F30V*. This variant was absent from dbSNP141, 1000 Genomes, Exome Aggregation Consortium and Exome Variant Server. The novel variant alters a highly conserved amino acid residue and was predicted by in silico prediction algorithms to be pathogenic. Parents were offered genetic testing of *SLC25A15* gene to phase the variants, as well as to determine their carrier status, but they declined due to financial constraints.

She was given intravenous dextrose drip after admission with improvements in her ammonia level to 44 µmol/L. After she was diagnosed with HHH syndrome, she was continued on a protein restricted diet (0.9 g protein/kg/day) and started on oral sodium benzoate which led to normal ammonia

Table 1. Comparison of the Clinical Presentation of Previously Reported Cases of HHH with Our Patient

	Debray et al[*]	**Miyamoto et al**[†]	**Tunali et al**[‡]	**Tezcan et al**[§]	**Lee et al**[‖]	**Our Patient**
Ethnic group	French Canadian	Japanese	Turkish	Indian	Chinese	Indian
Number of patients	16	2	1	1	1[¶]	1
Mutation	Homozygous *p.F188del*[**]	Homozygous *p.R179X*	Homozygous *p.A15V*	Compound heterozygous *p.G220R* and *p.R275del*	Compound heterozygous *p.R179X* and *p.T272I*	Compound heterozygous *p.F30V* and *p.Q38P*
Age of presentation (years)	2.7[#]	52[††] and 10[‡‡]	6	35	<1 (1 month)	11
Initial clinical presentation						
Neurological symptoms	9/16	2/2	Yes	Yes	No	Yes
Encephalopathy	3/16	2/2	Yes	Yes	No	Yes
Liver dysfunction	6/16	Unknown	Unknown	Unknown	Yes	Mildly elevated transaminases
Hyperammonaemia	12/16	2/2	Yes	Yes	Yes	Yes
Ammonia level at presentation (µmol/L)	146	90[††] and 132[‡‡]	300	114	132	84

[*]Debray FG, Lambert M, Lemieux B, Soucy JF, Drouin R, Fenyves D, et al. Phenotypic variability among patients with hyperornithinaemia-hyperammonaemia-homocitrullinuria syndrome homozygous for the *delF188* mutation in *SLC25A15*. J Med Genet 2008;45:759-64.
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[¶]Patient 2 in the study was excluded as he was diagnosed by screening due to family history.
[#]Median.
[**]All are homozygous *p.F188del* except 1 patient with *p.F188del* with a second unidentified mutation.
[††]Patient 1.
[‡‡]Patient 2.

levels as well as initial improvement in her cognition and academic performance. She was educated on emergency feeding regimen including being on protein-free diet and high caloric carbohydrate drinks during sick days. She is now 12 years old and occasionally misses her medications and medical appointments. We continue to engage her and her family to improve compliance.

Discussion

This is the first case reported in the local population and the second case reported in an individual of Indian ethnicity, the former being a 35-year-old college graduate male from India with a history of protein restriction in his diet who had no neurological or neurocognitive deficits prior to presentation.[7] Both individuals had a history of self-restriction of protein in the diet and thus were generally asymptomatic. This likely contributed to the late clinical presentation and diagnosis. They both had episodic decompensation causing neurological symptoms and their conditions are stable with diet control and medications. Our patient had homocitrullinuria, while this was absent in the previously published case.

Compared to the reported clinical features of patients with HHH syndrome,[6] she shared some of the commonest clinical features of pyramidal signs, lethargy and abnormal behaviour. Most patients, like ours, were diagnosed between 1 to 12 years of age. In Table 1, we compared our patient with those reported previously in literature and include individuals of French-Canadian, [8] Japanese,[9] Chinese[10] and Turkish[2] descent. Although, there is a common founder mutation in the French-Canadian patients (*p.F188del*), there are no obvious differences in the phenotype among patients of different ethnic groups. In addition, there is a lack of phenotype-genotype correlation among patients with HHH syndrome, where individuals with the same genetic mutation may have different age of presentation and varying clinical outcomes.[2] Affected individuals have unremarkable antenatal and birth histories and varied clinical presentations ranging from prolonged hyperbilirubinaemia,[10] mild neurocognitive deficits to seizures, gait disturbances, stroke-like episodes and life threatening presentations of encephalopathy and liver failure.[11] The diagnosis can be easily missed because the encephalopathy and mild hyperammonaemia can be treated merely by intravenous dextrose drip which is typically given for patients with vomiting and poor feeding.

