Antibiotic Resistance among Pathogens Causing Disease in Jamaican Children with HIV/AIDS

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ABSTRACT

Objective: *There are limited data regarding the antimicrobial resistance patterns of pathogens in children with HIV/AIDS from developing countries. We aimed to determine the prevalence and antibiotic susceptibility patterns of bacterial pathogens causing urinary tract infections (UTIs) and sepsis in a cohort of 219 HIV-infected Jamaican children.*

Methods: *This cross-sectional study examined clinical and microbiological data for children enrolled in the Kingston Paediatric/Perinatal HIV/AIDS programme from September 1, 2002 to May 31, 2007. Cases were defined as physician-diagnosed, laboratory confirmed UTIs and sepsis based on Centers for Disease Control and Prevention (CDC) criteria. Only isolates from urine, blood and sterile sites were considered.*

Results: *Forty-four patients (20.1%) accounted for 74 episodes of UTIs and sepsis. Mean number of infections was 1.7 ± 1.3 per patient. There were 31 males (70.5%) and mean age at time of infection was 5.6 ± 4.7 years. Bacterial infections comprised cystitis (n = 52, 70.3%), bacterial pneumonia (n = 15, 20.3%), meningitis (n = 4, 5.4%), septicaemia (n = 2, 2.7%) and bone infection (n = 1, 1.4%). Among 52 UTIs, 39 were caused by a single organism. The most common UTI isolates included* Escherichia coli *(n = 21, 53.8%) and* Enterobacter *spp (n = 5, 12.8%). Among 22 cases of sepsis, isolates included* Streptococcus pneumoniae *(n = 8, 36.4%) and coagulase negative* Staphylococcus *(n = 6, 27.3%). All* E coli *isolates at two of three clinical sites were resistant to cotrimoxazole. There were 79.7% (n = 51) of infectious episodes with a cotrimoxazole-resistant organism occurring among those on cotrimoxazole prophylaxis.*

Conclusions: Escherichia coli *was the most frequent bacterial isolate. Cotrimoxazole is a poor choice for empiric treatment of sepsis and UTIs in this clinical setting.*

Key words: Antibiotic resistance, bacterial pathogens, bacterial sepsis, paediatric HIV/AIDS, Jamaica, urinary tract infection

Resistencia Antibiótica Entre los Patógenos que Causan Enfermedades en los Niños Jamaicanos con VIH/SIDA

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RESUMEN

Objetivo: *Los datos existentes en relación con los patrones de resistencia antimicrobiana en los niños con VIH/SIDA de los países en vías de desarrollo, son limitados. Nuestro objetivo fue determinar la prevalencia y los patrones de susceptibilidad antibiótica de los patógenos bacterianos que causan*

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infecciones de las vías urinarias (IVU) y sepsis en una cohorte de 219 niños jamaicanos infectados con VIH.

Métodos: *Este estudio transversal examinó datos clínicos y microbiológicos de niños enrolados en el programa KPAIDS del 1ero. de septiembre de 2002 al 31 de mayo de 2007. Los casos se definieron como IVU y sepsis de diagnóstico médico, confirmada en el laboratorio, a partir de criterios de los Centros de Control y Prevención de Enfermedades (CCE). Solamente se tuvieron en cuenta aislados de orina, sangre y sitios estériles.*

Resultados: *Cuarenta y cuatro pacientes (20.1%) dieron lugar a 74 episodios de IVU y sepsis. El número promedio de infecciones fue 1.7 ± 1.3 por paciente. Hubo 31 varones (70.5%) y la edad promedio en el momento de la infección fue 5.6 ± 4.7 años. Las infecciones bacterianas abarcaron: cistitis (n = 52, 70.3%), pulmonía bacteriana (n = 15, 20.3%), meningitis (n = 4, 5.4%), septicemia (n = 2, 2.7%) e infección ósea (n = 1, 1.4%). De las 52 IVU, 39 fueron causadas por un solo microorganismo. Los aislados más comunes de IVU incluyeron* Escherichia coli *(n = 21, 53.8%) y* Enterobacter *spp (n = 5, 12.8%). De los 22 casos de sepsis, los aislados incluyeron* Streptococcus pneumoniae *(n = 8, 36.4%) y* Staphylococcus *coagulasa negativo (n = 6, 27.3%). Todos los aislados de* E coli *en dos o tres sitios clínicos eran resistentes al cotrimoxazol. Se produjeron 79.7% (n = 51) episodios infecciosos con un organismo resistente al cotrimoxazol entre los pacientes que se hallaban bajo profilaxis con cotrimoxazol.*

