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Clinical predictors of bloodstream infections and mortality in hospitalized Malawian children

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Background. **In sub-Saharan Africa, bloodstream infections (BSI) are a major cause of pediatric mortality. Because of limited resources and facilities in these developing countries, treatment often must be based solely on clinical observations and patient history and includes the use of broad spectrum antimicrobials, a factor in the emergence of antibiotic resistance.**

Methods. **During July 28 through August 18, 1998 we analyzed clinical, epidemiologic and microbiologic data from a cohort of 225 hospitalized children in Malawi, Africa, to determine clinical indices associated with the presence/absence of BSI and/or mortality for use in settings with minimal microbiologic laboratory and intensive care facilities.**

Results. **BSI (n = 35 children) were associated with malnutrition, chronic cough, lethargy by history, lethargy on examination and oral thrush; 92% of children without these symptoms were BSI-negative. Mortality (21 of 173 children with known mortality status) was associated with malnutrition, lethargy on examination, prior receipt of antimalarials and acute decreased feeding. Of those with ≥2 of these indices 69% died; of those with <2 of the indices 94% survived. Infection with human immunodeficiency virus was not significantly related to either BSI or mortality status.**

Conclusions. **Malnutrition, but not HIV, was strongly related to both BSI and mortality. Assessment of these BSI and mortality indices at hospital admission provides rapid, cost-free indication of which children are most/least in need of empiric antimicrobial therapy or intensive observation, thereby maximizing appropriate use of antimicrobials and limited facilities while minimizing inappropriate antimicrobial usage.**

INTRODUCTION

Bloodstream infections (BSI) are a major cause of pediatric mortality in developing countries.[1–6] The organisms causing BSI in children vary among countries and study populations.[3–7] Gram-negative organisms are frequent[4, 7–9] and often predominate, representing 74% of the organisms isolated in a Kenyan study,[10] 61% in a Panamanian study[11] and 67% in a Zimbabwe study of febrile children.[1] Gram-negative organisms often go untreated, causing serious morbidity and mortality, with case fatality rates of 30 to 40%.[10, 11] Further, Gram-negative organisms can be highly resistant to the antimicrobials commonly used in developing countries[4, 8, 10] or can develop resistance rapidly after antimicrobial use.[10]

In developing countries hospital personnel, equipment and finances are limited, often preventing routine performance of blood cultures.[12] Even when blood cultures can be obtained, results often are not available for days or weeks.[10] As a result antimicrobial therapy is begun empirically, based solely on clinical observations and patient histories.[10, 12, 13] The limited repertoire of available antimicrobials in these countries further complicates therapy, precluding the use of a specific drug even if the causative organism has been identified.[4, 10] This creates a serious dilemma, because empiric and broad spectrum antimicrobial use is a major factor in the emergence of antibiotic-resistant organisms.[4, 8, 10]

Antimicrobial resistance is increasing worldwide and is now considered a major international public health threat.[14, 15] The primary factor associated with the development of antimicrobial resistance is the overuse of antibiotics.[10] In areas where only a few

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relatively inexpensive antibiotics are available, studies have shown rapidly developing and widespread resistance to these agents, including penicillins, cephalosporins, chloramphenicol, aminoglycosides and trimethoprim-sulfamethoxazole.[1, 2, 4, 8, 10] Thus increased resistance not only affects individual patient treatment but also impacts at the community level and on a global scale.

Programs to educate physicians about appropriate and inappropriate antimicrobial use have been implemented in both developed and developing countries.[16–18] Adherence to treatment guidelines regarding antimicrobial use has greatly reduced or reversed the trend of increasing antimicrobial resistance.[17] A number of studies have attempted to develop clinical and/or laboratory indices for accurate prediction of BSI, thereby decreasing antimicrobial overuse. Some of these prediction models are rather complex[12, 19] and not practical in the setting of a developing country.[19, 20] Others include laboratory tests (e.g. leukocyte indices or sedimentation rates) that are readily available in developed countries but usually unavailable in developing countries.[20]

We analyzed clinical, epidemiologic and microbiologic data from a study of BSI in hospitalized children in Malawi, Africa to determine whether any historical or clinical indices might effectively predict the presence or absence of BSI, and thus be used to better target antimicrobial use in settings where microbiologic laboratory facilities are unavailable. In addition, because the HIV epidemic has overburdened African hospitals with extremely ill patients, we examined whether any indices might identify those at highest risk of death and thus in greatest need of closest observation.