Conclusion

In conclusion, we report the first local case of HHH syndrome. Although our patient is only the second case of Indian origin, she shared many clinical features with previously reported patients from other ethnic groups. HHH syndrome should be considered in any female with mild hyperammonaemia, raised urine orotic acid and negative gene analysis for *OTC* gene. Early diagnosis and appropriate management can prevent life threatening complications and improve overall quality of life.

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Right Iliac Fossa Pain

A 49-year-old male presented with sudden onset right iliac fossa (RIF) pain which was aggravated by walking or positioning. There was no associated fever. Rebound tenderness was elicited at the RIF. Full blood count was normal with no evidence of leucocytosis. Being a medical personnel, he requested an ultrasound of the abdomen to exclude acute appedicitis. As the ultrasound of the abdomen was negative, computed tomography (CT) of the abdomen was performed.

What is the cause of the patient's RIF pain?

A. Acute diverticulitis
B. Omental infarct
C. Epiploic appendagitis
D. Acute appendicitis
E. Mesenteric panniculitis

Findings

The axial CT scan image (Fig. 1) showed a well defined ovoid fat density structure with thin hyperdense rim and surrounding fat streakiness (arrow), representing an epiploic appendagitis.

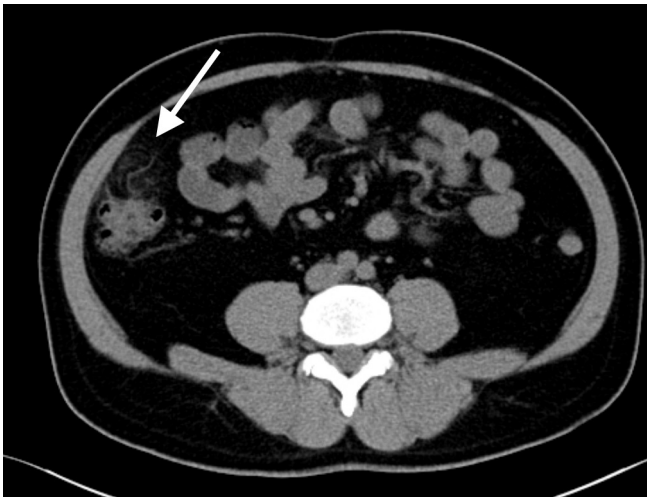

Fig. 1. An axial CT scan image of the abdomen.

Discussion

Epiploic appendagitis refers to an inflammation of the epiploic appendage which can be divided into primary and secondary.[1] Primary epiploic appendagitis is an ischaemic infarction of the appendage due to torsion or thrombosis of the epiploic central draining vein.[1] It has been associated with obesity, hernia and unaccustomed exercise.[2] Meanwhile, secondary epiploic appendagitis is an inflammation caused by other disease processes, such as diverticulitis, appendicitis, cholecystitis or pancreatitis.[1]

Primary epiploic appendagitis is a predominantly self-limiting disease which only requires symptomatic relief.[1,2] Rarely, it may be complicated by adhesion, bowel obstruction, peritonitis and abscess formation.[3]

Prior to the widespread use of CT scan, the majority of epiploic appendagitis cases were diagnosed intraoperatively.[2] Acute appendagitis most commonly involves the sigmoid colon, followed by descending colon and right hemicolon.[2] It is most commonly described on CT as an oval fat density lesion which abuts the anterior colonic wall and is surrounded by inflammatory changes.[2] Despite its self-limiting nature, with resolution of symptoms within 2 weeks, the CT findings usually last longer. However, CT features usually resolve within 6 months.[2]

The given choices for the differential diagnoses are acute diverticulitis, omental infarct, acute appendicitis and mesenteric panniculitis; however, this CT image has a typical appearance of an acute epiploic appendagitis.

