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Contents

Infection and COVID-19

I am writing this editorial with a mixed feeling, a sense of hope with different vaccines against SARS-CoV-2 arriving with preliminary data showing promising results. The vaccines come from China, the USA, the UK and Russia. On the other hand, the situation in my home town, Hong Kong, has taken a turn for the worse with an upsurge of COVID-19 after loosening of infection control measures for the community. Similar upsurge is seen all over the world. This is indeed time for people to pull together to fight this pandemic. It is also important to remember that other diseases continue to affect our children.

Co-infection is common in those with severe paediatric COVID-19, and Sitthikool and Aksilp[1] reported from Thailand the use of procalcitonin in the detection of bacterial infection in those critically ill children. A level of procalcitonin >1.1 ng/ml has a positive and a negative predictive value of around 70% for bacterial infection. Interestingly, the changes in procalcitonin correlated with the changes of the severity score, Pediatric Logistic Organ Dysfunction.

Nutrition is a key to health and prevention of diseases, COVID-19 included. Kuti and Oyelami[2] reported a very important finding about the impact of antioxidants and severity of pneumonia from Nigeria. They found a lower level of non-enzymatic antioxidants in those with severe pneumonia. As these antioxidants, that is flavonoids, phenols, carotenoids, Vitamin C and tocopherol, are found mainly in vegetables and fruits, it is important to advocate this healthy diet in any encounter with patients. It is well known that obesity is a risk factor for severe COVID-19; lower antioxidant level might well play a part as obese persons usually consume less vegetables and fruits.

Chronic respiratory diseases are risk factors for severe COVID-19, and cystic fibrosis (CF) patients would be at high risk for severe COVID-19. It was an assumption that CF is very rare in non-Caucasian population although we, the paediatric respirologist, know we do have CF cases in our practice, but we do not have the overall picture. In this issue, Kabra *et al*.[3] reported the first-ever CF survey in Asia involving 15 Asian countries that shed some light on this issue. In this survey, the personal observation of the paediatric respirologists was reported with all the limitations intrinsic to these personal observations. Nevertheless, it did show that paediatric respirologists must be trained to manage CF in Asia and Asian Paediatric Pulmonology Society (APPS) is ideally placed to provide this training. It is also noteworthy that none of the current diagnostic tests are available in Myanmar, Vietnam and Macao, and means to improve access to the tests should be undertaken.

I would also like to remind the readers that the current issue is labelled January–March 2020 although it is in fact published in November 2020 because of the publication delay. My sincerest apology for any inconvenience so caused to the authors.

May I end with a quote from Winston Churchill 'Success is not final. Failure is not fatal. It is the courage to continue that counts'.

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Original Article

Serum Nonenzymatic Anti-oxidants in Nigerian Children with Severe Pneumonia: Association with Complications and Hospital Outcomes

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Abstract

Background: Tissue damaging effects of free radicals generated during the acute inflammation processes of childhood pneumonia may be ameliorated by antioxidants. This study aimed to determine the serum non-enzymatic antioxidants {Total Phenols, Carotenoids, Flavoids, Ascorbic acid, Tocopherols and Total Antioxidant Contents (TAC)} of Nigerian children with or without severe pneumonia (SP) and relate these to the presence of parapneumonic effusions (PPE) and length of hospitalisation (LOH). **Methods:** Consecutive children two months to 14 years admitted with severe pneumonia and their age and sex matched controls were recruited over a 12-month period at a Nigerian Health facility. Serum antioxidants were assayed using chromatography method and related to PPE and LOH. **Results:** The majority (86.1%) of the 144 children (72 each with SP and controls) were under-fives and eight (11.1%) of SP group had PPE. Median (IQR) LOH was 5.0 (4.0 – 7.0) days and 45 (62.5%) had prolonged (≥5 days) hospital stay with 3 (4.2%) mortality. Serum Tocopherols, 10.1 (4.7) vs. 13.2 (7.6) µg/dl; total flavoids 1.0 (0.6) vs. 1.3 (0.8) µg/dl and TAC 6.1 (4.4-8.9) vs. 7.4 (5.0 – 13.3) ng/dl were significantly lower in children with SP ($p < 0.05$). Serum antioxidants levels were not related to the PPE, however children with prolonged LOH had lower TAC ($p<0.05$), which also correlated negatively with LOH ($r =- 0.418$; $p < 0.001$) **Conclusion:** Lower serum antioxidants observed in children with severe pneumonia may connote increased demand or increased predisposition to the infection. Antioxidant supplementation may aid recovery of Nigerian children with SP.

Keywords: Anti-oxidants, childhood pneumonia, length of hospitalization, oxidative stress

Introduction

Pneumonia causes more ill-health and deaths in children than malaria, HIV/AIDS and tuberculosis put together.[1] These pneumonia-related deaths in children are particularly more common in low- and middle-income countries (LMICs).[1] Community-acquired pneumonia (CAP) in children accounts for about 15% of under-five mortality, which translates to over 800,000 childhood deaths per year[2] Nigeria bears the global lion share of childhood deaths from CAP with over 162,000 annual childhood deaths from pneumonia reported in Nigeria in 2018.[2]

Childhood CAP is often acquired through inhalation of pathogenic microbes or less commonly through haematogenous spread of microbes to the lungs.[3] Acute inflammation of the lung parenchyma is then initiated through cytokines, chemokines and other inflammatory mediators.[3,4] There is also chemoattraction of inflammatory cells to the site and attempt to phagocytose and destroy the offending microorganisms - a process that involves respiratory burst and generation of reactive nitrogenous species (RNS) and reactive oxidative species (ROS).[3,4]

Oxidative stress from the generated free radicals requires the action of endogenous anti-oxidants to limit the cell damage effects of these oxidants. These endogenous anti-oxidants include enzymatic anti-oxidants such as superoxide dismutase, glutathione peroxidase, glutathione reductases and catalases.[5]

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The nonenzymatic anti-oxidants like phenols, carotenoids, Flavonoids, Vitamin C (ascorbic acids) and E (Tocopherols) are needed to ameliorate the inflammatory and cellular damage effects of oxidative stresses generated by immune cells.[5,6] While the enzymatic anti-oxidants act by converting oxidised metabolic products to hydrogen peroxide (H_2O_2) and water using cofactors such as iron, zinc, copper and manganese, nonenzymatic anti-oxidants intercept and terminate free radical chain reactions.[5,6] All these actions convert harmful cytopathic free radicals to harmless metabolites.[6] Total anti-oxidant capacity (TAC), which is a measure of the summation of nonenzymatic anti-oxidant activities in the serum[7] have been reported to influence the severity of illness in children with sepsis and acute respiratory tract infections.[8,9] The serum levels of anti-oxidants in children with CAP may, therefore, influence disease severity and outcome.

Nonenzymatic anti-oxidants are freely available in fruits and vegetables such as carrots, citrus fruits, lettuce, green leafy vegetables and tomatoes.[10] Nonetheless, many children in LMICs where the burden of childhood pneumonia is highest are deficient in many of these anti-oxidants as childhood undernutrition and micronutrient deficiencies are very common.[11] This may contribute to their increased susceptibility to pneumonia and other infections and probably their tendency to succumb to these infections. This study, therefore, aimed to compare the serum nonenzymatic anti-oxidants (total phenols, carotenoids, flavoids, ascorbic acids, tocopherols and TAC) of Nigerian children admitted with severe CAP and that of their age- and sex-matched apparently healthy controls and relate these anti-oxidants to pneumonia incidence, presence of PPE and length of hospitalisation (LOH).

