Can magnitude and days with fever predict urinary tract infection in infants with fever without source?

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Research Article

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Abstract

Introduction: Fever continues to be the most frequent cause of care in the pediatric population. It is frequently the use of invasive and unnecessary tests which results in discomfort to the patients. The present study aims to describe the epidemiology of urinary tract infection (UTI) in children with fever without source aged 0–36 months and to evaluate if there are differences in the magnitude and days with fever in patients with and without urinary tract infection and fever without focus.

Methods

We included children aged 0–36 months presenting with fever without source in our emergency unit. Demographic and clinical characteristics, investigations, and management procedures were recorded at the time of inclusion. Potential predictors of SBI-UTI were compared between patients with and without SBI-UTI.

Results

Between January 2015 to December 2017, 137 patients were included. Forty children (29.2%, CI 95% 21-36%) were diagnosed with SBI. A total of 32 children (43%) had a final diagnosis of SBI, which were all urinary tract infections (UTI). There were no differences statistically significantly between the groups in appearance in admission, magnitude and days with fever, white blood cell count, CPR levels.

Conclusions

In patients with FWS under 3 years of age, urinary tract infection is the main cause of SBI. A high degree of clinical suspicion should be maintained since neither symptoms, signs, CBC or CPR distinguish children with or without UTI in this population. Future studies should further validate, in a different setting and in a larger population, our results.

Introduction

Fever continues to be the most frequent cause of care in the pediatric population (1). Fever may be the only finding during clinical evaluation in infants younger than 3 years and can be an initial manifestation of potentially serious infections such as meningitis, pneumonia, urinary tract infection (2, 3). Fever without source (FWS) constituting a frequent cause of concern for both doctors and parents (4, 5). Despite reductions in serious bacterial infections (SBI) rates following the introduction of specific vaccination against *Haemophilus influenzae type b* and *Streptococcus pneumoniae*, other germs such as *E. coli*, S. pneumoniae serotypes not covered by these vaccines such as *Neisseria meningitidis, Staphylococcus aureus, Salmonella spp, and Enterococcus* have become more important (6–9). There is considerable controversy in the management of these patients with FWS. It frequently the use of invasive and unnecessary tests which results in discomfort to the patients and higher cost to the health system (10) (11). Most SBI is due to urinary tract infection (UTI) (5). The screening strategy for children with FWS

should be adapted to more accurately predict when children with FWS may have UTI. The present study aims to describe the epidemiology of urinary tract infection (UTI) in children with fever without source aged 0–36 months and to evaluate if there are differences in the magnitude and days with fever in patients with and without urinary tract infection and fever without focus.

Patients And Methods

We conducted a retrospective study in a tertiary care hospital in Rionegro, Colombia. Children aged 0–36 months with FWS, who were evaluated in our emergency department (ED) between January 2015 to December 2017, were eligible for inclusion in this study. FWS was defined as a temperature of ≥ 38 8C (less than 10 days of duration to avoid fever of unknown origin with different etiologies to FWS, including noninfectious cause) in the emergency room with no identified infectious source during a physical examination at the hospital (without associated respiratory symptoms including rhinorrhea or nasal congestion, diarrhea process, acute otitis media or other findings on physical examination that allows identifying the source of the fever). All patients with an acquired or congenital immunodeficiency or other major chronic condition (oncologic illness, chronic renal failure, transplant patient, sickles cell disease, presence of a mechanical device such as indwelling catheter, ventricle-peritoneal shunt, auditory prostheses, or an invasive diagnostic or therapeutic procedure in the previous 10 days) were excluded due to the different pathogens implicated in the case of FWS and the different management needed in these cases. Patients with ongoing antibiotic treatment or difficulties communicating due to language problems were also excluded. We considered serious bacterial infection (SBI) those infants finally diagnosed with bacteremia, urinary tract infection, bacterial meningitis, or pneumonia. In our hospital were adapted since 2010 the clinical guideline from the National Institute for Health and Clinical Excellence (NICE) of how to assess and initially manage feverish illness in children aged under 5 years (12). The decision for inpatient versus outpatient management and antibiotic treatment was supported by clinical and laboratory findings at the discretion of the treating physician on a patient-by-patient basis.

The protocol was approved by Review Boards of Clinica Somer and Uniremington University in accordance with the local regulations in clinical research. Informed consent was waived by Review Boards of Clinica Somer and Uniremington University, due to the retrospective nature of this research.

Of each patient, we collected the following data: age, sex, personal history, complete vaccination for *Haemophilus influenzae type b* (3 doses at 2,4, and 6 months of age) and *Streptococcus pneumoniae* (2 doses at 4 and 12 months of age), duration of fever, associated symptoms, temperature, previous consultation in the ED, appearance on arrival, physical examination, supplementary tests, isolated microorganism, final diagnosis, and disposition of the patient. In all patients were mandatory to obtain white blood cell counts (WBC), absolute neutrophil count (ANC), serum C-reactive protein (CRP), and Urine dipstick. Urinary tract infection (UTI) was defined as the presence of ≥ 10^4 colony-forming units per milliliter of a single uropathogen, cultured from a urine specimen obtained by bladder catheterization. Other tests (blood culture, urine culture, chest radiograph, cerebrospinal fluid examination) were obtained at the discretion of the physician in charge.

