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One-year epidemiology of fever at the Emergency Department

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ABSTRACT

Background: Although fever is recognised as a major presentation symptom at Emergency Departments (EDs) and is often used as a rationale for the institution of antibiotics, few studies describing patients with fever as the sole inclusion criterion at the ED of a general hospital have been performed. The objective of this study is to describe epidemiology of non-surgical febrile patients at the ED and to identify risk factors for adverse outcome.

Methods: Blood, sputum, urine and faeces cultures, urine sediments and throat swaps for viral diagnostics were obtained from febrile ED patients. Outcome parameters were bacterial/viral infection, non-bacterial/non-viral infection, non-infectious febrile disease; mortality, hospital admission, admission to the intensive care unit (ICU) and length of hospital stay.

Results: 213 Patients were included (87.8% were hospitalised, 8.5% were admitted to ICU, 4.2% died). In 75 patients (35.2%), bacterial infection was confirmed; in 78 patients (36.6%) bacterial infection was suspected. In nine patients (4.2%), viral diagnosis was confirmed; in six patients (2.8%), a viral condition was suspected. The most frequently encountered infection was bacterial pneumonia (58 patients, 27.2%). Only older age was correlated with mortality (ρ=0.176, p=0.01).

Conclusion: A majority of the febrile patients were admitted to the hospital, mostly for bacterial infection. An overall mortality rate of 4.2% was registered. Only a few risk factors for adverse outcome could be identified in this cohort. Overall, the outcome of patients presenting with fever at the ED is rather benign.

Keywords: Anti-bacterial agents; emergency service, hospital; fever; infection; prognosis

INTRODUCTION

Febrile illness is one of the most frequent causes of attendance at emergency departments (EDs) worldwide. Among the most frequently reported specific principal reasons for visiting an ED in the United States in 2005, fever was the third reported complaint, accounting for 4.4 to 7.5% of all ED consultations and up to 30% in non-surgical patients.[1,2] Although the underlying conditions causing the symptom of fever vary considerably, it requires a systematic approach regardless of the underlying condition, concentrating upon a primary division between bacterial infections and other conditions and subsequent risk stratification, often using the same parameters. Despite many efforts, including the implementation of faster and more accurate diagnostic tools, such as biomarkers, polymerase chain reactions (PCR) and radiological tests, the tests lack sufficient speed and reliability to justify clinical decision-making based on test results alone. Hence, both identification of bacterial infection and risk stratification remains very difficult in these patients in the emergency setting.[3-5] As a result, antibiotics are prescribed too frequently, leading to the worldwide problem of antibiotic resistance.

For an adequate risk stratification of febrile patients, a thorough knowledge about local epidemiology is required, and risk factors associated with adverse clinical outcome have to be identified. Moreover, as up to 50% of patients with fever may have a non-infectious aetiology,[6] better insight into the epidemiology of fever might also lead to a more restrictive use of antibiotics.

Although fever is recognised as a major presentation symptom at EDs and is often used as a rationale for the institution of antibiotics,[7] not many studies describing a cohort of patients with fever as the sole inclusion criterion

at the ED of a general hospital have been performed, especially not with the focus on non-surgical patients. Therefore, it remains unclear how many of these patients have been given antibiotics even though they did not actually suffer from a bacterial infection. Also, the epidemiology of patients with fever differs per region and changes over time,[8-12] which necessitates frequent epidemiological updates from different parts of the world. In addition, in many febrile cases the final diagnosis remains uncertain, due to sub-optimal supplementary diagnostics. A better insight into epidemiology may help to support or reject a diagnosis in these cases.

The purpose of this study was, first, to describe the epidemiology of non-surgical patients presenting with fever at the ED under optimal diagnostic conditions and, second, to identify risk factors for adverse outcome.

MATERIALS AND METHODS

Setting

ED of the Slotervaart Hospital, Amsterdam, the Netherlands, a general teaching hospital with a capacity of 410 beds with 70,000 new outpatients and 13,000 admissions yearly.

Design

Prospective cohort study of all adult, non-surgical patients presenting to the ED with fever (defined as tympanic temperature >38.2 °C), over a one-year period (January 2008 to January 2009). Non-surgical specialities included the departments of internal medicine, gastroenterology, cardiology, pulmonology, rheumatology, intensive care medicine and neurology.