Conclusiones: Escherichia coli *fue el aislado bacteriano más frecuente. El cotrimoxazol es una opción pobre para el tratamiento empírico de sepsis e IVU en esta situación clínica.*

Palabras claves: Resistencia antibiótica, patógenos bacterianos, sepsis bacteriana, VIH/SIDA pediátrico, Jamaica, infección de las vías urinarias

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INTRODUCTION

Antibiotic resistance is increasing worldwide (1). While bacterial pathogens and antibiotic susceptibility patterns vary by geographic region and disease entity, little is known about the antibiotic susceptibility patterns of invasive bacterial pathogens in HIV-infected children in developing countries (2). To guide appropriate antibiotic use, the prevalence of invasive bacterial infections and the antibiotic susceptibility patterns of bacterial pathogens causing urinary tract infections (UTIs) and sepsis in HIV-infected Jamaican children were determined.

Background

In Jamaica, AIDS is the second leading cause of death for children ages one to four years (3). The Kingston Paediatric/Perinatal HIV/AIDS (KPAIDS) initiative, a collaboration between the Ministry of Health and the University of the West Indies, provides healthcare for pregnant women and their HIV-exposed and HIV-infected children and adolescents in Jamaica (4). Beginning September 2002 to August 2005, the KPAIDS initiative reduced the risk of mother-to-child transmission of HIV (MTCT) from 29% to 6% (RR 0.27; 95% CI 0.10, 0.68) using the combination of zidovudine and single-dose nevirapine. In 2007, the use of highly active antiretroviral therapy further reduced MTCT rates to an estimated 1.6% (5). In 2004, pulmonary tuberculosis and *Pneumocystis jirovecii* pneumonia (PCP) were the most frequently detected opportunistic infections in 110 children with HIV/AIDS. *Escherichia coli* was the most common cause of UTIs, *Streptococcus pneumoniae* was the most common bacterial pathogen causing community-acquired sepsis, and coagulase negative *Staphlylococcus* was an important cause of nosocomial sepsis (6). A 2008 study reported *E Coli*, *Streptococcus* Group D and *Klebsiella pneumoniae* to be the most common causes of UTIs in this cohort (7). To prevent PCP, community-acquired sepsis, bacterial pneumonia and otitis media, cotrimoxazole prophylaxis is given to all HIV-infected and HIV-exposed infants beginning at 4–6 weeks of age (6).

Children infected with HIV have increased susceptibility to recurrent bacterial infections, including UTIs and sepsis (6, 8). The optimal treatment of UTIs and bacterial sepsis mandates the need for early determination of the antimicrobial susceptibility profile of organisms that cause infection (2, 8).

Many developing countries have antimicrobial susceptibility patterns that create barriers to adequate treatment for recurrent and severe infections seen in HIV-infected children (1). Since patients often cannot afford to pay for complex regimens of expensive antibiotics, there is often inadequate therapy for resistant pathogens (1). The development of antimicrobial resistance to cotrimoxazole has been associated with its widespread use and affordability (1).

Despite widespread antibiotic use for treatment and prophylaxis, there has been little research done in the Caribbean on bacterial resistance to commonly prescribed antibiotics. We aimed to: a) identify the most frequent types of invasive and semi-invasive (UTI) infections in paediatric

patients with HIV/AIDS, b) identify their most common aetiologic pathogens c) identify their susceptibility patterns, and d) propose recommendations for the empirical therapy of HIV-infected paediatric patients with UTI and sepsis in this setting.

SUBJECTS AND METHODS

In this cross-sectional study, clinical and microbiological data for children enrolled in the KPAIDS Initiative from September 1, 2002 to May 31, 2007 were examined. The medical records of 219 HIV-infected patients were reviewed for occurrences of UTIs and bacterial sepsis at three KPAIDS sites: University Hospital of the West Indies (UHWI), Bustamante Hospital for Children (BHC) and Spanish Town Hospital (STH).

