Helicobacter pylori: A Cause of Community-Acquired Pediatric Septic Shock: A Cross Sectional Study

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Abstract

Background: Blood culture negative sepsis is a diagnostic challenge to both clinicians and microbiologists. We aimed to investigate blood culture negative cases of community-acquired sepsis among children admitted at pediatric intensive care unit of Cairo University Specialized Children Hospital, Egypt.

Methodology: Our cross-sectional study was carried out over a period of six months. Electrical cardiometry was used to assess the patients' status. For blood culture negative samples, broad range bacterial and fungal PCR amplification and sequencing were performed.

Results: Among 43 patients, 9 samples were positive to pan bacterial 16srRNA gene, while five samples (20,22,23,24,25) were identified as *Helicobacter pylori* positive with the following sequence accession numbers respectively (KT198991.1, JQ323580.1, APEL01000010.1, APEL01000010.1, CP007603.1). Patients H pylori positive higher C reactive protein, longer duration of ventilation, higher stroke volume variation and pre-ejection period (P value= 0.005, 0.005, 0.043 & 0.043)

Conclusion: Detection of *Helicobacter pylori* in community acquired septic children alarms the necessity to conduct epidemiological studies on populations of septic shock in countries with high prevalence of H. pylori such as Egypt.

Background

In 2017, the World Health Organization adopted a resolution on improving the prevention, recognition, and management of sepsis. Most sepsis cases and deaths are estimated to occur in low and middle-income countries. Important differences in the populations at risk, infecting pathogens, and clinical capacity to manage sepsis in high and low-resource settings necessitate context-specific approaches to this significant problem. ^[1,2]

The microbiologic paradigm holds that the inflammatory response of severe sepsis and septic shock cannot be overcome unless the underlying infection has been effectively eradicated. Survival depends upon the timely reduction and eradication of infection after the onset of hypotension. Empiric antimicrobial therapy must assume a position of co-primacy in the initial resuscitation with an eye toward optimizing selection, and delivery at the first dose. ^[3]

The difficulties in identifying the responsible pathogens are global and become exaggerated with the use of the over the counter antibiotics in some developing countries. Multicenter studies published in the last decade found that culture-negative patients accounted for 28% - 49% of all cases of severe sepsis in North American, Spanish, French, and Canadian ICUs, respectively ^[4,5,6]. The figure was 40% in the pan-European Sepsis Occurrence in Acutely Ill Patients (SOAP) study ^[7].

A review of 15 studies of neonatal sepsis in developing countries, performed in the late 1990s found that the most commonly encountered species in blood culture-cases were *gram negative* spp. These studies were hospital-based, it was likely to be nosocomial and thus not reflective of community-acquired serious bacterial infection [WHO, 1999].^[8] Another large study of young infants aged 0–59 days demonstrated a broad array of Gram-positive and Gram-negative pathogens responsible for community-acquired bacteremia.^[9]

We aimed to investigate blood culture negative cases of community-acquired septic shock among children admitted to the pediatric intensive care unit (PICU) of Cairo University Specialized Children Hospital, Cairo Egypt.

Methodology

The present study was a cross-sectional study that was carried out over a period of six months at the PICU of Cairo University Specialized Children Hospital, Egypt. The study protocol was approved by our Institutional Review Board and Ethical Committee.

We included children who fulfilled the following criteria: children aged from 1 month to 12 years with strong clinical diagnosis of septic shock at time of admission. We defined pediatric septic shock based on the American college of critical care medicine and international pediatric Society of Critical Care definitions for sepsis.^[10] We excluded patients with known congenital heart disease or cardiomyopathy, or whose duration of stay in PICU was less than 48 hours. Children with known metabolic disorders or adrenal insufficiency were also excluded.

