Does HIV status affect the aetiology, bacterial resistance patterns and recommended empiric antibiotic treatment in adult patients with bloodstream infection in Cambodia?

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Abstract

OBJECTIVE The microbiologic causes of bloodstream infections (BSI) may differ between HIV-positive and HIV-negative patients and direct initial empiric antibiotic treatment (*i.e.* treatment before culture results are available). We retrospectively assessed community-acquired BSI episodes in adults in Cambodia according to HIV status for spectrum of bacterial pathogens, antibiotic resistance patterns and appropriateness of empiric antibiotics.

METHODS Blood cultures were systematically performed in patients suspected of BSI in a referral hospital in Phnom Penh, Cambodia. Data were collected between 1 January 2009 and 31 December 2011.

RESULTS A total of 452 culture-confirmed episodes of BSI were recorded in 435 patients, of whom 17.9% and 82.1% were HIV-positive and HIV-negative, respectively. *Escherichia coli* accounted for one-third (n = 155, 32.9%) of 471 organisms, with similar rates in both patient groups. *Staphylococcus aureus* and *Salmonella cholereasuis* were more frequent in HIV-positive *vs.* HIV-negative patients (17/88 *vs.* 38/383 (P = 0.02) and 10/88 *vs.* 5/383 (P < 0.001)). *Burkholderia pseudomallei* was more common in HIV-negative than in HIV-positive patients (39/383 *vs.* 2/88, P < 0.001). High resistance rates among commonly used antibiotics were observed, including 46.6% ceftriaxone resistance among *E. coli* isolates. Empiric antibiotic treatments were similarly appropriate in both patient groups but did not cover antibiotic-resistant *E. coli* (both patient groups), *S. aureus* (both groups) and *B. pseudomallei* (HIV-negative patients).

CONCLUSION The present data do not warrant different empiric antibiotic regimens for HIV-positive *vs.* HIV-negative patients in Cambodia. The overall resistance rates compromise the appropriateness of the current treatment guidelines.

keywords Bloodstream infection, human immunodeficiency virus(HIV), adult, Cambodia

Introduction

Bloodstream infection (BSI) is an important cause of morbidity and mortality worldwide (Becker *et al.* 2009). For successful management of BSI, appropriate antimicrobial treatment is required, and the choice of the initial empiric antibiotic regimen (*i.e.* antibiotics given before the results of microbiological diagnosis and susceptibility testing are available) is particularly important (Houck *et al.* 2004; Garnacho-Montero *et al.* 2006; Kumar *et al.* 2006). The choice of empiric antibiotics relies on accurate knowledge of bacterial pathogens prevalent in a specific location and on their resistance patterns (Ibrahim *et al.* 2000).

For the management of BSI, clinical practice guidelines for empiric antimicrobial treatment have been written and implemented since January 2009 in the Sihanouk Hospital Center of HOPE (SHCH), a referral hospital in the capital Phnom Penh, Cambodia. These guidelines were based at that time on a literature review and a preliminary analysis of 18-months surveillance data of antimicrobial resistance in the hospital. However, these guidelines had not yet been validated in the patient population attending SHCH. In addition, published data

on BSI pathogens and their antibiotic resistance profiles in patients infected with the human immunodeficiency virus (HIV) in Cambodia are lacking.

Patients infected with HIV are at increased risk of bacterial infections with case-fatality rates of up to 32% in patients with CD4 counts less than 200 cells/μl (Tumbarello *et al.* 1995; Perello *et al.* 2010). Moreover, many HIV-positive patients are given primary cotrimoxazole (trimethoprim/sulphamethoxazole) prophylaxis, and exposure to this antibiotic might increase the risk of antibiotic resistance in a variety of bacterial pathogens that may infect this high-risk population (Gill *et al.* 2004).

