

A HOSPITAL-BASED STUDY OF BLOODSTREAM INFECTIONS IN FEBRILE PATIENTS IN DHULIKHEL HOSPITAL KATHMANDU UNIVERSITY TEACHING HOSPITAL, NEPAL

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Abstract. The etiology of bloodstream infections in febrile patients remain poorly characterized in Nepal. A retrospective study of febrile patients presenting to Dhulikhel Hospital Kathmandu University Teaching Hospital from July 2002 to June 2004 was performed to evaluate the etiology of bloodstream infections and the drug sensitivity patterns of cultured organisms. The medical and laboratory records of all febrile patients with an axillary temperature $\geq 38^{\circ}\text{C}$ who had a blood culture taken ($n=1,774$) were retrieved and analyzed. Of these, 122 (6.9%) patients had positive blood cultures, of which 40.1% were age 11 to 20 years. The male to female ratio was 1.7:1. Antibiotics had been taken prior to hospital presentation by 39 (32%) patients. *Salmonella enterica* serovar Typhi and serovar Paratyphi A were isolated in 50 (41.0%) and 13 (10.7%) cases, respectively. All *S. Typhi* and *S. Paratyphi* isolates were susceptible to ceftriaxone, while susceptibility to ciprofloxacin and chloramphenicol was recorded in 94.8% and 94.5% of cases, respectively. Cephalexin and amoxicillin had the lowest rates of susceptibility (64.2% and 54.1%, respectively). *Salmonella* spp were usually sensitive to chloramphenicol. These findings provide clinicians in this region of Nepal with a better understanding of the spectrum of pathogens causing bloodstream infections and will help guide empiric antibiotic choice.

INTRODUCTION

Fever is a common clinical challenge in the tropical setting. Primary infections, such as respiratory, urinary tract and gastro-intestinal, often result in bloodstream infections (BSI) and may cause fever. BSI due to bacterial and fungal pathogens affects over 200,000 individuals annually in the United States alone (Pittet *et al*, 1997; Reimer *et al*, 1997; Weinstein *et al*, 1997).

In Nepal, febrile illness is one of the most common reasons for medical consultation. The etiology of bloodstream infection in febrile patients is poorly characterized in Nepal, mainly due to limited laboratory resources, a poor recording system and an inadequate number of

trained personnel (Archibald *et al*, 1999; Murdoch *et al*, 2004). While the burden of some infections (*eg* enteric fever) is believed to be substantial, the importance of others, such as leptospirosis and rickettsial diseases, is undefined. The management of febrile patients may be assisted by the detection of BSI. Since blood is a normally sterile site, blood cultures, properly performed, have a positive predictive value for BSI (Archibald *et al*, 2000).

Salmonella enterica serovars Typhi and Paratyphi A are the leading microbial pathogens isolated in BSI in febrile patients in Nepal. This is endemic in the mountains, valleys and southern belts of Nepal, with a peak incidence between May and August (Malla *et al*, 2005). It is one of the leading causes of fever in most hospitals in Nepal (Hale *et al*, 1999). There have been reports of seasonal typhoid outbreaks, with a recent outbreak in 2002 occurring in Bharatpur,

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central Nepal. This multi-drug resistant typhoid epidemic affected more than 6,000 patients over a 4 to 5 week period (Lewis *et al*, 2005). There has been increasing concern about the emergence of multi drug resistant *S. Typhi* and *S. Paratyphi* in Nepal (Murdoch *et al*, 2004; Malla *et al*, 2005; Lewis *et al*, 2005).

In this study, we performed a retrospective hospital based study of febrile patients presenting in Dhulekhel Hospital Kathmandu University Teaching Hospital (DHKUTH) between July 2002 to June 2004, to define the etiology of BSI and drug sensitivity pattern of the cultured organisms.

