Published in final edited form as:

Clin Pediatr (Phila). 2012 January ; 51(1): 51–57. doi:10.1177/0009922811417295.

Evaluation of the Precision of Emergency Department Diagnoses of Young Children with Fever

Joshua M Colvin, MD¹, David M Jaffe, MD², and Jared T Muenzer, MD²

¹Department of Pediatrics, Saint Louis University School of Medicine, St. Louis, Missouri, 63104

²Department of Pediatrics, Washington University in Saint Louis School of Medicine, St. Louis, Missouri 63110

Abstract

Objective—To characterize causes of fever in otherwise healthy children presenting to a pediatric emergency department (ED).

Methods—One-year retrospective review of ED records.

Inclusion criteria—2–36 months of age with a documented temperature $\geq 39^{\circ}\text{C}$ presenting between August 1st, 2006 and July 31st, 2007.

Exclusion criteria—elopement, repeat visit in < 1 month or underlying diagnosis with a predisposition to infection. Medical records were reviewed using a predefined, study-specific, data abstraction tool. Based on diagnosis and pathogen detection, visits were assigned to three groups, laboratory confirmed pathogen and focal or non-focal diagnosis without confirmed pathogen.

Results—1091 total visits met inclusion criteria (denominator for all percents). 14% had a pathogen detected: 8% viral and 6% bacterial. 56 % had a focal diagnosis without a confirmed pathogen: 21% otitis media, 13% upper respiratory infection, 7% pneumonia, 16% rarer diagnoses. 30% had a non-focal diagnosis without confirmed pathogen: 15% viral infection not otherwise specified, 8% fever of unknown etiology, 3% febrile seizure, 4% rarer diagnoses. Focal and non-focal diagnoses without detected pathogens had 35% and 61% microbiological tests performed respectively ($p<0.001$). Admission rates were 49% for patients with confirmed pathogens, 7% with focal diagnoses and 13% with non-focal diagnoses without confirmed pathogen ($p<0.001$).

Conclusions—In a cohort of febrile children 2–36 months of age evaluated in a pediatric emergency department, only 14% had a confirmed pathogen. New rapid viral diagnostic techniques may provide an opportunity to improve diagnostic certainty in young children presenting with fever.

Keywords

fever; children; infection; source

INTRODUCTION

Fever is the most common reason for pediatric emergency department visits [1,2]. Older studies from the 1970's and 1980's reported that approximately 2–5% of febrile children age 3–36 months had bacteremia with *S. pneumoniae* and *H. influenzae* type b being the most commonly identified pathogens [3,4,5,6]. The implementation of infant immunization with the *H. influenzae* type b and conjugate 7-serotype *S. pneumoniae* vaccines reduced the frequency of bacteremia to less than 1% [7,8]. Determining the etiology of febrile illness in young children is challenging. In absence of specific focal signs of infection, febrile illness is often attributed to a non-specific viral infection. Many studies have focused on the burden of single viral pathogens in this age group. For example, human herpes virus type 6 (HHV-6) may account for as many as 14% of febrile illnesses in children under 24 months of age [9,10]. Enteroviruses [11–13] and respiratory viruses, particularly influenza and adenoviruses [14,15] have been identified as important causes of fever, especially during the appropriate season. In order to direct management and therapy, a variety of laboratory based and point of care tests are used in emergency departments to help identify pathogens. These include rapid tests for respiratory syncytial virus (RSV) and influenza, as well as direct fluorescent antibody tests of nasopharyngeal fluid samples. While the most precise diagnosis can be made by identifying a specific pathogen using microbiological tests, more often clinicians diagnose a clinical syndrome or focal illness in order to direct specific therapy (pneumonia, gastroenteritis, etc.). When these strategies fail to yield a specific diagnosis, the clinician may assign a non-specific diagnosis such as viral syndrome, vomiting or fever. The purpose of this study was to characterize the distribution of diagnoses in a cohort of febrile children after the introduction of *H. influenzae* and conjugated pneumococcal vaccines. In order to evaluate our cohort we subdivided the diagnoses into three groups: patients in whom a specific pathogen was found, those with a focal diagnosis without identified pathogen and those with a non focal diagnosis without identified pathogen. Next, we evaluated the frequency and efficacy of microbiologic testing in this cohort of patients. Finally, we examined the distribution of testing across specific age groups