Diagnostic procedures

To ensure an optimal diagnostic work-up of febrile patients, one year prior to the start of the study, a standardised protocol was introduced, allowing nurses in the ED to start taking blood, sputum, urine, wound or faeces cultures without having to wait for a doctor's order. According to this protocol, three blood cultures (aerobic/anaerobic) from three different venipuncture sites were obtained from every febrile patient. In case of respiratory symptoms, throat swaps for viral diagnostics were standardly performed (polymerase chain reaction (PCR) on *Influenza-A* and *-B, Parainfluenza-1-4, Adenovirus, Respiratory Syncytial virus (RSV), human Rhinovirus, human Metapneumovirus, human Coronavirus OC43, human Coronavirus 229E, human Coronavirus NL63, Chlamydia pneumoniae, Mycoplasma pneumoniae* and *Legionella* species), combined with bacterial sputum culture. In case of urinary symptoms, a urine sediment and culture were taken. In case of diarrhoea, faeces cultures were performed. Other diagnostic tests were ordered at the discretion of the attending physician.

To ensure an optimal inclusion, every working day, all ED patients of the day and night before were checked; if a patient had been missed, the responsible nurse was informed.

Definitions and outcome parameters

Final diagnoses at admission were retrieved from subsequent clinical records during one year of patient follow-up. The patients were confined to one of the following groups:

- confirmed bacterial infection: positive culture result in concordance with clinical findings;
- suspected bacterial infection: clinical findings strongly suggestive for bacterial infection, but without positive culture result; for instance, a patient with fever, purulent cough, crackles on auscultation and a lobar infiltrate on the thoracic X-ray;
- confirmed viral infection: positive viral PCR in concordance with clinical findings;
- suspected viral infection: clinical findings indicative of viral disease in the absence of positive bacterial cultures despite extensive culture taking and in the absence of underlying auto-immune or auto-inflammatory disease, malignancy, thrombo-embolic disease or medication use that could explain clinical findings;
- non-bacterial/non-viral infection: positive fungal culture or proven parasite in concordance with clinical findings;
- non-infectious disease: no evidence of infectious fever despite extensive supplementary diagnostics and a strong alternative diagnosis.

Outcome parameters were bacterial infection (confirmed or strongly suspected), viral infection (confirmed or strongly suspected), non-bacterial/non-viral infection, non-infectious febrile disease; mortality, hospital admission, admission to the intensive care unit (ICU) and length of hospital stay. Outcome parameters were correlated with patient characteristics, such as presence of diabetes mellitus, malignancy or immunocompromised state; sex, age and temperature at admission.

Statistics

Data are presented as numbers with percentages and medians with interquartile ranges (IQR; 25 to 75%). Correlations were analysed with Pearson's correlation test and are expressed as a Pearson's ρ with p values. A p value <0.05 was considered statistically significant. All statistical analyses were performed by using SPSS Statistics 17.0.0 (Chicago, ILL, USA)

RESULTS

Patients

Altogether, 213 non-surgical, febrile patients (111 female, 52.1%) were included during the study period, with a median age of 66 years. (IQR 46 to 79 years). Further patient characteristics are presented in *table 1*.

A total of 187 patients (87.8%) were hospitalised, nine patients (4.2%) died within a 30-day follow-up period (bacterial pneumonia (n=6); sepsis without definite focus (n=1); cellulitis (n=1); metastatic coloncarcinoma (n=1)) and 18 patients (8.5%) were admitted to the Intensive Care Unit (bacterial pneumonia (n=10, 4 died); urosepsis (n=5, none died); sepsis without definite focus (n=3, 1 died)). A majority of 171 patients (80.3%) were eventually diagnosed with a proven or strongly suspected infectious disease. In 75 patients (35.2%), a bacterial infection was confirmed and in 78 patients (36.6%) a bacterial infection was strongly suspected based upon clinical grounds. In nine patients (4.2%), a confirmed viral diagnosis was made whereas in six patients (2.8%) a viral condition was strongly suspected. Other patients were diagnosed with non-bacterial/non-viral infections (n=3, 1.4%; 2 malarial, 1 fungal infection) or a non-infectious febrile episode (n=9, 4.2%; 2 malignancy, 2 drug-induced fever, 2 autoimmune disease, 1 autoinflammatory disease, 1 cerebrovascular accident, 1 femur fracture). In 33 patients (13.6%), no definite diagnosis could be established.