The SHCH treatment guidelines for BSI are not different for HIV-positive *vs.* HIV-negative patients. The HIV prevalence in Cambodia in the general population was estimated at 0.8% in 2010 (NCHADS 2011). However, as SHCH also has a large HIV treatment programme, HIV-positive patients account for about 20% of the blood cultures performed in SHCH. In studies from sub-Saharan Africa and Thailand, HIV-positive patients presenting with BSI often had different bacterial pathogens and antibiotic resistance profiles compared with those who were HIV-negative (Ssali *et al.* 1998; Mootsikapun 2007). Therefore, empiric antibiotic treatment recommendations of the current SHCH guidelines might not be appropriate for HIV-positive patients.

The aim of this study was to determine, in adult patients presenting at SHCH with community-acquired BSI and stratified according to HIV status (i) the bacterial pathogens identified, (ii) their profile of antibiotic resistance, and (iii) the appropriateness of current empiric antibiotic treatments.

Method

Study design

This was a retrospective study using data prospectively collected into a logbook of the surveillance of BSI in SHCH between 1 January 2009 and 31 December 2011.

Study site

The SHCH is a referral hospital operated by a non-governmental organisation, situated in the Cambodian capital, Phnom Penh. Cambodia is a low-income country in South-East Asia with a population of around 14 million inhabitants.

SHCH provides free care to poor adult patients, including treatment of opportunistic infections and antiretroviral treatment (ART) for HIV-positive adult patients. The hospital has 35 in-patient beds and annually about 1 500 patients are admitted through self-referrals or referrals from other healthcare facilities nationwide. It also treats approximately 120 000 outpatients annually. By December 2011, more than 3 200 HIV-positive patients were alive in the cohort of patients cared for in the hospital, of whom 2 900 were eligible for ART and currently on treatment.

Since 2007, SHCH has implemented, in collaboration with the Institute for Tropical Medicine (ITM), Antwerp, Belgium, a surveillance of antimicrobial resistance by performing systematic blood cultures in all patients seen at the hospital and suspected of BSI. This collaboration has resulted in the development of clinical practice guidelines for the management of BSI, with recommendations for empiric and culture-based antimicrobial treatment. An antibiotic surveillance logbook was created to record all patients having a positive blood culture with clinically significant pathogens.

HIV treatment and care

Voluntary confidential counselling and testing for HIV (VCCT) is available at the hospital for patients presenting to the outpatient department or admitted to the wards and is recommended if clinicians suspect HIV infection. HIV screening is carried out using a parallel system with two rapid tests [Determine (Determine, Inverness Medical, Japan) and HIV-1/2 Stat-Pak (Chembio Diagnostics, USA)], and if there are discordant results, an ELISA test is used to confirm the diagnosis. CD4-lymphocyte counts are measured at baseline and every 6 months using a FACScount (Becton Dickinson, Franklin Lakes, NJ). ART is provided in line with WHO guidelines (CD4 $\leq$ 350/μl or WHO Clinical Stage 4 disease, and recently, WHO Clinical Stage 3 disease, regardless of the CD4 cell count) (WHO 2010).

Bloodstream infection surveillance and antibiotic treatment

Blood cultures are systematically carried out in all patients (HIV-positive and HIV-negative) who present with systemic inflammatory response syndrome (SIRS). SIRS is defined as the presence of at least two of the following signs: fever/hypothermia (temperature <35 or >38 °C), tachycardia (heart rate >90 beats/min), tachypnea (respiratory rate >20/min) and hypo- or hyper-leukocytosis (white cells count <4 000 or >12 000/μl). In each patient, 2 × 10 ml of venous blood is drawn into BacTalert vials (bioMérieux Marcy l'Etoile, France) and incubated for 7 days at 35 °C while visual inspection of the chromogenic growth indicator is used for growth

monitoring. Identification to species level is performed using standard microbiological techniques. Antibiotic resistance testing is performed using disc diffusion with the additional use of the *E*-test (bioMérieux) for penicillin in *Streptococcus pneumoniae* and double-disc testing for extended-spectrum beta-lactamase (ESBL) production. Nalidixic acid resistance is used as a screening test for decreased ciprofloxacin susceptibility. All tests are performed according to Clinical Laboratory Standards Institute guidelines (CLSI 2012).