METHODS

Data Abstraction

We conducted a one-year retrospective review of medical records from an urban pediatric emergency department with approximately 55,000 annual visits. Eligible medical records were identified for inclusion through a query of emergency department electronic medical records (Wellsoft®) consisting of visits from August 1, 2006 through July 31, 2007. The following search criteria were used: age 2–36 months, (defined as the 2nd calendar month after the date of birth until the day of the 3rd birthday) and temperature (T) $\geq 39^{\circ}\text{C}$, as determined by tympanic membrane measurement. Repeat visits were analyzed as separate visits, but were only included in the analysis if they met the eligibility criteria for each visit and were separated by more than 1 month. Personal identifiers of eligible patient visits meeting the above criteria were exported into a database. These identifiers consisted of first and last name, date of birth, date of emergency department visit, medical record number, and a unique patient account number for each visit. One author, JMC, developed and pilot-

tested a predefined, study– specific, standardized data abstraction form and data dictionary. If a variable was not found in the emergency department record under review, it was considered missing. Laboratory data were only abstracted if the data were reported in the laboratory section of the medical chart. The temperature reported was the highest temperature recorded in the vital signs section of the emergency department chart. The abstractor was not blinded to the hypothesis being tested, or to the group assignment. Using the abstraction form as a tool, and the rule book as a guideline, one author (JMC) reviewed all records that had been identified by the electronic query for the following data elements: age, date of service, highest temperature, underlying medical condition predisposing to infection, presence of central-vascular catheter, diagnosis, disposition, complete blood count with differential, chest radiograph result, culture results for blood, urine, cerebrospinal fluid (CSF), wounds, stool for enteric pathogens, throat culture for group A streptococcus, results of viral culture and direct fluorescent antibody (DFA) test results from nasal secretions testing for influenza, parainfluenza, rhinovirus, adenovirus, RSV and human metapneumovirus, rapid influenza tests, molecular testing for rotavirus, mycoplasma, enterovirus, human herpesviruses, and antibody testing for cytomegalovirus (CMV) and ebstein-barr-virus (EBV). Visits were excluded for the following reasons: elopement, subsequent visits by the same subject within less than one month by calendar date, presence of an indwelling central-vascular catheter, medical problems predisposing to bloodstream infections, specifically cancer, sickle cell disease, primary immunodeficiency, HIV, AIDS, cystic fibrosis, complex congenital heart disease, or immunosuppressive therapy. Each blood and urine culture result was reviewed separately with a senior pediatric infectious disease specialist to verify pathogenicity. The emergency department medical record lists as many as three diagnoses. In the event of multiple diagnoses, the diagnosis that best explained the cause of the fever was reported. In the event that more than one diagnosis potentially explained the fever, the diagnosis that received a direct therapeutic intervention, such as antibiotics, was reported. If no therapy was initiated, or if there was no diagnosis explaining the fever, the first listed diagnosis was documented.

Subgroup Assignment

Visits were assigned to one of three subgroups based on diagnostic certainty. The first subgroup included any visit with a pathogen detected by microbiological testing. The second subgroup included any focal diagnosis or syndrome known to cause febrile illness. The last subgroup included visits where the diagnosis was a symptom, a broad non-specific category, or a diagnosis not known to cause fever, such as dehydration.

Age Stratification

Visits were stratified into three groups by the age of the child at the time of the emergency department visit. One group included all visits of children age 2 to 12 months, a second group included all visits of children age 13 to 24 months and another group included all visits of children age 25 to 36 months.