Methods

Study design and location

This hospital-based cross-sectional study design was carried out over a 12-month period (January to December 2019) at the Wesley Guild Hospital Ilesa, which is one of the tertiary units of the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Ile-Ife, Nigeria. Ilesa (Latitude 7°35'N and longitude 4°51'E) is located in the tropical rain forest region of southwest Nigeria.[12] The hospital offers primary, secondary and tertiary health-care services to the catchment population in Osun and neighbouring states in Southwest Nigeria.

Sample size estimation

The sample size was estimated using open Epi software®.[13] Based on the study of Cemek *et al*.,[14] the mean difference of serum ascorbic acid between children with CAP and controls was taken as 0.19 mg/dl and standard deviations from the mean for the two groups as 0.3 and 0.2 mg/dl respectively. At a 5% significance (alpha) level, 80% study power and 95% confidence interval and the ratio of cases to control being 1. The calculated sample size was 144 i.e., 72 children with CAP and 72 controls.

Study participants

These were children admitted with severe pneumonia between the ages of 2 months to 14 years and age- and sex-matched apparently healthy children. The controls were consecutively recruited from the daily child welfare clinic of the hospital after parental consent were obtained.

Study procedure

Definition of terms

Severe pneumonia was defined using the WHO criteria as age-specific tachypnoea (respiratory rate >50 breaths/min for children between 2 to <12 months; >40 breaths/min for those one to 5 years and >30 for those children >5–14 years); lower chest wall in-drawing; convulsions; central cyanosis; lethargy or altered sensorium and inability to feed or drink were classified as very severe pneumonia.[15] Parapneumonic effusion (PPE) was defined as the presence of pleural fluid collection on chest radiographs and/or with free-flowing fluid aspiration on percutaneous pleural tap.[16]

Children whose parents or caregivers did not give consent to participate in the study were excluded. Those with chronic cough (>2 weeks); acute or recurrent wheezing; and hospital-acquired pneumonia were also excluded.

Information obtained from the study participants and/or their parents included sociodemographic characteristics, housing, breastfeeding and immunisation history. Others included the use of biomass and other unclean fuel for cooking, lighting and heating. The children were classified into various nutrition categories based on the comparison of their weights and heights for age with the WHO growth reference standard for under-fives[17] and school-age children.[18] Socioeconomic class of the study participant was assigned using a validated tool[19] and overcrowding was defined as having three or more persons sharing the same standard room with the study participants.[20] The children were managed based on standard protocol and outcomes of hospital stay recorded.

Serum anti-oxidants and total antioxidant capacity assay

These were assayed by high-performance liquid chromatography (HPLC) methods using an automated 616/6265 transducer pump (Waters Incorporate, California, U.S.A) following standard protocol. The analysis was performed at the Analytical Services Laboratories of the International Institute of Tropical Agriculture, Ibadan, Nigeria. The summation of the individual HPLC peaks for total carotenoids, flavonoids, phenols and anti-oxidant vitamins defined the TAC. The background quality control check was done against Trolox®. Duplication of the blood sample was also done as quality control with the mean of the two results used as the estimated value. The inter-assay coefficient of variations (CVs) for TAC was ≤4.8%.

Ethical approval

This study was approved by the Ethics and Research Committee of the OAUTHC, Ile-Ife, Nigeria, with approval number ERC/2014/08/04. Written informed consent and

assent (for children >6 years) were obtained from the caregivers and study participants, respectively.

Data analysis

This was done using SPSS for Windows software version 17.0 (SPSS Inc., Chicago 2008). Continuous variables such as serum anti-oxidants, TAC, and age were tested for normality using Kolmogorov–Smirnov statistics and summarised using mean (standard deviation) or median (interquartile range) for Gaussian and non-Gaussian distributed variables. Differences between continuous variables were ascertained with Student's *t*-test or Mann–Whitney-U test as appropriate. The relationship between serum anti-oxidants, TAC and LOH were determined using Pearson or Spearman Rho correlations as appropriate. Age range, sex, socio-economic class categories and pneumonia severity were summarised using percentages and proportions, and the difference determined using Chi-squared or Fischer's exact test. The effect size was estimated using mean difference and the level of significance at 95% confidence interval (CI) was taken as $P < 0.05$.

Results

Characteristics of the study participants

A total of 144 (72 each for severe pneumonia and control) children were recruited. The median (IQR) age was 2.0 (0.8–3.5) years. There were 94 (65.3%) male children and the majority (80.6%) of the study participants were from middle and low SES. The sample population was enriched with children with appropriate immunisation status (84.0%), normal nutritional state (78.5%), but the use of clean fuel (30.6%) was less frequent. Table 1 highlights the characteristics of the study participants. No significant difference in the age, gender and Socio-economic classification of the children with severe pneumonia and controls. However living in crowded homes, inappropriate immunisation and undernutrition were significantly more common in the severe pneumonia group [Table 1].

Specific pneumonia complications

Figure 1 highlights the complications observed among children with severe pneumonia. Heart failure (30.7%), parapneumonic effusions (12.5%) including empyema thoracic (6.9%) and serous pleural effusions (5.6%) were the most common complications. Two children had more than one complication.

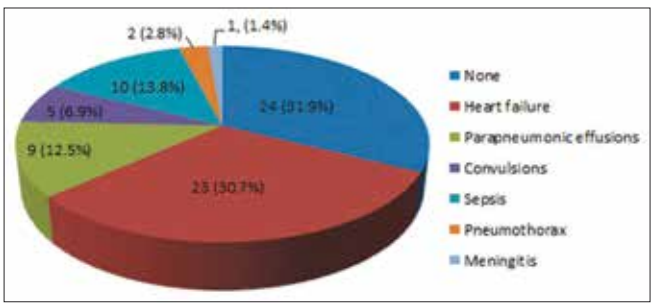

Figure 1: Complications of severe pneumonia

Outcome of hospitalisation

The median length of hospital stay was 5.0 (4.0–7.0) days, which ranged from 1 to 22 days. Forty-five (62.6%) had prolonged hospital stay (≥5 full days), sixty-nine (95.8%) were discharged home, while there were three (4.2%) cases of mortality.

Serum anti-oxidant profile of the study participants

Table 2 highlights the selected serum anti-oxidant profile in children with severe pneumonia and controls. Serum total flavonoids, phenols, tocopherols and TAC were significantly lower in children with severe pneumonia than their age- and sex-matched controls ($P < 0.05$).

No significant association between serum antioxidants and the presence of parapneumonic effusions [Table 3] and other complications (not shown).

Serum anti-oxidants and length of hospitalisation

The relationships between serum anti-oxidants and the presence and absence of prolonged hospital stay are highlighted in Table 4, while the correlations between the anti-oxidants and length of hospital stay in Table 5. Only TAC was significantly associated with the prolonged hospital stay. Similarly, there was a significant negative correlation between serum TAC and LOH.