Table 1. *Patient characteristics of patients (n=213), presenting with fever to the Emergency Department*

	n=213 **n (%) / median (IQR)**
Sex, female	111 (52.1)
Age, years	66 (46-79)
Diabetes mellitus	54 (25.4%)
Immunocompromised	33 (14.1%)
Malignancy	22 (10.3%)
Temperature, °C	38.9 (38.5-39.5)
Mean arterial pressure (MAP), mmHg	89 (74-103)
Heart rate, beats/min	103 (85-121)
Hospitalisation	187 (87.8%)
Duration of hospital stay, days	6 (4-11)
Admission to ICU	18 (8.5%)
Mortality	9 (4.2%)
Laboratory values at admission	
- Haemoglobin, mmol/l	8.1 (7.0-8.9)
- Leucocytes, giga/l	11.8 (8.4-15.5)
- Thrombocytes, giga/l	207 (153-263)
- C-reactive protein, mg/l	85.0 (36.3-175.1)
- Creatinine, μmol/l	94 (73.5-115.8)
- Albumin, g/l	33 (28-36)

Infections

The incidence of infections is shown in *table 2*. The most frequent infections were bacterial pneumonia (58 patients, 27.2%), urinary tract infections (45 patients, 21.1%), bacterial and/or viral upper respiratory tract infections (20 patients, 9.4%), skin infections (12 patients, 5.6%) and bacterial and/or viral gastroenteritis (8 patients, 3.8%).

Blood cultures were taken from 208 patients (97.7%); 52 were positive (24.3%) out of which 11 were probably contaminated. Of the blood cultures 41 (19.7%) were deemed truly positive. The most frequently encountered organisms were *S. pneumoniae* in pulmonary infections and *E. coli* in urinary tract infections. One Extended Spectrum β-Lactamase (ESBL) producing *E. coli* was cultured from the blood of a patient with urosepsis. No multi-resistant *S. aureus* (MRSA) were isolated.

Altogether, 151 additional cultures (urine, sputum, faeces, wound, liquor, throat, pleural fluid) were taken; 71 cultures (47.0%) were positive *(table 2)*.

Antibiotics

In 186 patients (87.8% of total) antibiotics were started. Amoxicillin/clavulanate was prescribed most frequently (26.9%), followed by ciprofloxacin (21.9%), ceftriaxon (12.0%), amoxicillin (9.0%) and metronidazole (7.0%). Double antibiotic regimens were administered in 48 patients, triple antibiotic regimens were administered in 11 patients. In the group of patients receiving antibiotics, 11 patients were later diagnosed as non-bacterial infection: viral diagnosis (n=6); non-bacterial/non-viral infection (n=2); no infection (n=3). Finally, 27 febrile patients did not receive antibiotics: non-infectious disease (n=8); no definite diagnosis (n=7); confirmed viral infection (n=1); suspected viral infection (n=5); suspected bacterial infection (n=5); confirmed bacterial infection (n=1). The one patient with a bacterial infection suffered from confirmed *C. jejuni* bacterial enteritis and made a full recovery with supportive therapy only. Immunocompromised state was strongly associated with the prescription of antibiotics (ρ 0.346, p<0.001). No significant correlation between prescription of antibiotics and comorbidity, such as diabetes mellitus or chronic pulmonary disease, could be observed.

Prognosis

Only older age was significantly correlated with mortality (ρ 0.176, p=0.01). No factors significantly correlated with ICU admission could be identified.

Factors correlating with hospital admission were older age (ρ 0.248, p<0.001), immunocompromised state (ρ 0.157, p=0.02) and the presence of a confirmed bacterial infection (ρ 0.155, p=0.04). Longer hospital stay was associated with female sex, older age and immunocompromised state (ρ 0.154, p=0.03; ρ 0.363, p<0.001; ρ 0.184, p=0.008, respectively), as were higher temperatures at

Table 2. *Incidence of febrile, non-surgical diseases, with most frequently confirmed pathogens in blood, urine, sputum, faeces and other sites at the Emergency Department*

Diagnosis	Blood	Urine	Sputum	Faeces	Other
Bacterial infections					
Pneumonia; n=58 (confirmed n=18; suspected n=40)	*S. pneumonia (8x)* *S. aureus (1x)* *E. coli (1x)*		*S. pneumonia (5x)* *K. pneumonia (2x)* *P. aeruginosa (1x)*		
Upper RTI; n=8 (confirmed n=3; suspected n=5)			*S. aureus (1x* *H. influenzae (1x)* *E. coli (1x)* *M. catarrhalis (1x)*		
UTI; n=45 (confirmed n=36; suspected n=9)	*E. coli (10x)* *P. mirabilis (3x)* *S. aureus (3x)* *E. faecalis (2x)* *K. pneumoniae (1x)*	*E. coli (16x)* *E. faecalis (5x)* *P. mirabilis (3x)* *P. aeruginosa (2x)* *K. pneumoniae (2x)* *S. aureus (2x)*			
Skin infection; n=3	*S. pyogenes (3x)*				
Cholangitis; n=3	*K. pneumoniae (2x)* *E. faecalis (1x)*				
Abscess; n=3	*E. coli (2x);* *Group C β-haemolytic streptococcus (1x)*				
Gastroenteritis; n=2				*C. jejuni (1x)* *C. difficile (1x)*	
Endocarditis; n=1	*S. constellatus*				
Diabetic foot; n=1	*S. aureus*				Wound culture: *S. aureus*
Tuberculosis; n=1					Pleural fluid culture: *M. tuberculosis*
Appendicitis; n=1	*E. coli*				
Viral infections					
Pneumonia; n=5					PCR on throat swap: *Influenza A- (2x); rhino- (1x); parainfluenza 1- (1x); respiratory syncytial virus (1x)*
Upper RTI; n=5 (confirmed n=3; suspected n=2)					PCR on throat swap: *respiratory syncytial - (2x); parainfluenza 1-virus (1x)*
Meningitis; n=1					PCR on liquor: *enterovirus (1x)*
Non-bacterial/ non-viral infections					
Malaria					Peripheral smear examination: *M. vivax (2x)*
Fungal infection		*C. albicans (1x)*			