In contrast, omental infarcts are typically represented as a solitary non-enhancing omental mass of heterogenous attenuation in the right lower quadrant.[2] The omentum can be identified by tracing the mass back to the epiploic vessels which are branches of gastroepiploic vessels. The omental infarcts, however, lack the hyperattenuating ring and central dot[1,2] which are seen in this case. The omental infarcts also tend to be larger and separated from the colon,[2] which are contrary to this case. It is important to note that the CT findings of the epiploic appendagitis and omental infarcts may overlap, thus making it difficult to differentiate between these two entities. However, both conditions are self-limiting and tend to resolve spontaneously.

Answer: C

Meanwhile, acute diverticulitis is an inflammation of the diverticula, which are the mucosal outpouchings through the weakened colonic wall between the mesenteric and antimesenteric taenia. It frequently affects patients over 50 years old.[1] Almost 95% of cases occur on the left side of the abdomen. However, 5% of the diverticula are located on the right side, which has a predilection for those of Asian descent.[1] Acute diverticulitis is commonly represented by paracolic fat stranding, which is apparent in this case. Typically, a blurry or ill-defined diverticulum would be present where the fat stranding is most pronounced[1] which is not demonstrated on this CT image. There is often associated segmental colonic wall thickening[1,4] which is also absent from the image.

Acute appendicitis may occur in all ages, but has the greatest incidence in the second decade of life. An abnormal appendix appears dilated on CT with the lumen measuring more than 6 mm in diameter. It has a thickened wall which may enhance homogenously on intravenous contrast media administration.[4] Acute appendicitis also presents on CT as a thick fluid-filled appendix with intramural gas, caecal apical thickening and adjacent fat stranding.[1,4] However, this CT image showed a fat density lesion rather than a fluid-filled structure. Furthermore, a normal appendix is identified for the case.

Mesenteric panniculitis, by contrast, is a condition where the fatty tissue of the bowel mesentery undergoes non-specific chronic inflammation and fibrosis.[1] It mainly involves the root of the small bowel mesentery and does not abut the colonic wall[1,2] as opposed to this particular image.

In conclusion, CT appearances are valuable in distinguishing these differential diagnoses, thus helping in decision-making and further management of patients.

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Neutrophilic Dermatoses as a Continuous Spectrum: An Illustrative Case

A 19-year-old Chinese male was referred to our department for bilateral preauricular and left cheek abscesses of 1-week duration. He had a significant past medical history of ulcerative colitis (UC) controlled on mesalazine (4 g/day) and short courses of oral steroids. The patient had received paracetamol, tramadol and lactulose 6 days prior to this admission for perianal pain, all of which he had taken before. There were no other new or traditional medicines prior to the development of facial lesions.

He initially presented to the surgeons and underwent incision and drainage of his cheek and preauricular lesions. The facial wounds then progressed into large ulcers with violaceous undermined borders and a necrotic centre (Fig. 1). This occurred together with a flare of his UC. He was also noted to have pustules on his chin and an ulcer on his left chest which had evolved from a pustule (Fig. 2a). During hospitalisation, he developed further chest and groin pustules (Fig. 2b) associated with fever. He had no joint pain or back stiffness. A formal pathergy test was not performed, but no papules, pustules or ulceration was observed at the sites of insertion of venipuncture or blood tests.

Laboratory results demonstrated elevated white cell count of 23.5 x 10^9/L (normal: 4.0 to 10.0 x 10^3/L), neutrophilia 89% (normal: 35% to 80%), C-reactive protein 241.7 mg/L (normal <3.0 mg/L), procalcitonin 0.29 µg/L (normal: 0 to 0.05 µg/L), erythrocyte sedimentation rate of 64 mm/h (normal: 3 to 15 mm/h). Renal panel was normal and liver function test showed albumin of 32 g/L (normal: 37 to 51 g/L) and mildly elevated alanine aminotransferase of 60 U/L (normal: 10 to 55 U/L). The autoimmune markers anti-nuclear antibody and anti-double stranded deoxyribonucleic acid (DNA) were negative. Chest x-ray was normal, blood and urine cultures showed no bacterial growth.