Discussion

This study highlights significantly lower serum nonenzymatic anti-oxidants (Flavonoids, Phenols and Vitamin E and TAC) in a group of Nigerian children with severe pneumonia compared to controls. These anti-oxidants were not associated with disease severity; however, lower serum TAC was associated with the prolonged hospital stay. Major pneumonia-related risk factors (crowded homes, undernutrition, lack of immunisation and exclusive breastfeeding) were also highlighted and were modifiable. The discussion will address the relationship between these anti-oxidants and pneumonia incidence, severity and LOH. The significant lower serum anti-oxidants observed in the children with severe pneumonia compared to controls in this study was similarly reported by Cemek *et al*.[14] in Turkey and Bhoite *et al*.[21] as well as Vaidyal and Bulakh[22] in India. Lower serum anti-oxidants may predispose these children to having severe pneumonia as it reduces their ability to get rid of infectious agents.[5] Nonenzymatic anti-oxidants prevent lipid peroxidation and subsequent damage to the cell membrane of immune cells.[5,6] Vitamin E is an anti-oxidant vitamin which had been shown to prevent the process of lipid peroxidation by trapping peroxyl radicals.[5,6] The inability to limit the tissue-damaging effects of ROS and other free radicals generated by immune cells leads to the generation of more free radicals and perpetuation of the vicious cycle.[5,6] Furthermore, children with infection may have more needs for anti-oxidants as they may have utilised the available serum anti-oxidants leading to relatively lower levels compared to controls. This cause-effect relationship may explain the lower

Table 1: Characteristics of the study participants

Variables	Severe pneumonia group (*n*=72), *n* (%)	Control group (*n*=72), *n* (%)	Total (*n*=144)	χ^2	*P*
Age range					
2 months-<1 year	30 (41.7)	26 (36.1)	56	0.528	0.768
≥1-<5 years	31 (43.1)	35 (48.6)	66		
≥5	11 (15.2)	11 (15.2)	22		
Gender					
Male	44 (61.1)	50 (69.4)	94	1.103	0.294
Female	28 (38.9)	22 (30.6)	50		
SES					
Upper	12 (16.7)	16 (22.2)	38	0.751	0.687
Middle	31 (43.1)	30 (41.7)	61		
Low	29 (40.2)	26 (36.1)	55		
Overcrowding					
Yes	21 (29.1)	12 (16.7)	33	3.923	0.048
No	51 (70.9)	60 (83.3)	111		
Exclusively breastfed					
Yes	39 (57.4)	46 (66.7)	85	4.159	0.041
No	43 (42.6)	26 (33.3)	69		
Household fuel					
Clean fuel	17 (23.6)	27 (37.5)	44	3.273	0.070
Unclean fuel	55 (76.4)	45 (62.5)	100		
Immunisation status					
Appropriate	51 (70.9)	70 (97.2)	121	21.290	<0.001*
Not appropriate	21 (21.1)	2 (2.8)	23		
Nutritional status					
Normal	52 (72.2)	61 (84.7)	113	10.610	0.005*
Undernourished	18 (25.0)	5 (6.9)	23		
Overweight/obese	2 (2.8)	6 (8.4)	8		

Figures in parentheses are percentages of the total along each column;*Fischer's exert test applied. SES=Socioeconomic status

Table 2: Serum anti-oxidants of the study participants

Variables	Range values	Severe P group (*n*=72)	Control group (*n*=72)	Mean difference (95% CI)	*P*
Serum flavonoids (ng/dl)	0.2-2.4	1.0 (0.6)	1.3 (0.8)	0.3 (0.1-0.5)	0.012
Serum phenols (ng/dl)	0.5-10.7	2.4 (1.6)	3.4 (3.1)	1.0 (0.2-1.8)	0.016
Serum carotenoids (ng/dl)	1.1-19.0	7.5 (5.0)	7.8 (4.3)	0.3 (−1.2-1.8)	0.700
TAC[#] (ng/dl)	0.9-53.5	6.1 (4.4-8.9)	7.4 (5.0-13.3)	−1.3 (−9.6–−1.1)	0.030*
Ascorbic acids (mg/dl)	0.2-3.2	1.4 (0.7)	1.3 (0.6)	0.1 (−0.1-0.3)	0.359
Tocopherol (ng/dl)	0.1-32.9	10.1 (4.7)	13.2 (7.6)	−3.0 (−5.1–−1.0)	0.004

*Mann–Whitney U applied; [#]Median (IQR); Mean (SD) used unless otherwise stated. P=Pneumonia, TAC=Total anti-oxidant capacity, IQR=Interquartile range, SD=Standard deviation, CI=Confidence interval

serum anti-oxidants observed in the children with severe pneumonia compared to the controls.

The presence of parapneumonic effusions among the children with SP was not significantly related to serum anti-oxidants levels. There is a paucity of studies relating pneumonia complications and parapneumonic effusions with serum nonenzymatic anti-oxidants. However, Narsimha *et al*.[23] in a study of 90 adults in India reported significantly higher serum levels of oxidative markers (Malondialdehyde and lactate dehydrogenase) in adults with exudative pleural effusions, including parapneumonic effusions than those with transudative pleural effusions. Increased markers of oxidative stress will invariably increase the demands for anti-oxidants. Nonetheless, the roles of oxidants/anti-oxidants in pneumonia-related complications and lung injuries have been described as complex.[24] Anti-oxidants include a wide variety of enzymatic and nonenzymatic substances, including uric acids whose roles in lung pathology and defenses are still being investigated.[13,25,26] In addition, anti-oxidants may sometimes exhibit pro-oxidant properties, and pro-oxidants may not always be harmful.[6,24,25] Further studies to investigate the complex interactions between pro- and anti-oxidants in lung health and disease, including childhood severe pneumonia and its complications, will be worthwhile.

Serum TAC in our cohort of children with severe pneumonia was significantly lower in those with prolonged length of

Table 3: Serum anti-oxidants as related to the presence of parapneumonic effusions

Variables	Parapneumonic effusions (*n*=9)	No effusions (*n*=63)	*P*
Serum flavonoids[#] (ng/dl)	0.5 (0.8-1.5)	0.9 (0.5-1.4)	0.303*
Serum phenols (ng/dl)	2.1 (1.1)	2.5 (1.6)	0.519
Serum carotenoids(ng/dl)	9.5 (5.5)	7.2 (4.9)	0.206
TAC[#] (ng/dl)	7.7 (5.3-9.3)	6.0 (4.1-8.4)	0.250*
Ascorbic acids (mg/dl)	1.6 (0.8)	1.3 (0.7)	0.282
Tocopherol (ng/dl)	11.3 (2.6)	10.0 (4.9)	0.416

*Mann–Whitney U applied; [#]Median (IQR); Mean (SD) used unless otherwise stated. P=Pneumonia, TAC=Total anti-oxidant capacity, IQR=Interquartile range, SD=Standard deviation

Table 4: Serum antioxidants as related to pronged hospitalisation

Variables	Prolonged hospital stay (*n*=27)	No prolonged stay (*n*=45)	*P*
Serum flavoids (ng/dl)	1.0 (0.7)	0.9 (0.5)	0.546
Serum phenols (ng/dl)	2.6 (1.8)	2.1 (0.9)	0.216
Serum carotenoids(ng/dl)	7.6 (5.2)	7.4 (4.7)	0.914
TAC[#] (ng/dl)	5.6 (3.1–6.5)	7.0 (4.9–10.6)	0.013
Ascorbic acids (mg/dl)	1.4 (0.8)	1.4 (0.7)	0.728
Tocopherol (ng/dl)	9.4 (4.1)	11.4 (5.4)	0.074

*Mann–Whitney U applied; [#]Median (IQR); Mean (SD) used unless otherwise stated. P=Pneumonia, TAC=Total antioxidant capacity, IQR=Interquartile range, SD=Standard deviation