A subject with HIV-infection was defined as a child > 18 months of age who was identified as being HIV antibody-positive using the enzyme-linked immunosorbent assay (ELISA) and a confirmatory test (Western Blot) [6]. Also, any child < 18 months of age born to a HIV-infected mother was considered HIV-infected if found to have symptoms fulfilling criteria for the acquired immunodeficiency syndrome (AIDS) based on the 1987 AIDS surveillance case definition and/or if confirmed by a positive HIV DNA polymerase chain reaction test (Roche® DNA Ampiclor per test) [6].

Cases were defined as physician-diagnosed, laboratory- confirmed episodes of UTIs and bacterial sepsis based on Centers for Disease Control and Prevention (CDC) criteria. Only isolates from urine, blood and other sterile sites were assessed (9). All episodes of UTIs were counted, but for the purposes of analysis only, UTIs caused by a single organism were included, unless otherwise noted. Bacterial pathogens were identified and antibiotic susceptibility testing was performed using standard microbiological procedures and an automated system (Vick®, BioMerieux Vitek Inc, Hazelwood, Missouri, USA) [10].

Demographic variables assessed included: age at time of infection, gender, parish of residence, clinic attended and mode of HIV transmission. Clinical variables assessed included: CDC clinical category and CDC immunological category at time of infection, length of hospital admission, length of intravenous (IV) antibiotic treatment, length of oral (PO) antibiotic treatment, causative bacterial pathogen by type of infection, antibiotic susceptibility patterns of the causative organism, previous antibiotic use and clinical outcome (death, resolution, recurrent infection).

Previous antibiotic use was assigned to one of two categories: for prophylaxis or for treatment. The empiric antibiotic chosen for initial treatment was also noted, as was the ultimate antibiotic choice. Clinical outcome was defined as: death, resolution, single infection, recurrent infection with the same bacterial species or recurrent infection with another species. Recurrent infection was defined as a bacterial infection occurring within three months of the previous infection. Data were analysed using Microsoft® Excel® for Mac 2004 (Cupertino, California, USA). Univariate analysis and descriptive statistics were used to calculate the frequency and antibiotic susceptibilities of bacterial pathogens. Approval for the ethical conduct of this project was obtained from the Faculty of Medical Sciences, The University of the West Indies/University Hospital of the West Indies Ethics Committee and the Human Investigation Committee of the Yale University School of Medicine.

RESULTS

Demographic Characteristics of Patients with Infection

Data were analysed from 44 patients who sustained episodes of UTIs and bacterial sepsis. These patients accounted for 74 discrete infectious episodes. Of the 44 patients, 70.5% (n = 31) were male and the mean age at first infection was 5.6 ± 4.7 years, with age at index infection ranging from newborn to 19.8 years of age. The primary mode of acquisition of HIV infection was vertical, *ie* mother-to-child transmission (MTCT).

Clinical Profile of Patients with Infection

Approximately 61% (n = 27) of patients were in the CDC clinical category C, *ie* severely symptomatic at the time of first infection. The distribution by clinical category is shown in (Table 1). A CDC immunological category was not

Table 1: Demographic and clinical profile of KPAIDS patients with bacterial infections (September 1, 2002 to May 31, 2007)

Variable	Frequency (n)	Per cent (%)
Gender		
Male	31	70.5
Female	13	29.5
Clinic attended		
University Hospital of the West Indies	28	63.6
Bustamante Children's Hospital	11	25.0
Spanish Town Hospital	5	11.4
CDC Clinical Category at first infection*		
Category N	0	0.0
Category A	4	9.1
Category B	8	18.2
Category C	27	61.4
Unknown	5	11.4
CDC Immunological Category at first infection		
Category 1	2	4.5
Category 2	3	6.8
Category 3	5	11.4
Unknown	34	77.3
Number on antiretroviral therapy at time of first infection		
ARV therapy for more than 6 months prior to infection	9	20.5
Not on ARV therapy within 6 months prior to infection	34	77.3
Unknown status	1	2.3

*Three patients changed clinical categories during subsequent infections

assigned to most patients [77.3% (n = 34)] because enumeration of T-cell subsets was not done. Only 23% of patients were on antiretroviral therapy at the time of the first infection (in Jamaica, public access to antiretroviral drugs and lymphocyte subset testing first began in September 2004 through a grant from the Global Fund.)