Patients with suspected BSI are treated with empiric antibiotics according to the SHCH guidelines. These guidelines are the same for HIV-positive and HIV-negative patients, except when *Pneumocystis jiroveci* pneumonia is suspected. When blood culture results are available, clinicians modify the empiric antibiotics according to the pathogen or its resistance pattern. If patients are not hospitalised, they are contacted by telephone. The liaison between the laboratory and the clinical wards is assured by two appointed clinicians who keep records in the logbook. This logbook contains basic demographic and clinical information as well as changes in antibiotic therapy and patients' outcome at discharge or at the end of treatment for ambulatory patients (at 7–14 days). The quality of the logbook data is routinely checked at regular intervals by an infectious diseases supervisor.

Study participants and study period

All adult patients aged 18 years or above with confirmed BSI based on positive blood culture seen in the SHCH and recorded between January 2009 and December 2011 were included. As the guidelines were essentially developed to guide treatment of community-acquired infections, BSIs that were hospital-acquired (occurring $\geq$48 h after admission) were excluded.

Definition of BSI episode and recurrent infection

We identified BSI as the presence of a clinically significant pathogen isolated from blood cultures. Isolates considered as contaminants were coagulase negative staphylococci, *Bacillus* species and *Corynebacterium* species. Repeat culture of an identical pathogen (same species and/or serotype) was considered as follows: if the repeat culture was performed within 14 days after the first one, both isolates were considered to be part of a single BSI episode; if the repeat culture was performed more than 14 days after the initial one, the repeat isolate was considered as part of a new BSI and called a recurrent infection.

Source of data, data variables and validation and data collection

The following variables were collected from the logbook: demographic data (age, sex), suspected focus of infection, duration of hospitalisation prior to sample collection, HIV status and other comorbidities, antiretroviral drugs used, empiric antibiotic treatment given, final bacterial identification, antibiotic resistance patterns, appropriateness of empiric antibiotic treatment, any change in the antibiotic treatment and its rationale, and outcome.

The appropriateness of empiric antibiotics was defined as a 'match' if the spectrum of the empiric antibiotics covered the isolated pathogen(s), and no antibiotic resistance had been demonstrated. A mismatch was considered when (i) if the spectrum of the empiric antibiotic did not cover the pathogen (such as in the case of amoxicillin and *Burkholderia pseudomallei*) or (ii) if the pathogen showed resistance to the antibiotic (such as in the case of methicillin-resistant *Staphylococcus aureus* and oxacillin).

Data analysis and statistics

Data from the logbook were single-entered into EPIDATA version 3.1 and checked for accuracy by comparing the logbook and laboratory database. EPIDATA data were transferred by Stat/Transfer software into STATA version 11.1 for analysis. For demographic and clinical data, we used as denominator either the number of patients with BSI or the number of BSI episodes where applicable, and for microbiological data, the total number of bacteria. Bacterial resistance rates were calculated using the 'first' (*i.e.* non-recurrent) isolates. Descriptive analysis was used to calculate the frequency and proportion of demographic and clinical/microbiological data. The chi-squared test or Fisher's exact test was used to compare differences in proportions and *t*-test for comparing the continuous data between HIV-positive and HIV-negative patients. All statistical tests were two sided, and statistical significance was defined as $P < 0.05$.

Ethics

The data collection was part of the study on 'surveillance of antibiotic resistance in the hospital' which was approved by the Institutional Review Board ITM (Institute of Tropical Medicine, Antwerp) and the Cambodian National Ethics Committee for Health Research. This protocol was approved by the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease, Paris, France. Also, this study met the Médecins

Sans Frontières' Ethics Review Board-approved criteria for analysis of routinely collected programme data.

Results

Figure 1 presents a flow chart of the study and the breakdown between HIV-positive and HIV-negative patients. Overall, 5 457 episodes of community-acquired SIRS were included, which yielded 452 culture-confirmed episodes of BSI in 435 patients, of whom 17.9% were HIV-positive and and 82.1% HIV-negative. The rate of clinical significant organisms did not differ between both groups. Twenty episodes (4.4%) were polymicrobial; 4 patients had second episodes of BSI with different isolates and 13 patients had recurrent BSI (one patient had two recurrences); the resulting total number of clinically significant organisms was 471.