Table 5: Correlation between serum anti-oxidants length of hospitalisation

Serum antioxidants	Correlation with length of hospital stay (days)
Serum flavonoids (ng/dl)	r=0.003; P=0.986
Serum phenols (ng/dl)	r=−0.181; P=0.234
Serum carotenoids(ng/dl)	r=−0.060; P=0.695
TAC[#] (ng/dl)	r=−0.418; P<0.01
Ascorbic acids (mg/dl)	r=−0.108; P=0.482
Tocopherol (ng/dl)	r=−0.233; P=0.123

*Spearman Rho applied; r=Pearson Correlation coefficient; bold figures denote statistical significance. TAC=Total antioxidant capacity

hospital stay. Implying serum anti-oxidants lower the period of hospitalisation as negative correlation was observed in this study. These support the findings of Wahed *et al*.[27] in India, where supplementation of children with anti-oxidant vitamins and micronutrients led to faster resolution of clinical signs of pneumonia and reduced LOH. Anti-oxidants prevent lung injuries by neutralising free radicals including ROS and RNS released by immune cells during the process of inflammations and preventing lipid peroxidation, thereby assisting in halting the vicious cycle of inflammation, free-radical generation, cellular damage and further acute inflammation. This explains the significant association of TAC with reduced hospitalisation in this study. However, a randomised controlled trial to determine the effects of anti-oxidants vitamin E and C as an adjunct therapy in the management of children with CAP reported no beneficial effects in terms of pneumonia outcome and LOH.[28] More studies on the roles of anti-oxidants in childhood pneumonia related morbidity and outcomes is hereby advocated.

Worthy of note from this study is that undernutrition, inappropriate immunisation and overcrowding were found to predispose to CAP among the recruited children. These were major risk factors to childhood pneumonia[2] and had also been reported by other workers in LMICs.[29,30] Undernourished children have been reported to have increased markers of oxidative stress and reduced anti-oxidants.[10] This not only predisposes them to infections, it also increases their propensity to succumb to infectious diseases. Inappropriate immunisation and living in overcrowded homes are intrinsically linked to poverty and underdevelopment, which also manifests as poor access to health and childhood undernutrition.[31] Reducing childhood undernutrition as well as the standard of living and health inequalities among the underprivileged in LMICs, will assist in tackling the burden of childhood pneumonia.

Our study has many strengths, which include the assaying of the selected serum nonenzymatic anti-oxidants using quality assured HPLC methods in children with severe pneumonia in an LMIC where the burden of childhood pneumonia is very high. Furthermore, our sample size was adequate and pneumonia mimics such as bronchiolitis and other wheezing disorders were excluded making our cohort of pneumonia cases very homogeneous. We, however, recognise few limitations of this study, which include our inability to define the aetiologies pneumonia in our sample population and we did not study enzymatic anti-oxidants in this report. Furthermore, recruiting malnourished children without pneumonia as controls was difficult as most malnourished children usually have one symptom or another and often do not qualify as apparently healthy children. Nonetheless, this study will add to the few available reports about the roles of nonenzymatic anti-oxidants in childhood pneumonia incidence, complications and outcomes in LMICs.

Conclusion

Modifiable factors such as crowded homes, inappropriate immunisation and undernutrition predispose Nigerian children to severe pneumonia. These children had significantly lower serum total flavonoids, phenols, tocopherols and TAC than controls. These anti-oxidants were however not associated with the presence of parapneumonic effusions and other complications. TAC nonetheless was associated with a prolonged hospital stay in the children with severe pneumonia. Appropriate housing and immunisation as well as adequate childhood nutrition, including anti-oxidant supplementation may reduce the burden of severe pneumonia in Nigerian children.

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Conflicts of interest
There are no conflicts of interest.

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Cystic Fibrosis in Asia

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Abstract

Background: Cystic fibrosis (CF) is the most common inherited life-limiting illness in the Caucasian population. It is considered to be rare in Asia, but recent reports suggest that CF does occur in Asia. **Methods:** We carried out a questionnaire-based survey to determine the prevalence of CF across Asian countries and the diagnostic and therapeutic capabilities available in member countries. A questionnaire was sent to member countries of the Asian Pediatric Pulmonology Society. The questionnaire included the total number of children diagnosed with CF seen in the country and the available resources. available resources for diagnosis and management. **Results:** Fifteen countries responded to the questionnaire. Three countries/regions (Myanmar, Vietnam, and Macau) have not recorded any case of CF. The remaining 12 countries have recorded a variable number of cases which have also been reported in the literature. Sweat chloride testing facilities were available in all the countries except Taiwan that reported cases of CF. Some countries such as India and Bangladesh have developed their own indigenous method for sweat testing. Some countries have facilities for mutation testing. Basic medications such as pancreatic enzyme supplementation and antibiotics were available in all the countries where children with CF have been diagnosed. Inhaled antibiotics and dornase alfa were available only in a few countries. Some other countries reported using the injectable preparation of gentamicin and amikacin for inhalation therapy. Testing for genetic mutation wherever available showed a low frequency of the Delta F 508 mutation which is the most common mutation found in the Caucasian population. Only two countries (India and Japan) have formal CF associations for the affected community. Two countries Japan and China maintain a CF registry, whereas India already started the process of developing it. **Conclusion:** CF is increasingly being diagnosed over the past two decades in Asian countries. There is a need to create awareness among pediatricians and to develop regional or country-specific protocols and tools for the diagnosis and treatment of children with CF.

Keywords: Child, cystic fibrosis, dornase alfa, pancreatic enzyme, sweat test, tobramycin

Introduction

Cystic fibrosis (CF) is the most common inherited life-limiting illness in the Caucasian population. Till a few years ago, it was considered extremely rare in the non-Caucasian community. With the publication of multiple reports over the last two decades from Asia and other parts of the world, it is clear that

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CF does occur in Asia.[1-8] The diagnosis is delayed due to multiple causes including the strong belief that CF does not occur in non-Caucasian populations and the nonavailability of diagnostic tests predominantly the analysis of sweat chloride. Now with the availability of genetic tests mainly new generation sequencing, many centers have confirmed cases of CF from this continent.

The management of CF has evolved over the past 6–7 decades with the improvement of survival to the fourth decade of life from a 6-month survival about six decades ago. The important contributing factors for improved survival include better understanding of the pathophysiology of illness, early diagnosis, and treatment by a multidisciplinary team.[9] With better awareness and well-developed networking, CF is diagnosed before 6 months of age at most centers[10] in the America and Europe.

It is important to assess the magnitude of the problem of CF in Asian countries to improve care and survival. Keeping this in mind, a study was conducted to have a broad understanding of the burden of CF and management capacities within Asia.

Methods

An estimation of the prevalence of CF was carried out by sending a questionnaire to members of the Asian Pediatric Pulmonology Society (APPS). The APPS has representation from 19 Asian countries. Excluded were countries that have a robust CF program and awareness such as Israel and Russia, Central Asian Republics, Turkey, and Arab countries in the Middle East. The questionnaire included the total number of children diagnosed with CF seen in the country and the available resources [Table 1]. To improve the response rate, reminders were sent through E-mail on three occasions with the help of the APPS secretariat.

The results of the questionnaire were compiled and a simple descriptive analysis for each variable was carried out.

Table 1: Questionnaire for cystic fibrosis in Asia

Total cases reported in literature (publication from your country)
Total estimated cases of CF in your country
Children with CF enrolled in your institution
Mutation profile if available (at least mention common mutations)
Diagnostic tests available
Sweat test: Yes/no
Mutation testing: Yes/no
Nasal transmembrane potential difference: Yes/no
Treatment being provided in each country
Pancreatic enzymes: Yes/no
Imhaled antibiotics Yes/no
Dornase alfa: Yes/no
Is there a formal parents association/self-help group in your country: Yes/no
Is there a formal CF registry: Yes/no?