The majority of patients (68.2%, n = 30) had only one infection (Table 2) and the mean number of infections per patient was 1.7 ± 1.3. Of the 74 infectious episodes, 73.0% (n = 54) required hospitalization; the median length of hospitalization was 20 days per episode (inter-quartile range 10 – 43.5 days). The mean duration of the intravenous and oral phases of antibiotic treatment was 13.5 ± 10.5 and 10 ± 3.8 days, respectively.

Table 2: Clinical profile of KPAIDS patients with bacterial infections sustained between September 1, 2002 to May 31, 2007

Variable	Frequency (n)	Per cent (%)
Number of infections per patient		
1 infection	30	68.2
2 infections	7	15.9
3 or more infections	7	15.9
Number of infectious episodes requiring hospitalization		
Hospitalized	54	73.0
Not hospitalized	20	27.0
Clinical outcome of each episode		
Death	4	5.4
Resolution or single infection	59	79.7
Recurrent infection with same species (within 3 months)	4	5.4
Recurrent infection with different species (within 3 months)	7	9.5

Infectious Episodes by Clinical Diagnosis

The frequency of infectious episodes by clinical diagnosis were examined (Table 3). Of the 74 infectious episodes, there were 52 UTIs (70.3%) and 22 episodes of sepsis (29.7%). Of 52 UTIs, 39 were caused by a single bacterial species. All episodes of UTI involved the bladder only; there were no cases of pyelonephritis.

Table 3: Frequency of infectious episodes seen in KPAIDS patients by clinical diagnosis (September 1, 2002 to May 31, 2007)

Infection	Frequency (n)	Per cent (%)
Urinary tract infections		
Cystitis	52	100.0
Pyelonephritis	0	0.0
Sepsis		
Pneumonia	15	68.2
Meningitis	4	18.2
Bacteraemia without a focus	2	9.1
Bone infection	1	4.5

Episodes of sepsis were categorized using Jankelevich's definition (2005); all episodes of sepsis included at least one positive blood culture (1). Episodes of sepsis included: meningitis, bacteraemia without a focus, pneumonia and bone infection. Among 22 episodes of sepsis, 68.2% (n = 15) presented with pneumonia, 18.2% (n = 4) with meningitis, 4.5% (n = 1) with bone infection and 9.1% (n = 2) with bacteraemia without a defined focus.

The majority of infectious episodes, 79.7% (n = 59) resolved either following antibiotic treatment or spontaneously; only 5.4% (n = 4) resulted in death. Approximately 10% of infectious episodes were followed within three months by recurrent invasive infection, half of which were caused by the original species and half by another.

Aetiologic Agents

Among the agents associated with 39 UTIs (Table 4), the most common isolates were *E coli* (n = 21, 53.8%), *Enterobacter* spp (n = 5, 12.8%), *Streptococcus* Group D (n = 4, 10.3%) and *K pneumoniae* (n = 3, 7.7%). Among 22 episodes of bacterial sepsis, isolates included *S pneumoniae* (n = 8, 36.4%) and coagulase negative *Staphylococcus* (n = 6, 27.3%). Among six episodes of bacterial sepsis associated with coagulase negative *Staphylococcus,* five (83.3%) were

Table 4: Aetiology of infectious episodes seen in KPAIDS patients categorized by clinical diagnosis

Diagnosis	Isolate	Frequency
Urinary tract infections* (n = 39)		
Cystitis	*Escherichia coli*	21
	Enterobacter spp	5
	Streptococcus Group D	4
	Klebsiella pneumoniae	3
	Gram negative species; various	3
	Gram positive species; various	2
	Candida albicans	1
Sepsis (n = 22)		
Meningitis	*Streptococcus pneumoniae*	2
	Coagulase negative S*taphylococcus*	1
	Cryptococcus	1
Bacteraemia	Coagulase negative S*taphylococcus*	1
	Klebsiella pneumoniae	1
Bacterial pneumonia	*Streptococcus pneumoniae*	6
	Gram negative species; various	5
	Coagulase negative *Staphylococcus*	4
Bone infection	*Pseudomonas fluorescens*	1

* Only single UTIs caused by a single organism were included

isolated from blood and one was isolated from cerebrospinal fluid. Ultimately, *E coli* was the agent responsible for the majority of UTIs and *S pneumoniae* was the most common organism causing sepsis.