A punch biopsy from the lower anterior edge of the patient's left cheek ulcer was taken. What is your diagnosis?

A. Subcorneal pustular dermatosis
B. Pyoderma gangrenosum with Sweet-like features
C. SAPHO syndrome
D. Atypical mycobacterial infection
E. Dermatitis artefacta

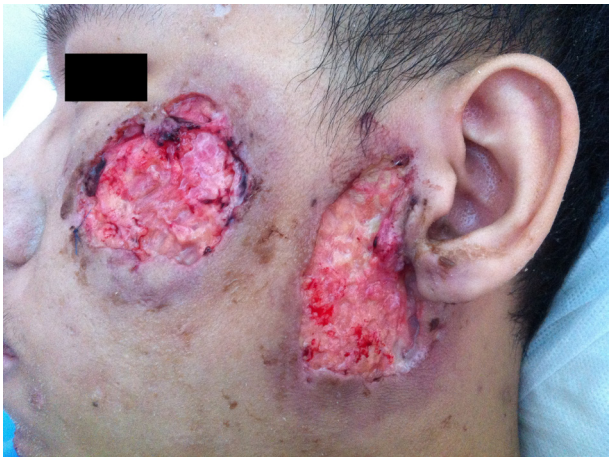

Fig. 1. Close-up view of an ulcer with violaceous undermined edges and devitalised yellow tissue on the left chest.

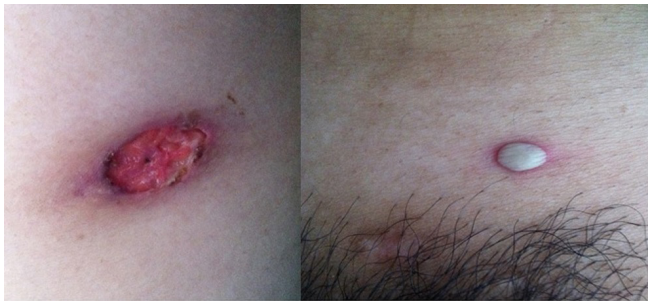

Fig. 2. A) Close-up view of an ulcer with violaceous undermined edges and devitalised yellow tissue on the left chest. B) Close-up view of a pustule with an erythematous halo in the suprapubic region.

Answer: B

Discussion

A 3 mm punch biopsy from the left cheek ulcer edge was obtained for haematoxylin and eosin (H&E) staining as well as for culture. Microbial and fungal culture were negative. Histopathology showed neutrophilic suppurative inflammation with vasculitis (Fig. 3). The epidermis was acanthotic and traversed by neutrophils and lymphocytes with aggregation of neutrophils in the stratum corneum. The dermis and subcutaneous fat was replaced by suppurative and necrotising inflammation. There was accompanying tissue lysis and abscess formation, mixed inflammatory exudation, fat necrosis and small vessel vasculitis which were felt to be secondary to the intense suppurative inflammation. There was no dermal papillary oedema.

Our patient was given empirical intravenous antibiotics in view of the fever and raised inflammatory markers. On day 5 of admission, he was commenced on oral prednisolone 40 mg daily (0.5 mg/kg) and discharged on a tailing regime. By the sixth day after commencement of prednisolone, the patient's chest and groin pustules had improved significantly. One month after being discharged, he was started on infliximab. Two months after first presenting with multiple facial lesions, the patient's facial ulcers had healed with hypertrophic scars and his chest and groin pustules had completely resolved, leaving hyperpigmented macules.

Neutrophilic dermatoses are a group of cutaneous conditions believed to be caused by an underlying neutrophil-mediated process in the absence of any infective process. They typically exhibit a dense infiltrate of normal polymorphonuclear leukocytes on histopathology.