CF=Cystic fibrosis

Results

E-mails were sent to all APPS member countries through their representatives (list provided by APPS office) in June 2018. Of the 19 countries contacted, a total of 15 questionnaires were available from 15 countries. A summary of the results is found in Table 2. Three countries (Myanmar, Vietnam, and Macau) have not recorded any case of CF and did not have facilities to perform sweat chloride analysis. The remaining 12 countries have recorded a variable number of cases which had also been reported in published literature.[1-8] Sweat chloride testing facilities were available in all the countries except Taiwan that reported cases of CF. However, in some countries such as India and Bangladesh, a locally developed machine was being used for sweat collection and testing. The method developed in India was validated[11] and is being used in a few centers across the country.

Pancreatic enzyme supplementation is available in all the countries where children with CF have been diagnosed. Dornase alfa is available in some countries (Japan, Hong Kong, Singapore, Bangladesh, Taiwan, and Malaysia), whereas India has reported some patchy availability in the gray market, through nonofficial channels. Inhaled antibiotics are available in Japan, Hong Kong, China, India, Bangladesh, Taiwan, and Malaysia. However, inhaled tobramycin is not available in all countries, resulting in the continued use of injectable preparations of gentamicin and amikacin through the inhalational routes in these countries (Malaysia).

Gene mutation analyses were performed either locally or the samples were sent to facilities in other countries. It was obvious that all countries that recorded mutations had very low prevalence of the delta F508 mutation, which is the most common mutation reported among Caucasians. The reported CF mutations were very variable across countries. Only two countries (India and Japan) have formal CF associations.

A CF registry is present in Japan and China and under development in India.

Discussion

The results of our survey support that CF does occur in the Asian population. The precise magnitude of the problem is not known from this survey as this was only based on the report of cases that were acknowledged by the responders who are members of APPS but do not necessarily have access to information in more remote areas of their countries, and many countries in the region lack the facilities to diagnose CF. The genetic mutations found in Asia are very different from the Caucasian population. The ability to manage and treat these children with CF is almost nonexistent in many countries such as the availability of pancreatic enzyme supplementation and inhaled antibiotics.

Asia, being a very large continent, has significant variability in its ethnic, historical, cultural, and socioeconomic background. All these may affect the epidemiology of diseases like CF.

Table 2: Cystic fibrosis in Asia overview

Information	Countries							
	Bangladesh	China	Hong Kong SAR China	Japan	S Korea	Malaysia	Myanmar	Iran
Total cases reported in literature (publication from your country)	82	130	NA	100	23	16	None	NA
Total estimated cases of CF in your country	95	Not known	<10	30	60-100	60	None	Not known
Children with CF enrolled in your institution	95	40	2	0	_	23	None	300
Mutation profile if available (at least mention common mutations)	Not available	Available variable	No delta F508	Available variable	Available, heterogenous	Variable	No	Variable
Diagnostic tests available:								
Sweat test: Yes/no	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Mutation testing: yes/no	NA	Yes	Yes	Yes	Yes	Yes	NA	Yes
Nasal transmembrane potential difference: Yes/no	NA	NA	NA	NA	NA	NA	NA	NA
Is there a formal parents association/self-help group in your country: Yes/no	No	No	No	No	No	No	No	No
Is there a CF registry	No	Yes	No	Yes	No	No	No	No

Information	Countries						
	Indonesia	Macau SAR, China	Thailand	Singapore	Taiwan	India	Vietnam
Total cases reported in literature (publication from your country)	NA	None	4	18	10	NA	None
Total estimated cases of CF in your country	6	None	40	18	12	NA	None
Children with CF enrolled in your institution	6	None	14	18	5	600	No
Mutation profile if available (at least mention common mutations)	No	No	Yes	Yes	Yes Heterogenous No Delta F508	Yes Variable Low Delta F 508	No
Diagnostic tests available:							
Sweat test: Yes/no	Yes	NA	Yes	Yes	NA	Yes	NA
Mutation testing: yes/no	NA	NA	Yes	Yes	Yes	Yes	NA
Nasal transmembrane potential difference: Yes/no	NA	NA	NA	NA	NA	NA	NA
Is there a formal parents association/self-help group in your country: Yes/no	No	No	No	No	No	Yes	No
Is there a CF registry	No	No	No	No	No	Yes	No

CF=Cystic fibrosis

The management of the disease is further affected as many Asian countries have health-care systems which are not so advanced and they are largely focused on managing the other common illnesses and malnutrition. Hence, the availability of diagnostics and medications may largely depend on the type of insurance available for indigent populations.

Information on CF in countries from Asia is limited to case series or case reports. Some reports estimating the prevalence of CF in Asian countries are based on CF found in the immigrant population in the United Kingdom, the United States of America, and Canada.

Information in the literature suggests that in West and Central Asia, which were not included in our present analysis, CF is well documented and is a significant problem. The incidence of CF in the Middle East varies according to the ethnic background and the degree of consanguinity. The expected rates of CF in these Middle Eastern countries range from 1 in 2560 to 1 in 15,876.[12] The incidence of CF is reported to be around 1 in 2500 live births in Jordan, in 5000 in Bahrain, while in Russia, it is about 1: 5263, and the UAE has the lowest at 1:15,876.[13-17] It is possible that the higher prevalence in some of these countries may be determined by the relative prevalence of Caucasian ancestries.

For the South Asian population, estimates from the immigrant population in the United Kingdom, United States, and Canada suggest a prevalence of CF in people from Asia as 1: 10,000, 1:40,000, and 1: 9000, respectively.[18-20] Majority of people included in these studies are migrant populations from the Indian subcontinent (India, Bangladesh, and Pakistan). A single study to estimate CF in India was based on the identification of the Delta F508 mutation in cord blood, and it suggested an incidence of 1 in 40,000–1 in 100,000 live births.[21] Information on CF from East Asia is limited to case series.[22,23] In Japan, it is as low as 1 in 350,000 live births.[24]

Results of our survey as well as information available in the literature suggest that CF is poorly recognized and reported in Asian countries, whereas in West and Central Asia, it is well recognized. It is getting recognized across South Asia only in the past two decades.

Recognition of CF in East Asia has started more recently. It is evident that in South and East Asia, the increased diagnosis of CF was based on the development of low-cost sweat chloride estimation[11] and by genetic testing. In other countries in Asia, the diagnosis of CF is missed mainly due to the lack of awareness among pediatricians and the nonavailability of diagnostic sweat testing facilities.

There is a wide heterogeneity in Asian countries in the availability of resources. Except for a few countries, most of the Asian countries have limited resources including the availability of diagnostic tests and trained manpower (respirologists, physiotherapists, respiratory nurses, dieticians, etc.,). The available guidelines for standard management and care of CF patients are largely developed keeping in mind the facilities in advanced health infrastructure in the US and Europe.[25] These cannot be effectively adopted in low- and middle-income countries.[26] Therefore, there is a need to develop cost-effective and country-specific or region-specific protocols for the diagnosis and management of children with CF.