Choices of Antibiotics for Bacterial Infections in Jamaica

In Jamaica, according to current clinical practice, the empiric antibiotic choices for UTIs in children are: parenteral ceftriaxone, cefotaxime, or gentamicin/amoxicillin and oral ampicillin-clavulanate, amoxicillin, cefuroxime or cefdinir. The empiric choices for uncomplicated sepsis are ceftriaxone, cefotaxime, ampicillin-clavulanate, amoxicillin and gentamicin. The choice of antibiotic depends on the clinical presentation of the episode and the probable site of infection. The antibiotic choices often change upon final identification of the causative organism.

Antibiotic Susceptibility

All of the Gram negative isolates were resistant to cotrimoxazole and most were resistant to ampicillin (Table 5).

Table 5: Resistant profile of bacterial isolates to commonly used antibiotics

Organism	Antibiotics Per cent (fraction)									
	Ampicillin	Ampicillin clavulanate	Cotrimoxazole	Ceftriaxone	Cefuroxime	Gentamicin	Norfloxacin	Nitrofurantoin	Nalidixic Acid	Penicillin
Gram negative bacteria										
Escherichia coli (UHWI)*	90.5 (19/21)	40.0 (8/20)	100.0 (22/22)	42.8 (3/7)	100.0 (5/5)	21.0 (4/19)	5.9 (1/17)	10.0 (2/20)	20.0 (4/20)	ND
Escherichia coli (STH and BCH)*	85.7 (6/7)	83.3 (5/6)	100.0 (7/7)	ND	57.1 (4/7)	0 (0/8)	ND	ND	ND	ND
Klebsiellia pneumonia	100.0 (8/8)	75.0 (3/4)	100.0 (8/8)	ND	ND	50.0 (4/8)	20.0 (1/5)	40.0 (2/5)	14.3 (1/7)	ND
Enterobacter spp.	100.0 (6/6)	33.3 (2/6)	100.0 (6/6)	ND	ND	0 (0/6)	0 (0/4)	20.0 (1/5)	ND	ND
Gram positive bacteria										
Streptococcus Group D	0 (0/10)	0 (0/6)	80.0 (8/10)	ND	ND	87.5 (7/8)	ND	0 (0/8)	ND	ND
Streptococcus pneumoniae	0 (0/6)	0 (0/6)	80.0 (4/5)	0 (0/6)	ND	ND	ND	ND	ND	0 (0/5)
Coagulase negative *staphylococcus*	ND	0 (0/5)	100.0 (4/4)	ND	ND	20.0 (1/5)	ND	ND	ND	100.0 (5/5)

ND= Lab tests not done

*** All pathogens from occurrences of UTIs and sepsis are included; UHWI used a different laboratory for microbial analysis than STH and BCH**

The majority of Gram positive isolates were resistant to cotrimoxazole and the rates of resistance ranged from 80–100%. In contrast, all Gram positive organisms were susceptible to ampicillin-clavulanate.

DISCUSSION

The finding of this study provide insight into the antibiotic susceptibility patterns of invasive bacterial pathogens in children with HIV/AIDS from developing countries. *Escherichia coli* was the most frequent pathogen responsible for bacterial infections of the urinary tract and both Gram positive and Gram negative isolates showed a high level of cotrimoxazole resistance (80%) in this Jamaican cohort.

The ascertainment of antibiotic susceptibility patterns in this study provides clinicians with critical knowledge concerning those antibiotics that are likely to be effective in the management of bacterial infections among HIV-infected children in Jamaica. Children with HIV/AIDS are vulnerable to UTIs and bacterial sepsis due to their immunocompromised condition (1, 6, 7). Since the prevalence and phenotypes of infectious aetiological agents vary by geographic population and antibiotic susceptibility pattern, this information will allow clinicians in Jamaica to make informed decisions regarding the choice of antibiotics for empiric treatment before definitive microbiologic results are available (2).

Escherichia coli was the most common organism isolated from those with UTIs followed by *Enterobacter* spp, *Streptococcus* Group D and *K pneumoniae*. This finding is consistent with data from previous studies of this population by Pierre *et al* and Steel-Duncan *et al* in which *E coli* was the most common bacterial isolate in UTIs, accounting for 34.2% and 36.8% of isolates, respectively (6, 7).