Patient characteristics

Table 1 shows the characteristics of HIV-positive and HIV-negative patients with BSI. HIV-positive patients were significantly younger and had less comorbidity, particularly diabetes and liver cirrhosis. Gastrointestinal, respiratory and urinary tract infections were the three most common presumed foci of BSI. There were no differences in the presumed foci between BSI in HIV-positive *vs.* HIV-negative patients. For the HIV-positive patients, median CD4 count was 159 (IQR 45–256) cells/μl; 51 (60.0%) episodes occurred in patients on ART, and 22 (25.6%) patients were on cotrimoxazole prophylaxis. For HIV-positive and HIV-negative patients combined, exposure to antibiotics prior to blood sampling was seen in 51.8%, with no difference among both groups.

Aetiology of bloodstream infections

Table 2 displays the relative frequencies of the bacterial pathogens. Gram-negative pathogens were more common than Gram-positive bacteria in both HIV-positive and HIV-negative patients. *Staphylococcus aureus* was the most common Gram-positive pathogen, and it was more frequent in HIV-positive patients (19.3% vs. 9.9% in HIV-negative patients; $P = 0.02$). Among the Gram-negative pathogens, *Escherichia coli* and *Salmonella choleraesuis* were the two leading species in HIV-positive patients (30.7% and 11.4%, respectively), whereas *Escherichia coli* and *Burkholderia pseudomallei* were predominant in HIV-negative patients (33.4% and 10.2%, respectively). Ten of 19 *Salmonella* species (52.6%) were *Salmonella choleraesuis* among

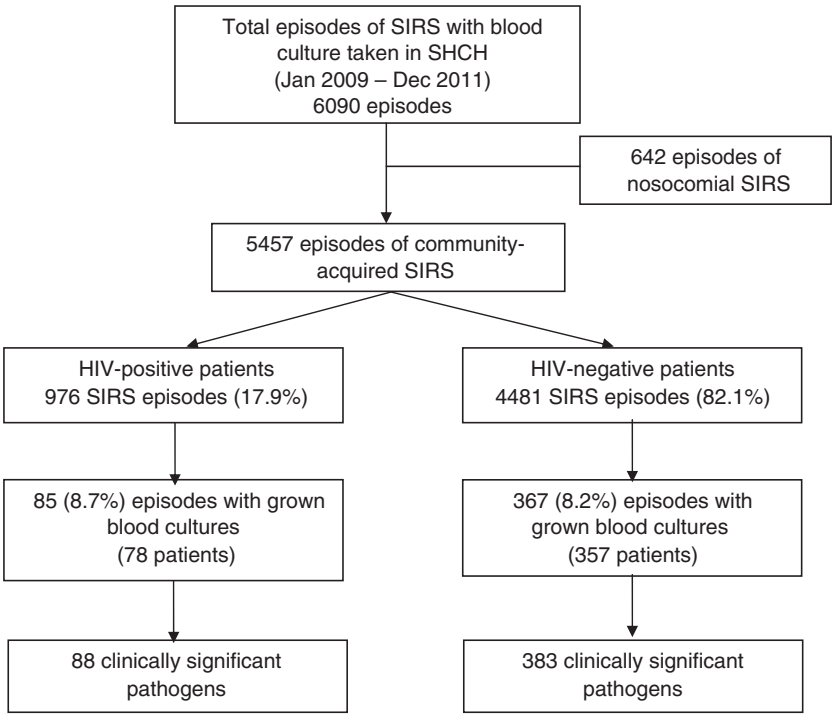

Figure 1 Flowchart of the patients with systemic inflammatory response syndrome (SIRS) included in the study, 2009-2011.