PATIENTS AND METHODS

This retrospective study was conducted in Dhulekhel Hospital Kathmandu University Teaching Hospital, Nepal. This 200 bed hospital is located in a central hilly region of Nepal near Kathmandu, and provides inpatient, outpatient and emergency services in medical and surgical disciplines. Annually there are approximately 65,000 outpatient and emergency consultations and 4,500 admissions. The bed occupancy for the medical ward runs at >80% occupancy.

We reviewed the medical and laboratory records of all the patients who presented to Dhulekhel Hospital from July 2002 to June 2004 with an axillary temperature $\geq 38^{\circ}\text{C}$ and who had a blood culture taken. The information obtained from the records included age, sex, signs and symptoms, clinical findings, antimicrobial therapy and laboratory reports. The study protocol was approved by the Kathmandu University Teaching Hospital Ethical Review Committee.

Blood culture

Blood samples were inoculated into blood culture bottles (Hi Media Laboratories Mumbai, India) and incubated at 37°C for 5 days, or longer as clinically indicated. Routine sub-culture was performed after 24 hours and on day 4 onto blood agar (BA), MacConkey agar (MA) and chocolate agar (CA). In addition, subculture was performed when there was obvious turbidity in the broth at other time periods. BA and CA were incubated using a candle jar, and MA was incu-

bated at ambient atmosphere.

Identification of the cultured isolates was performed using standard laboratory methodology. Antibiotic susceptibility testing was performed for *S. Typhi* and *S. Paratyphi* isolates using the Kirby-Bauer disk diffusion method for ceftriaxone, ciprofloxacin, cephalexin, trimethoprim-sulfamethoxazole, chloramphenicol and amoxicillin.

RESULTS

Patients

Blood samples from a total of 1,774 patients with febrile illness were sent for culture during the study period. Of these, 122 (6.9%) cases had one or more positive blood cultures. A history of taking antibiotics prior to hospital presentation was recorded in 32% of culture positive patients (n=39).

The 11 to 20 year age group accounted for 40.1% of all positive cases (Fig 1). The male to female ratio was 1.7:1. The presenting clinical features are shown in Table 1. Common clinical symptoms included headache (89.3%), malaise (59%), chills (44.3%) and cough (38.6%).

Bacteriological study

Positive blood culture cases were further evaluated according to organism isolated (Table

Table 1
Presenting signs and symptoms of patients with positive blood cultures.

Signs/Symptoms	Numbers	%
Fever	122	100
Headache	109	89.3
Malaise	59	48.4
Chills	54	44.2
Cough	47	38.5
Abnormal abdominal findings ^a	27	22.1
Abnormal CNS findings	21	17.2
Abnormal chest findings	19	15.6
Splenomegaly	17	13.9
Skin lesions	14	11.5
Hepatomegaly	13	10.7
Diarrhea	11	9.0
Lymphadenopathy	7	5.7

^aExcluding organomegaly

Table 2
Distribution of pathogens isolated from positive blood cultures (n=122).

Pathogen	Numbers	%
<i>Salmonella</i> Typhi	50	41.0
<i>Salmonella</i> Paratyphi A	13	10.7
<i>Streptococcus pneumoniae</i>	14	11.5
Coagulase negative Staphylococci	19	15.6
<i>Staphylococcus aureus</i>	6	4.9
<i>Escherichia coli</i>	2	1.6
<i>Pseudomonas</i> spp	2	1.6
Others	16	13.1

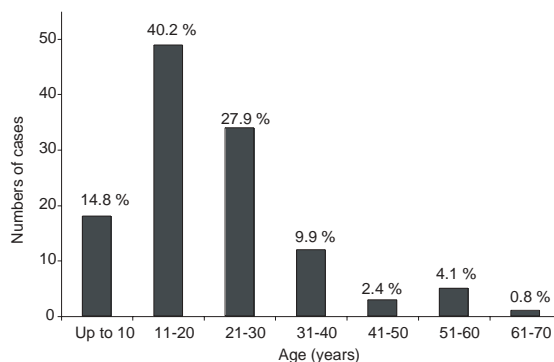


Fig 1—Age distribution of the febrile patients with positive blood cultures.