UTI = urinary tract infection; RTI = respiratory tract infection; PCR = polymerase chain reaction.

presentation (ρ 0.143, p=0.04). Having diabetes mellitus or underlying malignancy at presentation was niether significantly associated with worse outcome in terms of mortality, admission to special care unit or length of hospital stay, nor with the presence of bacterial and other infections.

DISCUSSION

Although fever is a very common complaint on EDs worldwide, studies describing the epidemiology of fever are scarce, perhaps because it is considered a commonplace and non-specific finding. Another reason for this lack of information, however, might be the fact that for a proper diagnosis of fever, accurate and extensive diagnostics have to be performed, which may be less of a priority in a hectic and crowded ED. Therefore, we sought to investigate the epidemiology of fever at the ED of a Dutch teaching hospital under optimal diagnostic conditions. Moreover, with a thorough knowledge of the local epidemiology, we tried to identify risk factors for adverse outcome in a febrile population.

The very high percentage of blood cultures taken shows that the implementation of our diagnostic protocol resulted in more extensive diagnostics. In the only earlier study, investigating a febrile population at an ED, blood cultures were taken in less than two thirds of all non-hospitalised

patients.[13] The high amount of other cultures taken underlines the optimal diagnostic conditions, enabling us to give a substantiated description of epidemiology.

We show that almost nine out of ten febrile patients are admitted to the hospital, with an average duration of a week. An overall mortality rate of 4.2% was registered, much lower than mortality rates as mentioned in two other ED studies in tropical countries[5,14] and in a Spanish study focusing on community-acquired bacteraemia,[12] but slightly higher than in an Australian cohort.[13] In our study, one in 20 patients were diagnosed with a non-infectious aetiology of the fever, which is lower than expected based on ICU findings,[6] but exactly as high as seen previously by our group in an Afro-Caribbean febrile population at the ED in Curaçao, Netherlands Antilles (*Limper et al, submitted for publication)*.

Gram-negative bacteria were the most frequent cause of bactaeremia, as was reported in an earlier European study.[12] However, upper and lower respiratory tract infections were the most common diagnoses in our cohort, most of these caused by gram-positive pathogens. This suggests that systemic infection with gram-negative pathogens is more common than with gram-positive bacteria in our population, contrasting with findings in the United Stated and Australia, where gram-positive bacteria have been shown to be the predominant cause of sepsis.[10,11] One might speculate that a relative increase of infections with multi-resistant streptococci and staphylococci in these countries is causing the difference.[15,16]

Only a few risk factors for adverse outcome could be identified in this cohort. As could be expected, age was strongly correlated with hospitalisation, longer hospital stay and mortality. Older people were relatively more prone to bacterial infections as a cause of the fever. Although an immunocompromised state was associated with worse outcome, presence of diabetes mellitus or underlying malignancy did not result in higher mortality numbers or more ICU admissions. The lack of increase in mortality within these groups may be due to the small numbers of fatalities in the overall group. The absence of association between malignancy and ICU admission may be attributed to a selective admission policy to this ward.

A relatively low total of 213 febrile patients were identified during this one-year study. This low number is largely due to the inclusion criteria, defining fever as a tympanic temperature >38.2 °C as measured at the ED, thus excluding febrile patients who had taken acetaminophen prior to the ED visit. However, by excluding those patients with self-reported fever, a 'clean' cohort of febrile patients could be constructed, resulting in stronger conclusions.

In conclusion, we show that the implementation of a diagnostic protocol at the ED is feasible, resulting in a high percentage of confirmed diagnoses of febrile patients and enabling us to give an overview of the epidemiology of fever in this group. Overall, the outcome of patients presenting with fever at the ED in this hospital is rather benign, only few patients suffering an adverse outcome.

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