Table 1 Characteristics of patients with bloodstream infection (BSI) presenting to SHCH according to HIV status, 2009–2011; (n = 435)

	HIV-positive n = 78	HIV-negative n = 357	p-value
Sex; n (ratio)			
Male: Female	36:42 (0.86)	158:199 (0.79)	0.76
Mean age, years (SD)	40.8 (10.9)	48.1 (16.4)	<0.001
Comorbidity; n (%)			
Diabetes	3 (3.9)	71 (19.9)	<0.001
Liver cirrhosis	2 (2.6)	52 (14.6)	0.002
Chronic renal failure	2 (2.6)	14 (3.9)	0.75
Exposure to antibiotics within 14 days prior to blood culture sampling of BSI episodes*; n (%)			
Cotrimoxazole prophylaxis	22/85 (25.6)	0	–
Total exposure to antibiotics	47/85 (55.3)	187/452 (50.9)	0.47
Antiretroviral therapy at the time of BSI; n (%)	51/85 (60.0)	NA	-
Presumed focus of BSI†; n (%)	102	427	0.63
Gastro-enteric infection	50 (49.0)	193 (45.2)	
Respiratory infection	22 (21.6)	84 (19.7)	
Urinary tract infection	13 (12.8)	67 (15.7)	
Skin and soft tissue infection	14 (13.7)	41 (9.6)	
Central nervous system infection	2 (2.0)	18 (4.2)	
Fever without clear source	1 (0.8)	8 (1.7)	
Osteo-articular infection	0 (0)	8 (1.7)	
Deep organ abscess	0 (0)	8 (1.7)	
Endocarditis	0 (0)	2 (0.4)	

IQR: Inter-quartile range, SD: standard deviation.
*Some patients had more than one episode of BSI.
†Some patients had more than one presumed focus of infection.

HIV-positive patients; in HIV-negative patients 5/31 (16.1%) were *Salmonella choleraesuis*.

Antibiotic resistance patterns

The resistance patterns of the key pathogens are shown in Table 3. Overall resistance rates for commonly used antibiotics were very high, especially among the Gram-negative pathogens. In particular, we noted in both HIV-positive and HIV-negative patients high rates (46.4%) of ceftriaxone resistance in *E. coli* and very high rates (87.0%) of decreased ciprofloxacin susceptibility in *Salmonella typhi*. Ciprofloxacin susceptibility appeared to be more preserved in the non-Typhoid *Salmonella* species. *Staphylococcus aureus* infecting HIV-positive patients tended to display resistance to oxacillin and cotrimoxazole more frequently.

Appropriateness of empiric antibiotic treatment and subsequent treatment changes

Overall, the proportions of appropriate empiric treatment were fairly similar for both patients groups (Table 4a). There were more mismatches due to resistance in the HIV-positive group, but this difference did not reach statistical significance. For this type of mismatch, antibiotic-resistant *E coli* was the main contributor in both groups (64.0%; 16/25 and 77.9%; 60/77 of such episodes in HIV-positive and HIV-negative individuals, respectively). Mismatch due to the fact that the empiric antibiotic regimens did not cover the putative pathogen was equally common in both groups. For HIV-positive individuals, this most commonly involved BSI with *Staphylococcus aureus* (4/16; 25.0%). In HIV-negative individuals, *Burkholderia pseudomallei* was most commonly implicated (26/77; 33.8%), followed by *Staphylococcus aureus* (11/64; 17.2%).

Empiric treatment was somewhat more frequently modified in HIV-positive than HIV-negative patients, most commonly because it did not cover the resistance pattern or the pathogen properly (Table 4b). Of note, of 41 BSI episodes in HIV-positive patients who had inappropriate empiric antibiotic treatment (mismatches), 13 (31.7%) failed to get modified treatment (no antibiotic change) compared with 65 of 152 (42.7%) in HIV-negative patients. This was because patients died

Table 2 Distribution of bacterial pathogens causing bloodstream infection according to HIV status in SHCH, 2009–2011 (n = 471)