Inter-rater Reliability

A random number generator (Research Randomizer®) identified 10% of charts for review. A second author (JTM), who was blinded to the outcomes, reviewed these charts and

independently collected data for the following variables: highest recorded temperature in the emergency department and emergency department diagnoses. Inter-rater reliability was calculated for emergency department diagnosis and for temperature. For temperature we used the intra-class correlation coefficient (ICC), and for diagnoses we determined the percent agreement and 95 percent confidence intervals, as a meaningful kappa statistic could not be calculated due to the large number of categories of diagnoses.

Data Analysis

We used descriptive statistics to analyze patient demographics, diagnoses, and microbiological testing performed during the emergency department visit. We reported frequencies, proportions, means with standard deviations, and ranges where applicable. Variables of interest were age, race / ethnicity, time of year the visit occurred, emergency department diagnosis, and results of microbiological tests ordered during the emergency department visit. We evaluated the yield of microbiological tests by age. To evaluate indicators for severity of illness, we calculated the rate of culture positive serious bacterial infections and compared admission rates by age and diagnostic subgroup. In addition, we compared microbiological testing performed in the focal and non-focal subgroups without identified pathogen. For statistical analysis of categorical variables, we used the chi-square test. All tests were two-sided and $p < .05$ was considered statistically significant. SPSS v. 17.0 (Chicago, IL) was used for all analyses. The study was approved by the Washington University IRB, and a waiver of informed consent was obtained.

RESULTS

Demographics

Review of 55,748 patient visits to the emergency department during the one-year study period yielded 1172 visits that met the inclusion criteria. Eighty-one visits were excluded: 33 for elopement, 19 for repeat visits within less than one month, 25 for medical problems predisposing to infection, and 4 based solely on the presence of an indwelling central vascular catheter. Of the patient visits excluded for medical problems predisposing to infection, 9 were excluded for sickle cell anemia, 13 for cancer, one for a bone marrow transplant, one for Di-George Syndrome, and one for complex congenital heart disease. There remained 1091 visits in 1051 patients eligible for the study. Of the 1051 patients, 38 patients had one repeat visit that was included, and one patient had 2 repeat visits that met eligibility for the study. The mean age was 17 months, and 574 (53%) of the visits were by males. The demographic characteristics of the study sample are listed in Table 1. Inter-rater agreement was assessed on 107 (10%) of the charts; results indicated 98.13% agreement (105/107, 95% CI 95.55%; 100%) for ED diagnosis reported and perfect agreement for the highest ED temperature (ICC 1.0).

Diagnostic Subgroups

The charts listed one diagnosis in 717 visits (66%); two diagnoses in 327 visits (30%); and 3 diagnoses in 50 visits (4%). One diagnosis was ascribed to each visit based on the criteria listed in the methods section (Table 2). Three subgroups were formed based on microbiological test results, and focality of diagnosis.

The first subgroup consisted of 150 (14%) visits, in which at least one pathogen was confirmed by microbiological testing. In this subgroup 166 pathogens were identified: 88 (59%) were viral and 65 (41%) were bacterial. The most common microorganisms were influenza A and B virus and respiratory syncytial virus (RSV) isolated from the respiratory tract, *Escherichia coli* isolated from urine cultures, and *Staphylococcus aureus* isolated from wound cultures (Table 3).

The second subgroup consisted of 617 (56%) visits with a focal diagnosis without a confirmed pathogen. The most common focal diagnosis in the subgroup was otitis media, followed by viral upper respiratory infection, pneumonia, gastroenteritis and bronchiolitis (Table 2).

The third subgroup consisted of 324 (30%) visits with a non-focal diagnosis without a confirmed pathogen. In this subgroup the most common diagnoses were viral infection not otherwise specified (NOS), fever without a source, and febrile seizure (Table 2).