Clinical and socio-demographic variables information were compared between groups (SBI and non-SBI) with Student's t-tests or Kruskal–Wallis tests for continuous variables and with Chi2 tests or Fisher's exact tests for categorical variables. Medians are reported with interquartile ranges (IQRs). All tests were two-tailed, and a value of $P \leq 0.05$ was considered statistically significant. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each of the possible predictor variables of SBI using logistic regression models, adjusting for potential confounders. We carried out the statistical analysis using STATA 17.0.

Results

Between January 2015 to December 2017, 137 patients were included, Table 1. Forty-one children (29.9%, CI 95% 22-38%) were diagnosed with SBI, and 96 were diagnosed as non-SBI patients (16 had upper respiratory, 11 gastroenteritis, 6 viral rashes, and 63 patients were diagnosed with FWS without a documented etiology). Among infants with SBI, the discharge diagnosis most frequently were urinary tract infection (n=32, 78%), pneumonia (n=3, 7%), bacteremia (n=4, 9%), meningitis (n=2, 4%). The following pathogens were isolated from urine cultures: Escherichia coli (n = 22), Klebsiella pneumoniae (n = 2), Proteus mirabilis (n=3), Pseudomonas (n=1), Enterococcus faecalis (n=2) and Enterobacter cloacae (n=1). The pathogens that were isolated from the blood were: Streptococcus pneumoniae (n = 2) Pseudomonas (n=1), staphylococcus epidermidis (n=1), and staphylococcus aureus (n=1) isolated from the blood culture of the infant diagnosed with meningitis.

Table 1
Clinical and sociodemographic characteristics of study population

Variable		n	%
Age	<3 months	9	6,6
	3 to 6 months	21	15,3
	>6 months	107	78,1
Sex	Male	58	42,3
	Female	79	57,7
Vaccination for streptococcus pneumoniae	Yes	136	99,3
	Not	1	0,7
Underlying pathology	Not	82	59,9
	Yes	55	40,1
Recurrent urinary tract infections	Not	119	86,9
	Yes	18	13,1
Recurrent wheezing	Not	132	96,4
	Yes	5	3,6
Good general appearance at admission	Yes	102	74,5
	Not	35	25,5
Adequate hydration status	Yes	123	89,8
	Not	14	10,2
Colour	Normal colour	127	92,7
	Pale/mottled/blue	10	7,3
Temperature	<39°C	97	70,8
	>39°C	40	29,2
Days with fever	<3 days	44	32,1
	<3 days	93	67,9
Traffic light system for identifying risk of serious illness (NICE)	Low risk	70	51
	Intermediate risk	52	38
	High risk	15	11

Variable		n	%
White blood cell count (103/Ml)	<15000	68	49,6
	>15000	69	50,4
Serum C-reactive protein (mg/L)	<20	50	36,5
	>20	87	63,5
Antimicrobials	Not	20	14,6
	Yes	117	85,4
Length of hospital stay		mean : 4,23	SD: 2
Pediatric intensive care unit management	Not	131	95,6
	Yes	6	4,4
Serious bacterial infections	Not	97	70,8
	Yes	40	29,2
Pneumonia		3	4
UTI		32	42,6
Meningitis		2	2,6
Bacteremia		3	4

Patients with UTI were significantly younger than non-UTI. A greater proportion of patients in the UTI group were less than 6 months (44% vs. 15%, p<0.002). A higher proportion of patients in the UTI group had recurrent urinary tract infections (18% vs. 11%) differences were not statistically significant (p=0.32). A higher proportion of patients in the UTI group had not good general appearance in admission (36% vs. 22%) but this difference was not statistically significant (p=0.10). 36% of the patients in the UTI group had a temperature >39°C respect to 23% of the patients with the same temperature in a non-UTI group. A higher proportion of patients in the UTI group were classified as high risk (15% vs 9%) using the Traffic light system for identifying risk of serious illness (NICE) to a non-UTI group. but this difference was not statistically significant (p=0.67). There were no differences statistically significantly between the group's days with fever, white blood cell count, CPR levels, Table 2.

Table 2
Predictors of serious bacterial infections (urinary tract infections)– univariate analysis.