Organisms	HIV-positive; n (%) (n = 88)	HIV-negative; n (%) (n = 383)
Gram-negative bacteria		
Escherichia coli	27 (30.7)	128 (33.4)
Salmonella choleraesuis	10 (11.4)	5 (1.3)
Other Non-Typhoid *Salmonella* species	6 (6.8)	3 (0.8)
Salmonella typhi	2 (2.3)	21 (5.5)
Salmonella paratyphi A	0	2 (0.5)
Klebsiella species	5 (5.7)	28 (7.3)
Enterobacter species	3 (3.4)	4 (1.0)
Burkholderia pseudomallei	2 (2.3)	39 (10.2)
Pseudomonas species	3 (3.4)	4 (1.0)
Acinetobacter species	3 (2.9)	4 (1.0)
Other Gram-negative bacteria	8 (9.1)	32 (8.4)
Gram-positive bacteria		
Staphylococcus aureus	17 (19.3)	38 (9.9)
Streptococcus pneumoniae	0 (0)	8 (2.1)
Streptococcus suis	1 (1.1)	9 (2.4)
Other streptococci	0 (0)	28 (7.3)
Enterococci	1 (1.1)	12 (3.1)
Other Gram-positive bacteria	1 (1.0)	15 (3.5)

Note: some patients had two or more pathogens (435 patients; 471 isolates).

before the results of culture and antibiotic susceptibility were communicated in 6/13 (46.2%) BSI episodes in HIV-positive and 44/65 (67.7%) BSI episodes in HIV-negative patients.

Treatment outcomes

Overall mortality was 21.5% (97/452). As can be seen in Table 5, there was no difference in patient outcomes at the end of treatment (as noted at day 7 or day 14), in the HIV-positive and HIV-negative patients. We found higher rates of recurrent infections in the HIV-positive group (10.3% *vs*. 2.3%; P = 0.003): Five were caused by *Escherichia coli* (3.2%; one HIV-positive), 3 by *Salmonella choleraesuis* (20%; two HIV-positive), four *by Staphylococcus aureus* (7.3%; two HIV-positive) and one by *Aeromonas sp*. (in an HIV-positive patient).

Discussion

This study describes the prevalence of bacterial pathogens and their resistance patterns causing BSI in adult patients with and without HIV. Overall, pathogens and resistance distribution were fairly similar between the two patient groups. *E. coli* was the most common pathogen in both groups and occurred with comparable frequency. However, particular pathogens were more prevalent in some patient groups. *Salmonella choleraesuis* and *S. aureus* were more common in HIV-positive patients, while *B. pseudomallei and Salmonella typhi* occurred predominantly in HIV-negative patients. Possibly, older age and higher frequency of comorbidity in the HIV-negative patients might have increased their risk of melioidosis – the disease caused by *B. pseudomallei*. Melioidosis was recently found to be endemic in Cambodia (Vlieghe *et al.* 2011a).

In general, Gram-negative pathogens predominated in our study in both HIV-positive and HIV-negative patients, as has been described in other studies on BSI in tropical low-resource settings (Archibald *et al.* 2000; Phetsouvanh *et al.* 2006). In line with our findings, studies from Thailand (Srifuengfung *et al.* 2005; Mootsikapun 2007) also reported a high prevalence of *Salmonella* species in HIV-positive patients and of *Burkholderia pseudomallei* in HIV-negative patients. However, in the Thai studies, *E. coli* occurred less frequently in HIV-positive patients, while we found this isolate the most common cause of BSI in both HIV-positive and HIV-negative patients. A recent systematic review of BSI in developing countries in South and South-East Asia, mainly including HIV-negative individuals, also reported a high proportion of Gram-negative isolates of which *Salmonella typhi* was the most common pathogen in adults patients (Deen *et al.* 2012). The predominance of Gram-negative pathogens contrasts with reports from North America and European BSI studies in HIV-positive patients, where Gram-positive bacteria were more common (Fichtenbaum *et al.* 1995; Ortega *et al.* 2008).