S pneumoniae was the most frequent organism causing sepsis, followed by coagulase negative *Staphylococcus*. These findings are consistent with the pattern of invasive bacterial disease seen worldwide in which *S pneumoniae* is the isolate most frequently associated with bacterial sepsis in children with HIV/AIDS (1, 9). It is also consistent with a 2004 study by Pierre *et al* (6) which found *S pneumoniae* and coagulase negative *Staphylococcus* to be the most common isolates associated with episodes of bacterial sepsis, in 30.3% and 27.2%, of cases respectively.

An examination of the antibiotic susceptibility patterns of Gram negative bacteria indicated that 100% of Gram negative isolates were resistant to cotrimoxazole. This is a cause for concern, because in 86.5% (n = 64) of infectious episodes, patients were taking cotrimoxazole to prevent PCP and otitis media. These findings are consistent with those of Martin *et al* who noted a marked increase in cotrimoxazole resistant *E coli* strains isolated from HIV-infected adults at the San Francisco General Hospital (11). The rate of resis-

tance to cotrimoxazole at this hospital rose from 24% in 1988 to 74% in 1995. The diminished effectiveness of cotrimoxazole prophylaxis for the prevention of invasive bacterial infections such as bacterial sepsis and UTIs may be a more widespread phenomenon than previously appreciated (1).

Gram negative isolates also showed high levels of resistance to ampicillin; 100% of *K pneumoniae* and *Enterobacter* spp isolates exhibited resistance to this antibiotic. In contrast, Gram negative isolates displayed much greater susceptibility to norfloxacin (100% of *Enterobacter* spp isolates were susceptible). Gram negative isolates were more likely to be susceptible to the more widely used "first line" drug, gentamicin, indicating that it may sometimes be useful in this setting.

Gram positive isolates, especially pneumococci, showed consistently high rates (80–100%) of resistance to cotrimoxazole. These findings are consistent with the extant literature on this subject. One study from India found that 56% of pneumococcal isolates were resistant to cotrimoxazole (12). In contrast, streptococcal isolates were from the present study universally susceptible to both ampicillin and ampicillin-clavulanate. Therefore, ampicillin-clavulanate is likely to be an effective agent for the initial empiric treatment of streptococcal infections in this clinical setting.

The causes of the antibiotic resistance patterns identified cannot be definitively explained in this cross-sectional study. Factors such as physician prescribing characteristics, the degree of patient drug adherence, immune status and the quality of antibiotics provided may affect antimicrobial resistance patterns (1). Factors not addressed in this study, such as the nutritional status of the patients at the time of infection, may affect the prevalence of invasive bacterial infections in this population. In addition, since there was no control group, *eg*, age-matched HIV-negative Jamaican children, it could not be determined whether the high degree of resistance observed was due to the widespread use of antibiotic prophylaxis in the HIV-positive group or to evolutionary trends among bacteria in the general population. Furthermore, due to the small number of infections and the few bacterial isolates, the data cannot be generalized beyond this cohort to the paediatric population of Jamaica or to the larger developing world.

There may have been an element of laboratory bias in this study. The University Hospital of the West Indies used a different microbiology laboratory than the other two clinical sites. Laboratory procedures may have differed at the two laboratory sites, differentially affecting the laboratory results. Since the majority of patients were seen at the University Hospital of the West Indies, and the majority of infections occurred at that site, the laboratory bias should be minimal. Finally, since there was limited access to lymphocyte subsets during the study period, immunological status could not be established for all of the study participants.

In summary, this study provides data to support the need for continued surveillance for the antibiotic susceptibility patterns of common bacterial pathogens. Such data are critical for informing good clinical practice in the management of bacterial infections in HIV-positive children around the world. Further studies should be performed to evaluate the long-term impact of these findings, not only within this limited HIV-infected population, but also within the general paediatric population of Jamaica.

In light of findings in this study, cotrimoxazole is not a drug to be considered for empiric therapy of HIV/AIDS Jamaican children with UTI or more severe infections. Ampicillin-clavulanate or gentamicin may be better empiric choices depending on the range of likely aetiologic microorganisms and the results of definitive antibiotic sensitivity tests. Furthermore, cotrimoxazole should not be considered for prophylaxis (secondary prevention) of UTIs in this cohort of children. Ampicillin-clavulanate and gentamicin or ceftriaxone remain reasonable initial options for combination empiric therapy of invasive bacterial infections (*eg* pneumonia and meningitis) in this clinical setting.

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