In visits with focal diagnoses with no pathogen identified 221/615 (36%) had microbiological testing performed, compared to 193/323 (60%) visits with non-focal diagnoses with no pathogen identified ($p<0.001$).

Microbiological Testing

In total, 1021 microbiological tests were performed in 564 of the 1091 patient visits (52%) with a mean of 0.94 tests per patient visit (range 0–6). In 150 (14%) patient visits at least one microbiological test was positive. Fifty-seven percent of children with an identified pathogen had a virus and 43% had a confirmed bacterial infection. Urine culture was the most frequently performed test (23%). Of the 247 urine cultures obtained, 10% (24/247) were positive. The most common urine pathogen recovered was *E. coli*, accounting for 75% of positive tests. Blood cultures were obtained in 22% (240) of visits. Of these, 7 (0.6%) yielded results consistent with bacteremia, and 4 (0.4%) were determined to be contaminants. The four contaminants were two bacillus species, one beta hemolytic *Streptococcus*, and one *brevundimonas* species. Of the positive blood cultures 57% grew Gram-positive bacteria, 43% Gram-negative enteric organisms. Of the seven blood cultures that were positive for pathogens two grew *Klebsiella* species, two methicillin resistant *Staphylococcus aureus*, one *E.coli*, one *Streptococcus pneumoniae*, and one Anaerobic gram positive cocci.

Rapid influenza testing was performed in 15% (167) of visits and 22% of those were positive. Nasopharyngeal samples for viral DFA and culture were obtained in 11% (118) of the ED visits and 42% of those were positive for a virus (Table 3).

Yield by Age

We compared the yield of the microbiological test results by age. Only the results for urine cultures and nasopharyngeal fluid swabs were significantly different by age (Table 4). Eighty percent of positive urine cultures were in the youngest subcategory.

Indicators of Severity of Illness

We considered serious bacterial infection (SBI) and inpatient hospital admissions as indicators of severity of illness.

SBI was confirmed by culture in 2.9% (31) of visits. Of these 2.2% (24) had a positive urine culture and 0.7% (7) had culture confirmed bacteremia. The overall admission rate was 15%, with no significant differences among the three age categories. Admission rates varied by diagnostic subgroup (chi square, $p < .001$). The highest rate of admissions was found in the subgroup with an identified pathogen (49%). The admission rates for focal and non-focal diagnoses without pathogen confirmation were 7% and 13% respectively.

DISCUSSION

Febrile illnesses account for a significant proportion of pediatric emergency department visits in the United States. In this study we reviewed the evaluation of febrile children age 2–36 months over a one-year period. We found that despite using a wide range of microbiological techniques, a pathogen was only found in a minority (14%) of cases. Of these cases, 57% of children with an identified pathogen had a virus and 43% had a confirmed bacterial infection. The most common viruses detected were influenza and RSV, which have been reported by several other investigators to cause a significant burden of illness in young children [14, 16–17]. The majority of children in our cohort with identified bacterial infections had either a urinary tract infection or an abscess. Overall, evaluation for serious bacterial infection (SBI) in our cohort revealed 2.9% had a culture confirmed SBI: 0.7% bacteremia, 2.2% UTI. Our bacteremia rate is comparable to recent reports ranging from 0.4% to 0.7% [7,8,18]. In addition, the rate of UTI is similar to previous published reports ranging from 2.1% to 4.5% [18–20].

The largest subgroup of patients in our cohort had a focal diagnosis without an identified pathogen. The proportion of patients admitted in this group was significantly lower than the other subgroups. This group also had a significantly lower rate of negative microbiological testing compared to the group with non-focal diagnoses and no identified pathogen. The majority of children in this group had a suspected bacterial infection, most frequently acute otitis media or pneumonia. In support of our findings, it has been reported that the majority of children with fever presenting for medical evaluation have presumed bacterial infections and that most of these children do not require hospital admission [21]. A possible explanation for the difference in admission rates and negative microbiological testing is that children with focal diagnoses may have less need for additional tests and admissions because clinicians have a higher degree of diagnostic certainty compared to children presenting with a non focal febrile illness.