Table 3 Antibiotic resistance of key pathogens* according to HIV status in SHCH, 2009–2011

	HIV-positive *n* (%)	HIV-negative *n* (%)
Escherichia coli	*n* = 26	*n* = 125
Amoxicillin	25 (96.2)	117 (93.3)
Cotrimoxazole	21 (80.8)	104 (83.2)
Ciprofloxacin	16 (61.5)	97 (77.6)
Amoxicillin-clavulanic acid	15 (57.7)	61 (48.8)
Ceftriaxone	12 (46.2)	58 (46.4)
Gentamicin	15 (57.7)	63 (50.4)
Amikacin	2 (7.7)	1 (0.8)
Meropenem	0 (0)	0 (0)
Salmonella typhi	*n* = 2	*n* = 21
Amoxicillin	1	15 (71.4)
Cotrimoxazole	1	15 (71.4)
Ciprofloxacin	2	18 (85.7)
Ceftriaxone	0	0
Meropenem	0	0
Non-Typhoid *Salmonella* species	*n* = 15	*n* = 7
Amoxicillin	12 (80.0)	6 (85.7)
Cotrimoxazole	9 (60.0)	4 (57.1)
Ciprofloxacin	6 (40.0)	3 (42.9)
Ceftriaxone	1 (6.7)	1 (14.3)
Meropenem	0	0
Staphylococcus aureus	*n* = 14	*n* = 37
Oxacillin	4 (28.6)	7 (18.6)
Cotrimoxazole	4 (28.6)	3 (8.1)
Lincomycin	6 (42.9)	17 (46.0)
Ciprofloxacin	3 (21.4)	8 (21.6)
Vancomycin	0	0

*Only isolates from the first episodes of bloodstream infection were considered.

This might be due to the lower rate of intravenous drug users and patients with medical devices (*e.g.* prosthesis and catheters) in our cohort as well as the high prevalence of Gram-negative pathogens in the environment of tropical low-resource countries (Kaushik *et al.* 2012). Data from BSI in Ugandan HIV patients described a high prevalence of *Streptococcus pneumoniae* followed by non-Typhoid *Salmonella* species and *E. coli* (Mayanja *et al.* 2010). The relative paucity of *Streptococcus pneumoniae* in our population may be due to the intrinsic difficulty to cultivate this fastidious organism (especially given the high rates of antibiotic use prior to sampling, also in the community), a different study population (different level of CD4 cell counts, no children included) or genuine differences in local microbiological ecology.

In the present study, cases in which the empiric treatment did not cover the isolated pathogen were observed in around 20% of BSI episodes, with *S. aureus* and *B. pseudomallei* accounting for over half of them. It remains to be assessed whether clinical practice guidelines can be further improved or whether this could be overcome by more accurate clinical evaluation prior to the selection of empiric antibiotics. In-depth evaluation of the adherence to the established guidelines should also be performed. All these issues will be the focus of future research.

We found overall high resistance rates of the key pathogens to the commonly used antibiotics in both HIV-positive and HIV-negative patients, especially among the Gram-negative pathogens. This confirms previous findings from our hospital (Vlieghe *et al.* 2011b, 2012) and other settings in Cambodia (Ruppe *et al.* 2009) and is in line with findings from other countries in the region (Apisarnthanarak *et al.* 2007; Chau *et al.* 2007). Other reports from Asia have shown relatively lower resistance rates for the key pathogens (Srifuengfung *et al.* 2005; Mootsikapun 2007; Deen *et al.* 2012). More microbiological studies from a wide range of settings should be conducted in this region, to better define how rates of resistance vary across and within countries and populations. This requires ongoing efforts in implementing and strengthening diagnostic microbiological capacities in the region.

In terms of broader public health implications, the observed high resistance rates seriously compromise the treatment options for community-acquired BSI in both HIV-positive and HIV-negative patients in Cambodia. Based on the microbiological data, more than 30% of individuals with BSI in SHCH would require treatment with expensive antibiotics that are usually not available

Table 4-a Appropriateness of empiric antibiotic treatment in 452 episodes of bloodstream infection in SHCH, 2009–2011

	HIV-positive n (%) (*n* = 85)	HIV-negative n (%) (*n* = 367)	*p*-value
Antibiotic matches the pathogen and susceptibility pattern	43 (50.6)	206 (56.1)	0.35
Antibiotic matches the pathogen but not the susceptibility pattern	25 (29.4)	77 (21.0)	0.11
Antibiotic does not match the pathogen	16 (18.8)	75 (20.4)	0.88
No empiric antibiotics prescribed	1 (1.2)	9 (2.5)	0.70