There are a number of limitations of this study including the relatively small numbers of countries involved and the limited response rate (prominent in absence is the Philippines). Also the uncertainty as to the extent that the information captured by the few specialists reporting the data, actually captures the wider population of large and hugely dispersed populations (e.g., the very small numbers in Indonesia). However, this should be viewed as an exploratory effort, and as such the lead taken by APPS to get a broad-based survey about the disease in this continent is the first step in the right direction. The respective participants need to develop a curriculum in medical schools and engage governmental agencies in allocating resources to develop regional bona fide sweat testing centers, and for those, who develop their own test, to ascertain rigorous controls compared to standard sweat testing. They should also take lead for developing a program to increase the awareness among pediatricians, as well as to develop region-specific management protocols by promoting interaction between its members.

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Conflicts of interest

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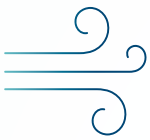

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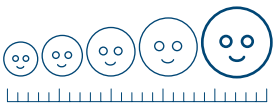

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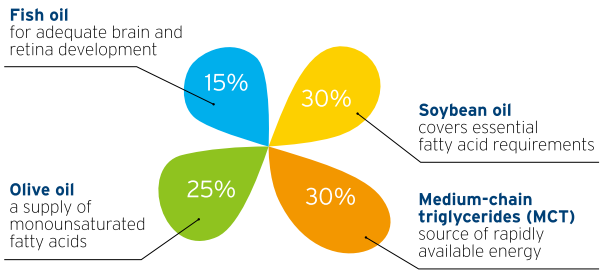

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Original Article

Accuracy of Procalcitonin in Detecting Severe Bacterial Infections among Critically Ill Children

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Abstract

Objectives: The aims of this study are to determine the accuracy of serum procalcitonin (PCT) in the early detection of severe bacterial infections among critically ill children and to establish the correlation between PCT changes and clinical outcomes. **Design:** This was a prospective, observational study at Queen Sirikit National Institute of Child Health, Bangkok, Thailand, between March 2014 and December 2014. **Materials and Methods:** Children aged between 1 month and 15 years with acute severe life-threatening conditions were included. Microbiologic specimens were sent for multiplex polymerase chain reaction and bacterial culture on day 1 of hospitalization. PCT was obtained on days 1, 2, 3, and 5. **Measurement and Main Results:** A total of 61 patients with a mean age of 21.2 months were enrolled. Microbiologic specimens were sent for multiplex polymerase chain reaction and bacterial culture on day 1 of hospitalization. PCT was obtained on days 1, 2, 3, and 5. The medians of PCT levels on days 1 and 2 from the bacterial infections group were significantly higher than those from the viral infections group and the mixed infections group. The sensitivity, specificity, and area under the PCT curve (cutoff value ≥1.1 ng/ml) employed to predict bacterial infections were 67.7%, 73.7%, and 0.72, respectively. The percentage changes of PCT levels on days 2–5 correlated with those of pediatric logistic organ dysfunction (PELOD) scores on days 1–5 but did not correlate significantly with the lengths of PICU stay. **Conclusions:** PCT is a moderately accurate option for the early detection of bacterial infections among children with acute severe life-threatening conditions since there is a correlation between the percentage changes of PCT levels and PELOD scores but no significant correlation between the percentage changes of PCT levels and the length of PICU stay.W

Keywords: Acute severe life-threatening conditions, critically ill children, procalcitonin, procalcitonin, severe bacterial infections

Introduction

Severe bacterial infections and sepsis are common causes of morbidity and mortality in children. These conditions are usually accompanied by clinical and laboratory signs, including fever or subtemperature, abnormal heart and respiratory rates, and leukocytosis. However, these manifestations may be noninfectious and traumatic in origin and are neither specific nor sensitive to bacterial infections or sepsis.[1-4]

Traditional diagnosis includes assessment of clinical symptoms and culturing techniques. However, although a positive culture from blood, bronchoalveolar lavage, and cerebrospinal fluid generally leads to a reliable result, certain limitations, such as false negatives and timing delay in diagnosis, may arise.[5] To deal with such issues, biomarkers have been used to diagnose and monitor the evolution of infection processes.

Serum procalcitonin (PCT) is a 114–116-amino acid and a propeptide of calcitonin produced in the C-cell of the thyroid gland. This biomarker of bacterial infections correlates with the extent and severity of microbial invasion in several types of infection. Thus, PCT levels are very low (<0.1 ng/ml) in healthy humans.[6,7] In contrast, bacterial infections induce systemic inflammation reactions, elevating plasma PCT within 2–6 h.[8,9]

The objective of this study is to determine the accuracy of PCT in the early detection of severe bacterial infections among critically ill children. In addition, it seeks to establish the correlation between PCT changes and clinical outcomes.

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Materials and Methods

This research was a prospective, observational study conducted on patients with acute severe life-threatening conditions admitted in the Queen Sirikit National Institute of Child Health, Bangkok, from March 2014 to December 2014. The patients included in the study met the following criteria: (1) children aged 1 month to 15 years and (2) a diagnosis of an acute severe life-threatening condition, namely acute lower respiratory infection (ALRI) with acute respiratory failure, severe sepsis, septic shock, myocarditis, and severe encephalitis. In contrast, the patients excluded from the research were those with an underlying disease, such as congenital heart disease, chronic lung disease, and immunodeficiency. The study was approved by the institutional review board.

Procalcitonin measurement

The measurement of the patients' PCT concentrations was conducted in the laboratory using BRAHMS PCT immunofluorescent assays. PCT levels were initially measured on day 1 of admission, before being assessed daily on days 2, 3, and 5. The research personnel performing the measurement were blinded to the clinical information.

Pathogen testing

On day 1 of hospitalization, microbiological specimens were obtained from the following sources: (1) serum, (2) nasal or throat swab, (3) tracheal suction (in the event of intubated patients), and (4) cerebrospinal fluid (in the event of suspected central nervous system infection), for the detection of bacteria, viruses, and fungi using multiplex polymerase chain reaction (PCR). In addition, a bacterial culture could be dispatched for the purpose of routine clinical care at the discretion of the attending clinicians.

Definitions and outcome measures of different pathogen groups

The patients were classified into one of the following pathogen groups based on their test results: (1) bacterial infections, referring to the detection of bacteria from any sterile sources; (2) viral infections, referring to the detection of viruses without any co-detection of bacteria; (3) mixed infections, referring to the detection of both bacterial and viral infections or (4) negative, referring to the detection of no pathogens.

Statistical analysis

Statistical analysis was performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA) to compare the demographic characteristics and laboratory measurements of the subjects across four groups. For continuous variables, a Chi-square was employed. For two-group comparisons (nonnormal distribution), the Mann–Whitney test and the Kruskal–Wallis test were utilized. Group differences associated with a $P \leq 0.05$ were considered statistically significant. The test accuracy of PCT in identifying bacterial and mixed infection groups was reviewed using a receiver operating characteristic (ROC) curve analysis. The sensitivity, specificity, PPV, and NPV were calculated to determine the PCT cutoff value. The Pearson's correlation analysis was performed to determine the correlation of PCT changes and clinical outcomes.

Results

A total of 61 patients with a severe life-threatening condition were recruited to participate in the research. The median age of the patients was 1.8 years (0.92–4.41 years), and 58.9% were male. The mean lengths of hospital stay and PICU stay were 13.57 and 4.16 days, respectively. The overall mortality rate was 6.5%. The most common diagnosis was ALRI with respiratory failure (67.3%), followed by pneumonia with sepsis (21.3%), as shown in Table 1. The majority of the patients (31.2%) were classified into the viral infection group, as shown in Table 2. The positive results for viral infection group were detected from nasal/throat swab, tracheal suction, or serum PCR; meanwhile, bacterial infections were detected by positive results in any sterile sources. No patients had positive nasal/throat swabs for bacteria. The baseline characteristics of the four groups of patients were not statistically different, as shown in Table 3.