Variable		NO UTI (n=104)	UTI (n= 33)	p-value
Age	<3 months	2 (1.9%)	7 (21.2%)	<0.001
	3 to 6 months	14 (13.5%)	7 (21.2%)	
	>6 months	88 (84.6%)	19 (57.6%)	
Sex	Male	43 (41.3%)	15 (45.5%)	0.68
	Female	61 (58.7%)	18 (54.5%)	
Vaccination for streptococcus pneumoniae	Yes	104 (100.0%)	32 (97.0%)	0.075
	Not	0 (0.0%)	1 (3.0%)	
Recurrent urinary tract infections	Not	92 (88.5%)	27 (81.8%)	0.32
	Yes	12 (11.5%)	6 (18.2%)	
Recurrent wheezing	Not	100 (96.2%)	32 (97.0%)	0.83
	Yes	4 (3.8%)	1 (3.0%)	
Good general appearance at admission	Yes	81 (77.9%)	21 (63.6%)	0.10
	Not	23 (22.1%)	12 (36.4%)	
Adequate hydration status	Yes	90 (86.5%)	33 (100.0%)	0.26
	Not	14 (13.5%)	0 (0.0%)	
Colour	Normal colour	95 (91.3%)	32 (97.0%)	0.28
	Pale/mottled/blue	9 (8.7%)	1 (3.0%)	
Temperature	<38°C	32 (30.8%)	9 (27.3%)	0.31

Variable		NO UTI (n=104)	UTI (n= 33)	p-value
	38-38,9°C	48 (46.2%)	12 (36.4%)	
	>39°C	24 (23.1%)	12 (36.4%)	
Days with fever	<3 days	31 (29.8%)	13 (39.4%)	0.30
	<3 days	73 (70.2%)	20 (60.6%)	
Traffic light system for identifying risk of serious illness (NICE)	Low risk	54 (51.9%)	16 (48.5%)	0.67
	Intermediate risk	40 (38.5%)	12 (36.4%)	
	High risk	10 (9.6%)	5 (15.2%)	
Urine Gram stain	Negative for any organisms	101 (97.1%)	12 (36.4%)	<0.001
	Positive for any organisms	3 (2.9%)	21 (63.6%)	
Abnormal leukocyte esterase or nitrites	Not	102 (98.1%)	9 (27.3%)	<0.001
	Yes	2 (1.9%)	24 (72.7%)	
White blood cell count (103/Ml)	<15000	49 (47.1%)	19 (57.6%)	0.30
	>15000	55 (52.9%)	14 (42.4%)	
Serum C-reactive protein (mg/L) (mg/L)	<20	40 (38.5%)	10 (30.3%)	0.40
	>20	64 (61.5%)	23 (69.7%)	
Antimicrobials	Not	20 (19.2%)	0 (0.0%)	0.006
	Yes	84 (80.8%)	33 (100.0%)	

Discussion

We describe the epidemiology of SBI and UTI in a population of highly vaccinated infants with FWS. Of 137 infants 40 (29%) had SBI and of them 32 (80%) had UTI. The prevalence of SBI in our study was higher than in previous studies (13). In this Colombian prospective study with 101 patients less than 36 months of age the prevalence of SBI was 25%. These discrepancies could be explained by not all patients who underwent hemogram and urinalysis plus urine gram (91 and 64%) in this study; and this could lower the level of detection, especially of UTI. The predominance of UTI are consistent with recent studies conducted in the post-pneumococcal vaccine era in which there was an increase in the rate of UTI and decreasing in the rate of others diagnosis(14)

In infants with FWS, always some uncertainty is still encountered because the symptoms are unspecific and sometimes do little to elucidate whether or not the patient's condition is the result of a urinary tract infection(15). Patients with UTI were significantly younger than non-UTI. It was the only variable that distinguished between patients with and without UTI. Interestingly, no single biological marker, such as CRP or WBC, or another clinical variable such as the magnitude of the fever or its duration or general appearance in admission could efficiently identify patients with UTI. This reinforces the need to screen for UTI in all patients with FWS given the frequency of UTI and the poor association with signs, symptoms, or other biomarkers. Most infants with UTI (72%) had positive leukocyte esterase and nitrite in the urinalysis, as well as positive gram staining for germs (64%). In the present study, these parameters were more useful in discriminating patients with or without SBI than CPR or WBC or clinical characteristics. The germ most frequently isolated in the urine cultures was *Escherichia coli*, confirming it as the most frequent cause of urinary tract infection, a finding similar to that found in other reports (16).

Our study has certain limitations. The sample size was small, which limited to some extent the multivariate analyses and the performance of a predictive model; although this was not the objective of this study from the beginning. Additionally, the retrospective nature of the secondary source information may generate information biases; however, all the information from the patients was available at least to guarantee the completeness of the information presented here.

In conclusion, patients with FWS under 3 years of age, urinary tract infection is the main cause of SBI. A high degree of clinical suspicion should be maintained since neither symptoms, signs, CBC or CPR distinguish children with or without UTI in this population. Future studies should further validate, in a different setting and in a larger population, our results.

Declarations

Ethics approval and consent to participate: The protocol was approved by Review Boards of Clinica Somer and Uniremington University in accordance with the local regulations in clinical research. Informed consent was waived by Review Boards of Clinica Somer and Uniremington University, due to the retrospective nature of this research.

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Availability of data and materials: The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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