The Electrical Cardiometry (EC, manufactured by Oskypa Medical Data) parameters were measured in the emergency department after fluid boluses. Cold septic shock was defined as cardiac index <3.3 L/min/m² and systemic vascular resistance index >1600 (dyne s/cm⁵/m²) while warm septic shock was defined as cardiac index >5.5 L/min/m² and systemic vascular resistance index <800 (dyne s/cm⁵/m²).^[11]

Sepsis profile was withdrawn before antibiotics administration in the hospital, including: complete blood count, C-reactive protein and blood culture (BACTEC Plus aerobic/F and BACTEC Plus anaerobic/F blood culture bottles; Becton, Dickinson and Company, Spain). Subcultures were done on blood, MacConkey's and chocolate agars incubated in 5 % CO₂ at 35 °C for 48 hours and on Sabouraud's dextrose agar incubated at 25 °C for up to 14 days and examined every 48 hours for any growth. Further growth identification was done by Vitek 2 compact system (Biomérieux, France). Additionally, a broad-range bacterial and fungal PCR amplification for all culture negative samples was done^[12, 13]

Amplified DNA fragments were separated by agarose gel electrophoresis and stained with ethidium bromide and visualized under UV light, using pan bacterial 536f 5'CAGCAGCCGCGGTAATAC^[14] and the pan fungal ITS–1 5'TCCGTAGGTGAACCTGCGGG. The molecular sizes of fragments generated by

electrophoresis were judged by comparison with the molecular weight standards as previously described [15]. An extracted DNA of *E coli* strain was used as a positive control, whereas the negative control to detect reagent contamination was included in each PCR reaction, containing all components except the DNA extract, which was replaced by 2 µl of sterile distilled H₂O.

Sequencing analysis

Culture negative samples were negative for ITS–1 pan fungal gene, whereas positive for pan bacterial 16srRNA gene and were subjected to sequencing. All procedures for sequencing were conducted by MacroGen (Seoul, South Korea) using ABI PRISM BigDye Terminator Cycle Sequencing Kit with AmpliTaq DNA polymerase (FS enzyme; Applied Biosystems) according to manufacturer instruction. All fluorescent-labeled fragments were purified from the unincorporated terminators with an ethanol precipitation protocol. The samples were resuspended in distilled water and subjected to electrophoresis in an ABI 3730x1 sequencer (Applied Biosystem, USA). Nucleotide sequence similarities were determined using other known sequences found in the GenBank database using BLAST program of National Center for Biotechnology Information (NCBI) databases (<http://www.ncbi.nlm.nih.gov/blast>).

Statistical Analysis:

An Excel spreadsheet was established for the entry of data. We used validation checks on numerical variables and option-based data entry method for categorical variables to reduce potential errors. The analyses were carried with SPSS software (Statistical Package for the Social Sciences, version 24, SSPS Inc, Chicago, IL, USA). Frequency tables with percentages were used for categorical variables and descriptive statistics (median and interquartile range [IQR]) were used for numerical variables. Independent Student t-test, paired t-test, or Mann-Whitney tests were used to compare quantitative variables, while Chi-square test or McNemar-Bowker tests were used to analyze categorical variables. A p-value < 0.05 is considered statistically significant.

Results

Difference in baseline characters: Among 400 admissions in PICU of Cairo University Specialized Children Hospital over a 6-month period from March 2017 to September 2017, 43 patients were diagnosed as septic shock; cold septic shock constituted 53% (n = 23); 62% were males, with a median weight of 8 kg. Gastroenteritis was the most common septic focus. Only seven patients had positive blood culture on admission. There was no statistically significant difference between warm and cold septic shock patients in terms of age (p = 0.102), gender (p = 0.091), weight (p = 0.125), diagnosis (p = 0.12), need for ventilation (p = 0.32), duration of hospital stay (p = 0.975), Pediatric Index of Mortality2 (PIM2) score (p = 0.212), blood culture (p = 0.309), or PCR results (p = 0.67) (Table 1).

Regarding the EC parameters after fluid boluses, apart from the known hemodynamic difference between warm and cold shock in cardiac index and systemic vascular resistance index, the median index of

contractility (ICON) was significantly higher among patients with warm septic shock than patients with cold septic shock ($p = 0.008$). The thoracic fluid content (TFC), diffusion of oxygen (DO_2) and stroke volume (SV) were significantly higher in warm septic shock ($p = 0.007, 0.003$ and <0.001 , respectively) (Table 2).

Microbiology results: Out of 43 septic shock cases, 7 blood culture samples were positive (3 *Escherichia coli*, 2 *Staph. epidermidis*, 1 *Pseudomonas aeruginosa*, 1 *Candida tropicalis*). 28 culture negative samples were negative for ITS-1 pan fungal gene, whereas 9 samples were positive to pan bacterial 16srRNA gene. By sequencing, 5 samples (20, 22, 23, 24 and 25) were identified as *Helicobacter pylori* with the following sequence accession numbers respectively (KT198991.1, JQ323580.1, APEL01000010.1, APEL01000010.1, CP007603.1). while, the rest of the 9 samples hit negative in the sequencing.