The median PCT levels on day 1 were 9.16 (1.60–100.97), 0.51 (0.15–1.18), and 1.12 (0.25–12.2) ng/ml for the bacterial infection, viral infection, and mixed infection groups, respectively. In comparison, the figures on day 2 were 18.12 (2.20–56.48) ng/ml, 0.50 (0.24–6.26) ng/ml, and 2.08 (0.67–13.61) ng/ml for the bacterial infections, viral infections, and mixed infections groups, respectively. Further analysis showed that the PCT levels associated with the bacterial infection group were significantly higher than those associated with the viral infection group and the mixed infection group on both days 1 and 2. The findings are presented in Table 4.

The cutoff value of the PCT levels on both days 1 and 2 was 1.1 ng/ml, with sensitivity, specificity, PPV, NPV, and AUC figures on day 1 standing at 67.7%, 73.7%, 72.6%, 68.8%, and 0.72, respectively, and on day 2 equaling 74.2%, 68.4%, 70.0%,

Table 1: Subjects' diagnoses (n=61)

Diagnoses	Number of patients (%)
ALRI with respiratory failure	41 (67.3)
Severe sepsis/septic shock (n=19)	
Pneumonia	13 (21.3)
Meningoencephalitis	5 (8.2)
Abscess at scalp	1 (1.6)
Viral myocarditis with cardiogenic shock	1 (1.6)

ALRI=Acute lower respiratory infection

Table 2: Pathogen groups of the subjects

	Number of patients (%) (n=61)
Viral infections	19 (31.2)
Bacterial infections	16 (26.2)
Mixed infections	15 (24.6)
Negative	11 (18.0)

71.9%, and 0.74, respectively, as shown in Figure 1. In addition, the percentage changes of PCT levels on days 2–5 correlated with those of PELOD scores on days 1–5, as shown in Figure 2.

Discussion

This prospective, observational research aims to assess the accuracy of PCT in detecting the early stages of severe bacterial infections among critically ill children and to determine the correlation between PCT changes and clinical outcomes. All patients in this study presented with life-threatening condition. At that time, we did not know the cause of diseases. Furthermore, clinical manifestations cannot distinguish between bacterial and viral infection. Therefore, we obtained serum PCT in every patient who presented with severe life-threatening condition. It was found that the accuracy of PCT was moderate with the cutoff value of ≥1.1 ng/ml and sensitivity, specificity, and AUC figures equaling 67.7%, 73.7%, and 0.72, respectively. Subgroup analysis was analyzed in patients aged ≤2 years, and we found that PCT is not more useful in this population. Such findings resonate with those discovered in previous studies. A case in point is Moulin *et al*.'s work, in which PCT >1 ng/ml could differentiate between viral and bacterial community-acquired pneumonia (AUC = 0.93).[10] In addition, PCT ≥2.5 ng/ml could be employed to predict systemic inflammatory response syndrome (SIRS) with moderate accuracy (sensitivity = 68%, specificity = 74%, AUC = 0.71).[11] In another study, higher PCT levels were found to be higher among patients in the bacterial infection group (cutoff ≥0.5 ng/ml, sensitivity = 67.8%, specificity = 80.4%, AUC = 0.764).[12] Although a sizeable number of critical ill patients were included in this research, most received antibiotics before the PCT collection process, leading to reductions in PCT levels, and hence lower PCT accuracy and sensitivity. These findings suggest that cutoff, sensitivity, and specificity values are likely to vary across studies depending on the population, the timing of PCT measurement, and the severity scores associated with patients. In this study, we also found low PCT levels in mixed

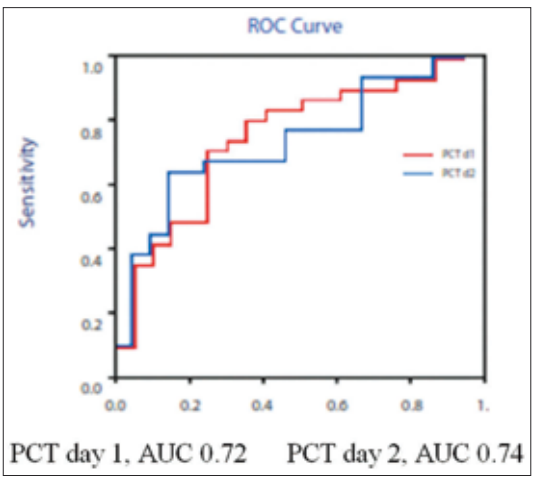

Figure 1: Receiver operating characteristic curves of procalcitonin days 1 and 2 for the bacterial infections group and the mixed infection group combined.

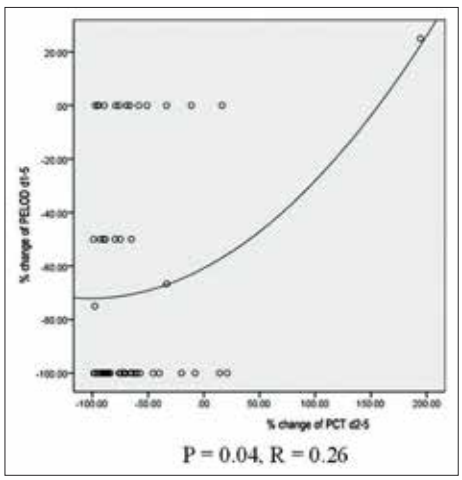

Figure 2: Correlation between the percentage changes of procalcitonin levels and PELOD scores.

Table 3: Baseline characteristics of the patients by pathogen group

	Viral (*n*=19)	Bacterial (*n*=16)	Mixed (*n*=15)	Negative (*n*=11)	*P*
Male, *n* (%)	12 (70.5)	10 (83.3)	13 (68.4)	8 (61.5)	0.69
Age (years), mean±SD	0.92±0.86	1.84±3.11	1.75±1.03	3.5±4.41	0.38
Body weight (kg)	7.95±3.29	11.0±10.15	11.07±7.9	14.7±10.98	0.32
PRISM III score, mean±SD	0.52±0.87	3.3±4.37	1.05±2.41	3.69±6.92	0.10
Temperature (°C), mean±SD	38±0.89	38.57±0.96	38.25±1.01	37.93±1.16	0.12
WBC count (×10³/μl), mean±SD	20.3±7.05	14.85±5.57	15.29±6.47	15.37±6.62	0.40
Administration of ATB before PCT					
None	4	5	5	2	0.22
ATB <12 h	7	4	5	5	0.22
ATB ≥12 h	8	7	5	4	0.22
Length of hospital stay (days), mean±SD	11.9±5.62	16.26±8.18	15.8±9.85	10.66±6.8	0.12
Length of PICU stay (days), mean±SD	3.73±2.55	3.68±0.4	5.2±2.27	4.18±2.13	0.33
Deaths, *n* (%)	0	1 (6.2)	1 (6.6)	2 (18.2)	0.08

SD=Standard deviation, PICU=Pediatric intensive care unit, PCT=Procalcitonin, ATB=Antibiotics, PRISM III=Pediatric Risk of Mortality III, WBC=White blood cell

Table 4: Procalcitonin levels from microbiological results by pathogen group

	Bacterial (*n*=16)	Viral (*n*=19)	Mixed (*n*=15)	*P*
PCT level on day 1, median (IQ1-IQ3)	9.16, 1.60-100.97	0.51, 0.15-1.18	1.12, 0.25-12.2	0.009*
PCT level on day 2, median (IQ1-IQ3)	18.12, 2.20-56.48	0.50, 0.24-6.26	2.08, 0.67-13.61	0.003*

PCT=Procalcitonin

infection group due to the fact that PCT is released in response to bacterial infections via a direct stimulation of cytokines, such as interleukin (IL)-1β, tumor necrosis factor-alpha, and IL-6. On the other hand, interferon-γ, a cytokine released in response to viral infections, blocks the upregulation of PCT, resulting in low PCT in viral infection. Therefore, PCT levels in mixed infection group were not as high as bacterial infection group. However, it can be seen that PCT levels associated with the mixed infection group were higher than those associated with the viral infection group on both days 1 and 2.