2) and their drug susceptibility pattern. Over half of the isolated organisms were *Salmonella* species (51.6%, n=63). *Salmonella* Typhi and *Salmonella* Paratyphi A accounted for 41% (n=50) and 10.7% (n=13) of all culture positive cases, respectively. Other organisms isolated were coagulase-negative staphylococci (15.6% n=19) and *Streptococcus pneumoniae* (11.5% n=14). No pathogenic fungi or mycobacteria cultures were performed.

Antimicrobial susceptibility testing

The results of *in-vitro* drug sensitivity testing revealed that all the isolates of *S. Typhi* and *S. Paratyphi* from the studied cases were susceptible to ceftriaxone (Fig 2). The majority of the isolates were also susceptible to ciprofloxacin (94.8%) and chloramphenicol (94.5). Only 82.2% of the isolates were sensitive to trimethoprim- sulfamethoxazole, while the susceptibilities to cephalexin and amoxicillin were 64% and 54%, respectively (Fig 2).

DISCUSSION

Microbiological services are essential elements in identifying BSI in febrile patients, monitoring changes in antimicrobial resistance and helping physicians in clinical decision making. In our study, the blood culture positivity rate was lower and the range of bloodstream pathogens was different from that reported in other similar studies from Africa and Asia (Ssali *et al*, 1998; Archibald *et al*, 1999, 2000; Biswas *et al*, 2004;

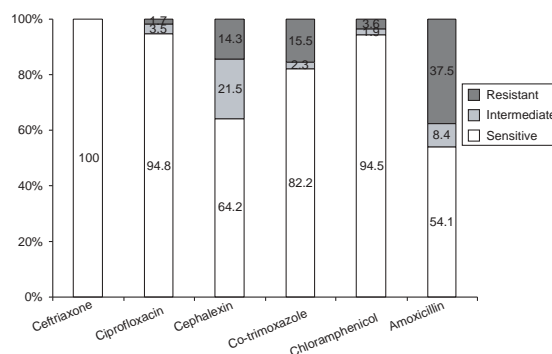


Fig 2—Antibiotic susceptibilities of *Salmonella* spp. Data are shown as %.

Murdoch *et al*, 2004; Malla *et al*, 2005). Febrile illnesses due to fungal or viral infection, which were common causes of fever in previous reports from Thailand and Malawi by Archibald *et al* (1999, 2000) were not detected due to limited clinical microbiological resources. Another limitation of our study was that a single blood culture was taken from each patient. Two or three sets per patient may have resulted in greater positivity rates (Tenney *et al*, 1982; Weinstein *et al*, 1983; NCCLS, 1997) and would have helped to determine whether any of the *Staphylococcus epidermidis* isolates were true positives rather than contaminants. However, various factors, such as difficult venous access and patient attitudes towards repeated blood tests in our setting significantly limits the possibility of obtaining more than one blood sample. In addition, a considerable number of patients had taken antibiot-

ics prior to hospital presentation (Murdoch *et al*, 2004), which significantly reduces the likelihood of a positive blood culture. Our study showed that 32% of patients reported having taken antibiotics prior to presentation. However, urinary antimicrobial activity, which could have confirmed the extent of antimicrobial use amongst the patients, was not assessed in this study. Antibiotics are sold as over the counter drugs in Nepal, and the vast majority of sales are made by inadequately trained personnel.