In all five positive for *H. pylori*, we could observe a higher CRP, longer duration of ventilation, higher stroke volume variation and pre-ejection period (P value = 0.005, 0.005, 0.043 & 0.043) in patients with *H. pylori* positive septic shock *H. pylori* cases and the rest of the no growth group (Table 3)

Discussion

Sepsis is the primary cause of death from infection, especially if not recognized and treated promptly. Its recognition mandates urgent attention. ^[16] Delayed antimicrobial therapy was an independent risk factor for mortality and prolonged organ dysfunction in pediatric sepsis. ^[17] SPROUT study included 6925 children from 26 countries; 500 were diagnosed as severe sepsis. The etiology was gram negative in 158 patients and gram positive in 150. ^[18]

H. pylori DNA was identified from 5 of our community acquired septic shock patients with negative blood cultures. However, in Egyptian school children, *H. pylori* infection prevalence was 73% in 2008. ^[19] The prevalence of *H. pylori* is not evenly distributed worldwide. It depends on socio-economic status and overcrowding. *H. pylori*, which is transmitted by the oral–oral or fecal–oral route, is rampant in low middle income countries owing to overcrowding and poor sanitation and hygiene. ^[20] There are some reports about the link of *H. pylori* to extragastric disease. In their latest guidelines, ESPGHAN/NASPGHAN provided one weak recommendation for testing and treating *H. pylori* infection in the patient with idiopathic thrombocytopenic purpura. ^[21] *H. pylori* is linked in recent review to adult cardiovascular, neurologic, dermatologic, obstetric, immunologic, and metabolic diseases. ^[22] Increase in serum levels of IL1 β and TNF- α cytokines were reported in serum of people infected with *H. pylori*. ^[23] Previous reports described a significant increase in oxidative stress in the blood of infected adults. ^[24–25]

Numerous factors are known to control the translocation of the microbe across the gastrointestinal barrier. *H. pylori* may influence the ecology of gastrointestinal microflora causing disturbance of intestinal mucosal barrier. These effects may contribute to invasion of the bloodstream by the bacterium. ^[26] Sepsis syndrome by *H. pylori* was mentioned in the literature in case report with respiratory failure as the

initial presentation. ^[27] *H. fennelliae* was previously described to cause sepsis in a child with leukemia and adult with HIV ^[28–29]

Conclusion: Detection of *Helicobacter pylori* in the blood of 5 children alerts the need to conduct epidemiological studies on populations of septic shock in countries with high prevalence of *H. pylori*.

Declarations

- The study protocol was approved by our Institutional Review Board and Ethical Committee. Prof. Ayman Saed Salem. Faculty of medicine, Cairo University.
- Written consent from the caregiver was obtained
- Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
- There is no competing interests
- The study received no Funding
- Authors' contributions: HF was the author of the idea, study design, results and major contributor to the manuscript, NM revised the process, BS collected the data, RE analyzed the PCR data, DG analyzed the sequence data. All authors have read and approved the manuscript.
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Abbreviations

CI: cardiac index, CPI: cardiac performance index, DO₂: oxygen delivery, HR: heart rate, ICON: index of contractility, PCR: polymerase chain reaction, SV: stroke volume, SVRI: systemic vascular resistance index, TFC: thoracic fluid content. CONS: coagulase-negative *Staphylococci*, *E. coli*: *Escherichia coli*, PCR: Polymerase chain reaction, PIM2: Pediatric index of mortality2. PEP: prejection period, SV: stroke volume, SVV: stroke volume variation,

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Table 1: Characteristics of the study population

Variables	Patients (N =43)	
	No	%
Age in Months; Median (IQR)	10 (6 - 48)	
Male	27	62.7
Female	16	37.3
Weight in Kg; Median (IQR)	8.3 (6 - 14.2)	
Septic focus		
Gastroenteritis	18	41.9
Pneumonia	12	27.9
Meningitis	11	25.6
Bloodstream infection	1	2.3
Blood Culture results		
Candida	1	2.3
CONS*	2	4.7
E. coli*	3	5.9
No growth	36	81.4
Pseudomonas	1	2.3
PCR results		
PCR Positive*	9	25
PCR Negative	27	75
Duration of hospital stay in days; Median (IQR)	11.5 (8 - 26.2)	
Ventilation	N=40	93%
Duration of ventilation in days; Median (IQR)	10.5 (6.8 - 20)	
PIM2 score* Mean (SD)	75.91 (5.3)	
Type of septic shock		
Warm	20	46.5
Cold	23	53.5