Table 4-b Changes of empiric antibiotic treatment and associated reasons in 442 episodes of bloodstream infection*

	HIV-positive*n* (%)	HIV-negative*n* (%)	*P*-value
Total episodes of antibiotic changes	41/84 (48.8)	137/358 (38.3)	0.08
Reason for change of empiric antibiotic (*n*=178)	*n* = 41	*n* = 137	
Empiric antibiotic not appropriate for the pathogen	10 (24.4)	50 (36.5)	0.19
Organism resistant to empiric antibiotic	19 (46.3)	47 (34.3)	0.20
Antibiotic simplification (step down to smaller spectrum antibiotic)	10 (24.4)	31 (22.6)	0.83
Change to IV antibiotic (clinical deterioration)	2 (4.9)	9 (6.6)	1.0

*Excluding 10 episodes for which no empiric antibiotic treatment had been installed.

in public hospitals in Cambodia. Our findings stress the urgent need for sustainable and affordable access to broad-spectrum antibiotics such as carbapenem antibiotics (*e.g.* for ESBL-positive *E. coli*), ceftazidime and amoxicillin–clavulanic acid (*i.e.* for the treatment of melioidosis) and vancomycin (*i.e.* for treatment of invasive MRSA infections). This should go hand in hand with the development of tools to optimise appropriate use of antibiotics, including improved diagnostic capacity or clinical scoring systems to predict antibiotic resistance (Bowman *et al.* 2012) while antibiotic stewardship and infection control programmes at local and national levels will be essential to prevent the occurrence and spread of antibiotic resistance.

Our study had a number of limitations. First, the baseline characteristics of the HIV-positive and negative patient groups were not truly comparable. HIV-negative patients were older and had more underlying diseases, especially diabetes, liver cirrhosis and chronic renal failure, making this group vulnerable to specific infections (such as melioidosis) and worse outcomes. Therefore, our findings may not be easily applicable to other settings where HIV-negative patients have lower rates of underlying diseases. In addition, our sample size was fairly small, especially for HIV-positive patients, and the antibiotic resistance data were based on routinely collected data and not on prospective batch-testing of isolates. Moreover, only short-term outcome data were available. Although, based on ongoing supervision, adherence to the clinical guidelines in the hospital appeared to be good, we did not evaluate whether all empiric antibiotic prescriptions were in line with the clinical practice guidelines. Finally, we selected only bacterial and not fungal or mycobacterial pathogens, which are important pathogens in HIV-positive patients (Archibald *et al.* 2000). A strength of our study relates to the fact that data originate from a microbiological surveillance setting where blood cultures were systematically performed for all patients meeting the criteria of sepsis. Moreover, patients came from different areas of the country.

Table 5 Treatment outcome of 452 episodes of bloodstream infection according to HIV status, SHCH, 2009–2011

	HIV-positive	HIV-negative	*p*-value
Cured	68 (80.0)	277 (70.0)	0.06
Died/discharged for palliative care at home	16 (18.8)	81 (22.1)	0.39
Transferred out (to other hospitals)	1 (1.2)	23 (6.3)	0.06
Unknown	0 (0)	6 (1.6)	0.59
Recurrence	7 (10.3)	6 (2.3)	0.003

In conclusion, *Salmonella choleraesuis* and *Staphylococcus aureus* were relatively more common in HIV-positive patients than in HIV-negative patients and were likely to recur. Resistance rates were high but not significantly different between the HIV-positive and HIV-negative groups. The present data do not warrant different empiric antibiotic regimens for HIV-positive *vs.* HIV-negative patients. Further analysis of the mismatches of empiric antibiotic prescriptions in SHCH is warranted while the antibiotic resistance data suggest the need for nationwide enhanced diagnostic capacity, access to effective antibiotics and regulatory measures to contain antibiotic resistance in Cambodia.

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