The high prevalence of *Salmonella* spp in bloodstream isolates in febrile patients in our study corresponds to the findings of previous studies performed in Nepal (Biswas *et al*, 2004; Murdoch *et al*, 2004). Enteric fever is one of the causes of fever in most of the hospitals in this country (Hale *et al*, 1999). Biswas *et al* (2004) reported that enteric fever accounted for 56.8% of all patients presenting with fever in a hospital from a western hilly region of Nepal. The relative isolation frequency of *S. Typhi* followed by *S. Paratyphi A* in the *Salmonella* spp isolates in our study correspond to previous reports (Murdoch *et al*, 2004; Malla *et al*, 2005). This does not have implications for therapy, but does have implications for vaccination strategies in that current typhoid vaccines do not protect against paratyphoid fever. Vollard *et al* (2004) concluded that there were distinct routes of transmission of typhoid and paratyphoid, with risk factors for disease either mainly within the household (typhoid) or outside the household (paratyphoid). Similar studies on this topic in Nepal are necessary to determine other differences in risk factors for typhoid and paratyphoid.

The drug susceptibility patterns for *Salmonella* spp to ceftriaxone, ciprofloxacin, ampicillin and trimethoprim-sulfamethoxazole in our study correspond to findings of previous studies (Sharma *et al*, 2003; Murdoch *et al*, 2004; Lewis *et al*, 2005; Malla *et al*, 2005). However, our results showed a higher sensitivity to chloramphenicol than described previously (Murdoch *et al*, 2004; Lewis *et al*, 2005; Malla *et al*, 2005). A second study in our setting also showed higher susceptibility rates for chloramphenicol (92.7%) (Sharma *et al*, 2003). Multi-drug resistance is plasmid mediated and several reports have sug-

gested the international transfer of R-plasmids is common. These plasmids, which belong to the Inc HI incompatibility group, frequently encode resistance to chloramphenicol, trimethoprim-sulfamethoxazole, ampicillin and tetracycline (Goldstein *et al*, 1986; Karmakar *et al*, 1991; Finch *et al*, 1992; Mirza and Itast, 1993). The sparing of chloramphenicol in the resistance pattern in our study demands a molecular assessment to determine the mechanism for this observation. Long-term disuse of chloramphenicol in medical practice may be one of the reasons for the relatively high rate of chloramphenicol susceptibility. Increasing rates of resistance to quinolones and decreased susceptibility to fluoroquinolones reported in some studies (Butt *et al*, 2003; Rahman *et al*, 2005) may make us consider chloramphenicol as an alternative drug for the treatment of resistant strains of *Salmonella*. However, further multi-center studies with molecular analyses are necessary to further evaluate this finding.

Coagulase-negative staphylococci were isolated during this study from 19 patients. One of the major challenges facing laboratories is to distinguish isolates causing disease from contaminant strains. One of the limitations of the current study is that relying on a single blood culture result makes this impossible. Bacteremia caused by coagulase-negative staphylococci is seldom life threatening if treated promptly, although frank sepsis syndrome may occur, especially in immuno-compromised patients and neonates (von Eiff *et al*, 2001).

The proportion of *Streptococci pneumoniae* in our study (11.5%) supports other reports that highlight pneumonia as an important cause of febrile illness (Archibald *et al*, 2000; Bell *et al*, 2001; Crump *et al*, 2003; Murdoch *et al*, 2004). The findings of contaminant organisms (*Enterococcus* spp, *Citrobacter* spp, *Micrococcus* spp, *Diphtheroids* and *Bacillus* spp) from the bloodstream isolates emphasize the need for appropriate clinical correlation with laboratory findings.

Bias of the physicians in selecting patients for blood culture may have influenced the ultimate outcome of our study. It is a general practice not to perform a blood culture when the diagnosis is highly suggested by other diagnostic

modalities, eg chest X ray in the case of pneumonia, and urine culture in the case of urinary tract infection. A multi-center prospective study with blood cultures for all the febrile cases is necessary to obtain more accurate information on BSI. The alarming trend of increasing antibiotic resistance, widespread misuse of antibiotics and the inconsistency in diagnostic and therapeutic protocols further necessitates a broader study. The findings of this study are not definitive and are not necessarily generalizable to the whole of Nepal. However, they give an indication of which major pathogens are causing BSI in febrile patients and their drug susceptibilities.

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