CONS: coagulase-negative *Staphylococci*, *E. coli*: *Escherichia coli*, PCR: Polymerase chain reaction, PIM2: Pediatric index of mortality²

Table 2: Difference in clinical parameters between patients with warm and cold septic shock on admission to the emergency room

Variables	Warm shock (N = 20)		Cold Shock (N =23)		P-value
Age in months;					
Median (IQR)	17 (7.5 -66)		8 (4 -30)		0.102
Male	10	50.0	17	73.9	0.091
Female	10	50.0	6	36.1	
Weight in kg; Median (IQR)	9 (7.5 - 15)		8 (5.5-13)		0.125
Septic focus					
Bloodstream; N (%)	1 (5)		0 (0)		0.123
Gastroenteritis; N (%)	6 (30)		12 (52.2)		
Meningitis; N (%)	8 (40)		3 (13.3)		
Pneumonia; N (%)	5 (25)		7 (30.5)		
Blood Culture results					
PCR Positive*	5 (25)		9 (39.1)		0.67
PCR Negative	15 (75)		14 (60.9)		
CI, median (IQR)	6 (5.9 – 6.4)		2.8 (2.5 – 3.1)		<0.001
ICON, median (IQR)	106 (82.5 – 133.5)		68 (50 – 93)		0.008
SVRI, median (IQR)	790 (763 - 903)		1921(1700 – 2203.5)		<0.001
TFC, median (IQR)	282.5 (247 - 320)		232 (198 – 265)		0.007
DO ₂ , median (IQR)	340.5 (255.5 – 421.5)		249 (144 – 301)		0.003
CPI, median (IQR)	0.74 (0.61 – 1.19)		0.5 (0.44 – 0.71)		0.002
HR, median (IQR)	149 (134 - 159)		139.25 (151.5 – 161)		0.214
SV, median (IQR)	23 (14.5 – 32.25)		7.5 (6.1 – 11)		<0.001

CI: cardiac index, CPI: cardiac performance index, DO₂: oxygen delivery, HR: heart rate, ICON: index of contractility, PCR: polymerase chain reaction, SV: stroke volume, SVRI: systemic vascular resistance index, TFC: thoracic fluid content.

Table 3: Difference in clinical and EC parameters on admission between patients with *H. pylori* positive and *H. pylori* negative septic shock

Variables (median &IQ)	<i>H. pylori</i> negative (n=23)	<i>H. pylori</i> positive (n=5)	P value
Age	10(5:72)	24(9:30)	0.664
Weight	8(6:15)	10(8.5:13)	0.453
Duration of MV	9(7:15)	24(20:35)	0.005
Duration of stay	11(8:18)	24(20:38)	0.183
CRP	91(48:96)	190(96:220)	0.005
PIM 2 Score	75.5(71:80)	80(75:81)	0.155
CI	5.6(2.8:6)	6.3(3.1:7)	0.155
TFC	43.5(28:53)	45(33:46)	0.6
ICON	92(68:107)	80(70:109)	0.94
SVV	16(13:18)	9 (9:14)	0.043
SVRI	1079(795:1921)	920(780:1700)	0.567
PEP	77.5(67:93)	100(86:115)	0.043
DO2	277.5(155:388)	302(251:322)	0.567
CPI	0.6(0.5:0.8)	0.5(0.5:1.2)	0.945
HR	154.5(137:163)	151(149:155)	0.631
Suspected initial diagnosis	N(%)	N(%)	
Encephalitis	2(6.7)	0(0)	0.367
Gastroenteritis	13(40)	1(20)	
Meningitis	5(16.7)	3(60)	
Pneumonia	10(33.3)	1(20)	

CI: cardiac index, CPI: cardiac performance index, DO₂: oxygen delivery, HR: heart rate, ICON: index of contractility, PCR: polymerase chain reaction, PEP: prejection period, SV: stroke volume, SVV: stroke volume variation, SVRI: systemic vascular resistance index, TFC: thoracic fluid content