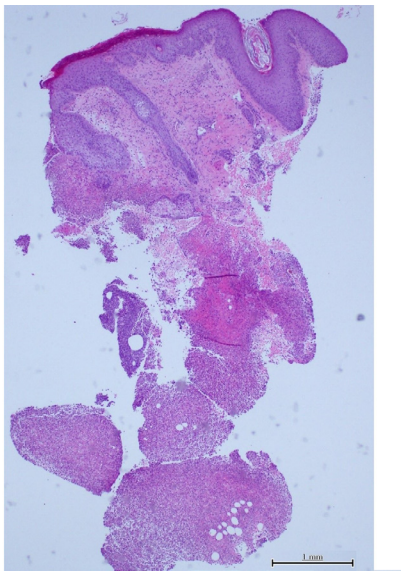

Fig. 3. Histopathology showing dense neutrophilic infiltration in the dermis and subcutis with small vessel vasculitis (original H&E magnification 200x).

The scope of neutrophilic dermatoses, first described by Caughman et al[1] in 1983, has been expanded to include pyoderma gangrenosum (PG), Sweet's syndrome, erythema elevatum diutinum, and subcorneal pustular dermatosis.

Clinical differences between subtypes of neutrophilic dermatoses may be attributed to differences in the intensity and extent of inflammatory response and may represent 2 different points on a spectrum. There are several reports in the literature of PG associated with Sweet's syndrome, and multiple forms of neutrophilic dermatoses existing in the same patient.

Two case reports, in particular, highlight the difficulty in distinguishing PG from Sweet's syndrome. In the first case, reported as PG in a patient with myelofibrosis, the authors received a correspondence by Sherertz contesting the diagnosis to be Sweet's syndrome. In the second case of a patient reported to have Sweet's syndrome on a background of ulcerative colitis, correspondence to the authors contested the diagnosis as bullous PG.[2]

In UC specifically, there have been several case reports of multiple forms of neutrophilic dermatoses occurring in the same patient, commonly that of PG and Sweet's syndrome. Salmon et al described a patient who presented with concurrent lesions of Sweet's syndrome and PG;[3] while Benton et al reported a patient who presented with PG initially, and 9 months later, developed Sweet's syndrome.[4]

Our patient described in this report had an eruption of pustules with a course correlating to the severity of his bowel disease. Coinciding with the flare of UC, one of the pustules eventually progressed to ulcerate, forming a tender ulcer with violaceous and undermined border, typical of PG. The pustules quickly subsided with systemic corticosteroids. This is similar to the pustular variant of PG reported in the patients described by O'Loughlin and Perry.[5] Pustular eruptions have been reported in UC and range from 1% to 6%. Many of these case reports describe lesions which share overlapping features between PG and Sweet's syndrome.

Interestingly in our patient, the lesions showed a predilection for the face and upper trunk, a feature of Sweet's syndrome. Although our patient fulfilled the diagnostic criteria for Sweet's syndrome (fever with leucocytosis and raised ESR, marked improvement with systemic steroids and histopathology showing inflammation composed mainly of neutrophils without primary vasculitis), the clinical feature of rapid progressive ulcers were not classical of Sweet's syndrome.

The exact pathogenesis of neutrophilic dermatoses is still unknown. Many cytokines and granulocyte colony-stimulating factor (GCSF) have been implicated in both Sweet's syndrome and PG,[6] in addition to granulocyte-

macrophage colony stimulating factor and adhesion molecules. This may represent a shared pathogenesis between PG and Sweet's syndrome.

As we progress in our understanding of neutrophilic dermatoses, we may consider approaching this group of conditions as a continuous spectrum with varying presentations. More research is needed to pave the way in understanding the pathogenesis and relationship between the different presentations of neutrophilic dermatoses. In summary, this case of pustular PG with Sweet-like features further substantiates the hypothesis that neutrophilic dermatoses may be a continuum with many overlapping features.

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