As for the correlation between PCT levels and PELOD scores, in this study, the percentage changes of PCT levels on days 2–5 were found to correlate with the percentage changes of PELOD scores on days 1–5 but insignificantly with the lengths of PICU stay. Similar results were reported by Qi, who discovered a poor prognosis in pediatric sepsis patients with high PCT levels and mild pediatric clinical illness scores.[13] Based on these findings, it can thus be presumed that the incorporation of the percentage changes of both PCT levels and PELOD scores is vital for enhancing the prediction of an adverse outcome.

Owing to its satisfactory accuracy, PCT has been widely used as an indicator of bacterial infections. In the present research, the PCT levels caused by bacterial infections were significantly higher than those resulting from viral and mixed infections. In addition, PCT was also proven to increase markedly among pediatric patients with sepsis and bacterial sepsis patients.[14-17] Further, increased PCT with a positive pneumococcal urinary antigen was found to correlate with pneumococcal community-acquired pneumonia.[18] In addition, meta-analysis findings demonstrate that a PCT assay is a potentially effective test for distinguishing between bacterial and viral meningitis in pediatric patients.[19] Finally, PCT is regarded as an accurate biomarker for telling bacterial and viral pneumonia apart.[20]

Despite the foregoing discussion, it is worth mentioning several limitations to the present study. First, a subgroup analysis could not be conducted because of the small subgroup size. Second, the lower respiratory tract specimens were collected through tracheal suction, contributing to low sensitivity and specificity in pathogen detection as well as possible upper respiratory tract contamination. Third, a urine culture was not collected from all the patients, potentially undermining the diagnosis of urinary tract infection. Fourth, multiplex PCR is not pertinent to all respiratory pathogens, such as *Chlamydia trachomatis* and *Streptococcal gr A*. Finally, it was not possible to determine the correlation between PCT levels and mortality rates in this research since the latter were insignificant.

Conclusions

PCT levels associated with the bacterial infection group were significantly higher than those associated with the viral infection and the mixed infection group. PCT is a moderately accurate option for the early detection of bacterial infections among children with acute severe life-threatening conditions since there is a correlation between the percentage changes of PCT levels and PELOD scores.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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HIGH RESPONDER RATE

in Asthma Control Questionnaire measures of **sleep, activity limitations, and breathing**[1]

SELF-INJECTABLE

Convenient subcutaneous injection[1]

LIBERTY ASTHMA VENTURE Study Design[1]: 210 patients were randomly assigned with oral glucocorticoid-treated asthma to receive add-on DUPIXENT (at a dose of 300 mg) or placebo every 2 weeks for 24 weeks. After a glucocorticoid dose-adjustment period before randomization, glucocorticoid doses were adjusted in a downward trend from week 4 to week 20 and then maintained at a stable dose for 4 weeks. The primary endpoint was the percentage reduction in the glucocorticoid dose at weeks 24. Key secondary endpoint were the proportion of patients at weeks 24 with a reduction of at least 50% in the glucocorticoid dose and the proportion of patients with a reduction to a glucocorticoid dose of less than 5 mg per day. Severe exacerbation rates and the forced expiratory volume in 1 second (FEV_1) before bronchodilator use were also examined.

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

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

References: 1. DUPIXENT Summary of Product Characteristics, May 2020. **2.** Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med. 2018;378(26):2475-2485. **3.** Castro M, Corren J, Pavord ID, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. N Engl J Med. 2018;378(26):2486-2496.

Presentation: Dupilumab solution for injection in a pre-filled syringe with needle shield. **Indications:** Atopic Dermatitis (AD): Moderate-to-severe AD in adults and adolescents ≥12 years who are candidates for systemic therapy. Asthma: In adults and adolescents ≥12 years as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised $FeNO$, who are inadequately controlled with high-dose ICS plus another medicinal product for maintenance treatment. **Dosage & Administration:** Subcutaneous injection. AD adults: initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week. AD adolescents: Body weight <60 kg: initial dose of 400 mg (two 200mg injections), followed by 200 mg every other week. Body weight ≥60 kg: same dosage as adults. Dupilumab can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, e.g. face, neck, intertriginous and genital areas. Consider discontinuing treatment in patients who have shown no response after 16 weeks. Asthma: initial dose of 400 mg, followed by 200 mg every other week. For patients with severe asthma and co-morbid moderate-to-severe AD: initial dose of 600 mg, followed by 300 mg every other week. Patients receiving concomitant oral corticosteroids may reduce steroid dose gradually once clinical improvement with dupilumab has occurred. The need for continued dupilumab therapy should be considered at least annually as determined by a physician. If a dose is missed, administer it asap and thereafter resume dosing at the regular scheduled time. **Contraindications:** Hypersensitivity to dupilumab or any of the excipients. **Precautions:** Safety and efficacy in children <12 years not been established. Not be used to treat acute asthma symptoms, acute exacerbations, acute bronchospasm or status asthmaticus. Do not discontinue corticosteroids abruptly upon start of dupilumab. Reduction should be gradual and performed under supervision of a physician. It may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid use. If systemic hypersensitivity reaction occurs, discontinue dupilumab and initiate appropriate therapy. Be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in patients with eosinophilia. Treat pre-existing helminth infections before initiating dupilumab. If patients become infected while receiving dupilumab and do not respond to anti-helminth treatment, discontinue dupilumab until infection resolves. Patients who develop conjunctivitis that does not resolve following standard treatment should undergo ophthalmological examination. AD patients with comorbid asthma should not adjust or stop asthma treatments without consultation with physicians. Carefully monitor patients after discontinuation of dupilumab. Do not give live and live attenuated vaccines concurrently with dupilumab. Patients should be brought up to date with immunisations before starting dupilumab. **Drug Interactions:** Immune responses to TdaP vaccine and meningococcal polysaccharide vaccine were assessed. Patients receiving dupilumab may receive concurrent inactivated or non-live vaccinations. **Pregnancy and lactation:** Should be used during pregnancy only if potential benefit justifies potential risk to foetus. Unknown whether dupilumab is excreted in human milk or absorbed systemically after ingestion. Decision must be made whether to discontinue breast-feeding or dupilumab taking into account benefit of breast-feeding for the child and benefit of therapy for the woman. **Undesirable effects:** AD: Most common adverse reactions reported: injection site reactions, conjunctivitis, blepharitis and oral herpes. Safety profile observed in adolescents consistent with that seen in adults. Asthma: Most common adverse reaction reported: injection site erythema. For other undesirable effects, please refer to the full prescribing information. Preparation: 2 x 300mg/2ml in pre-filled syringe with needle shield, 2 x 200mg/1.14ml in pre-filled syringe with needle shield. **Legal Classification:** Part I, First & Third Schedules Poison. **Full prescribing information is available upon request.** APHK-DUP-2003

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