Despite improvements in diagnostic techniques, there remains a large subgroup of febrile children, 30% in our cohort, who have a non-focal illness with no specific etiology. There are several explanations for this inability to make a specific diagnosis. One reason is that 41% of these patients did not receive any microbiological testing. It should be noted that the most likely reason for not testing is that the low severity of illness did not warrant further diagnostic evaluation. However, some of them may have benefitted from an NP viral swab,

as 42% of all patients swabbed yielded a positive result, despite the use in only 11% of patient visits. Possible explanations for the failure to identify pathogens in the 59% of patients who did undergo testing include, insufficient sensitivity of certain tests, testing for the wrong pathogens, and/or testing at the wrong site i.e., nasopharynx versus blood.

Failure to accurately identify the source of a fever, especially in non-focal febrile illness, may lead to unnecessary hospital admissions (13% in our cohort), more invasive testing, multiple visits to emergency departments, parent dissatisfaction and inappropriate use of antibiotics [22]. Several studies have focused on the large burden of viral infections in febrile children that often go unrecognized in clinical practice. Taken together, these studies have identified HHV-6, adenovirus, enterovirus, and influenza as important pathogens in this age group. These viruses may account for many non-focal febrile illnesses in which no pathogen is identified [13–15, 21, 22]. The development of rapid assays to identify the key viral pathogens in both blood and respiratory secretions can help us provide more appropriate care and anticipatory guidance for caretakers of young febrile children.

Our study has several important limitations. It is a retrospective study and was performed in a single academic children's hospital with a predominantly urban population. The microbiological testing and the emergency department diagnosis were at the discretion of the treating physician. We limited our study to the emergency department visit and do not report testing performed outside the emergency department. Each reported diagnosis was abstracted from as many as three diagnoses listed in each chart. Occasionally the history and physical examination findings described in the chart may favor an alternative diagnosis, but in order to minimize bias in our study, the reported results were always abstracted from the diagnosis section of the chart.

In conclusion, we found that 30% of otherwise healthy febrile children evaluated in the Emergency Department have no specific diagnosis or pathogen identified. Although an additional 56% received specific clinical diagnoses, only 14% of all patients had a specific pathogen detected. Bacterial pathogens were slightly less common than viral pathogens (43% vs 57%), with urinary tract infections and abscesses accounting for the majority of identified bacterial disease. Bacteremia was rare, and bacterial meningitis did not occur in this study. The large cohort of undiagnosed patients combined with a relatively small percentage of specifically identified pathogens provides an opportunity to apply rapid assays for viral pathogens in blood and nasal secretions to decrease diagnostic uncertainty in young children with fever.

ACKNOWLEDGMENTS

The authors would like to acknowledge Chris G Davis for his help in preparing the manuscript, and Missy Krauss, MPH for her help with the statistical analysis.

This publication was made possible by Grant Number UL1 RR024992 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Supported in part by NIH GM084143 (JTM).

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Table 1

Characteristics of 1091 ED Visits with Fever

Variable	N (%)
Age, mo, mean $\pm$ SD [range]	17 $\pm$ 9 [2–35]
subgroups, mo	
2–12	391 (36)
13–24	437 (40)
25–35	263 (24)
574 (53) Race / Ethnicity	
Black	721 (66) White
	289 (27) Hispanic
(3) Asian	14 (1) Other
(3)	34
Temperature $^{\circ}$ C, mean $\pm$ SD [range]	39.5 $\pm$ 0.4 [39 – 41.2]
Time of presentation	
January – March	303 (28)
April – June	241 (22)
July – September	
170 (16) October – December	377 (34)

*
mo: months, SD: standard deviation, N: number

Table 2

Subgroups Based on Pathogen Confirmation and Focality of Diagnosis in 1091 Visits

Variable	N (%)
Subgroup 1: Visits with laboratory confirmed pathogens	150 (14)
Total N pathogens identified	156
Influenza	41 (4)
RSV	26 (2.4)
Urine culture positive (75% E.coli)	24 (2.2)
Wound culture positive (95% S. aureus)	22 (2.2)
Parainfluenza	8 (0.7)
Bacteremia	7 (0.7)
Adenovirus	6 (0.6)
Group A Streptococcus (throat culture)	5 (0.5)
Rhinovirus	4 (<0.05)
Shigella sonnei	4 (<0.05)
Enterovirus in CSF	3 (<0.05)
Rotavirus	2 (<0.05)
Salmonella typhimurium	1 (<0.05)
Subgroup 2: Focal diagnoses, no confirmed pathogen	615 (56)
Otitis Media	236 (22)
URI	144 (13)
Pneumonia	85 (8)
Gastroenteritis	49 (5)
Bronchiolitis	24 (2) Croup
	16 (1)
Pharyngitis	14 (1) UTI
without confirmed culture	8 (0.5)
Influenza	4 (<0.5) Rarer
diagnoses	37 (3)
Subgroup 3: Non-focal diagnoses, no confirmed pathogen	324 (30) Viral
Infection (NOS)	161 (15)
Fever of unknown origin	87 (8) Febrile
Seizure	29 (3) Asthma
	10 (1)
Diarrhea	5 (0.5)
Vomiting	5 (0.5)
Dehydration	3 (<0.5) Rarer
diagnoses	24 (2)

N: Number

Table 3**Microbiological Testing Performed in 1091 Visits**

Test	N (%)	N+ (%)	+N/N (%)
Urine culture	247 (23)	24 (2)	24/247 (10)
Blood culture	240 (22)	11 (1)	11/240 (5)
Rapid influenza test (nasal)	167 (15)	37 (3)	37/167 (22)
Nasopharyngeal viral DFA and culture	118 (11)	50 (5)	50/118 (42)
RSV		26 (2)	26/118 (22)
Parainfluenza		8 (0.7)	8/118 (7)
Influenza		6 (0.05)	6/118 (5)
Adenovirus		6 (0.05)	6/118 (5)
Rhinovirus		4 (<0.05)	4/118 (3)
Metapneumovirus		0 (0)	0/118 (0)
Throat culture	98 (9)	5 (0.5)	5/98 (5)
CSF culture	43 (4)	0 (0)	0/43 (0)
Stool culture	41 (4)	5 (0.5)	5/41 (12)
Wound culture	23 (2)	22 (2)	22/23 (96)
Enterovirus PCR of CSF	16 (1.5)	3 (0.3)	3/16 (19)
Rotavirus antigen test	8 (0.7)	2 (0)	2/8 (25)
HSV PCR (CSF)	8 (0.7)	0 (0)	0/8 (0)
EBV Titers	4 (<0.05)	0 (0)	0/4 (0)
Pertussis PCR (nasal)	4 (<0.05)	0 (0)	0/4 (0)
C. Difficile Toxin	2 (<0.05)	0 (0)	0/2 (0)
Mycoplasma titers blood	1 (<0.05))	0 (0)	0/1 (0)
Bartonella titers blood	1 (<0.05))	0 (0)	0/1 (0)

N: total number of tests performed, N+: total number of tests positive, N+/N: yield of test

Table 4

Yield For Urine Culture and Viral Nasopharyngeal Fluid Swabs by Age

Age Group	N+ Urine / N (%)	P*
2–12 mo	19/122 (16)	.007
13–24 mo	2/78 (3)	
25–36 mo	3/47 (6)	
Age Group	N+ NP / N (%)	P*
2–12 mo	15/48 (31)	.029
13–24 mo	24/41 (59)	
25–36 mo	11/29 (40)	

Number, N+: Number positive %: percent, mo: months,

*
chi square test