PARTICIPANTS AND METHODS

Patients. During July 28 through August 18, 1998, we enrolled all 225 acutely ill children (<13 years old) admitted to the Lilongwe Central Hospital, Malawi, into a study of BSI.[21] All hospitalized children were included because infected children do not necessarily present with fever. For each patient at admission, epidemiologic data and a medical history were obtained, and a physical examination was performed by one of the investigators. In accordance with current hospital procedures at the time of the study, all patients received antibiotics after blood drawing (neonatal patients received a combination of ampicillin and gentamicin or crystalline penicillin and gentamicin, whereas all other patients received a combination of chloramphenicol and gentamicin). The study protocol was approved by the institutional review boards of the CDC and the Malawian Health Sciences Research Committee; informed consent was obtained from the parents or guardians of all participants. US Department of Health and Human Services guidelines were followed in the conduct of this research.

Clinical definitions. The presence of a chronic cough (>1 month) was based on the history provided by a child's caretaker, in response to questioning by one collaborator. A history of lethargy was present if a caretaker reported that the child was recently sluggish, inordinately sleepy or inactive compared with his/her usual self. Lethargy on physical examination was based on the subjective impression of the admitting doctor that the child appeared sluggish, drowsy or floppy. Malnutrition was considered present if, on physical examination, the child had obvious signs of marasmus or kwashiorkor.[22] A full list of all variables examined is available by request from the authors.

Laboratory procedures. *Blood cultures.* Blood cultures were performed as described previously.[21] BACTEC MYCO/F LYTIC bottles (Becton Dickinson Microbiology Systems, Sparks, MD) were incubated at 35°C for 7 days and examined each day. With 5 ml of blood, this culture technique has a 92% recovery rate for bacteria, fungi and mycobacteria.[21] Any isolated organisms were further characterized at Duke University Medical Center.

HIV. HIV antibody testing was done at study enrollment, using enzyme-linked immunosorbent assay test kits (HIV-1 and –2; Murex Diagnostics, Inc., Norcross, GA). All parents or guardians of children participating in the study received HIV pre- and posttest counseling.

Malaria. Thick and thin smears were procured from each patient at admission. A smear was considered positive if any *Plasmodium* asexual parasites were seen on examination of peripheral blood smears (thick films and the tails of thin films). All patients with positive smears were treated with chloroquine, quinine or Fansidar, the standard of care at the time of the study.

Statistical techniques Comparisons of continuous data between dichotomized categories were made with the Wilcoxon rank sum and logistic regression analyses. Proportions were compared with the chi square or Fisher's exact test.

Standard statistical definitions used for BSI calculations (or mortality calculations) were as follows.[23] Sensitivity was the extent to which patients who proved to have a BSI (or subsequently died) were so classified, based on the particular predictive characteristic(s) (e.g. the proportion of children who proved to have a BSI who also had a history of lethargy). Specificity was the extent to which patients who proved to not have a BSI (or did not die) did not have the predictive characteristic(s). Positive predictive value (PPV) was the probability that persons who exhibited the predictive characteristic(s) would be found to have a BSI (or would die). Negative predictive value (NPV) was the probability that patients without the predictive characteris-

tics were found to not have a BSI (or would not die). Percentage correct was the percentage of patients with the predictive characteristic who had a BSI (or died) plus the percentage of patients who had neither the characteristic nor a BSI (or did not die). The significance level was set at $P < 0.05$; data not provided herein did not reach that level of significance on any type of analysis.

RESULTS

BSI results and clinical predictors. Of the 225 children entered into the study, 35 (15.5%) had positive blood cultures (Table 1). Organisms isolated from the blood included *Salmonella* ($n = 27$), *Escherichia coli* ($n = 4$), an unidentified Gram-negative rod ($n = 1$), *Acinetobacter* ($n = 1$), *Bacillus cereus* ($n = 1$) and a fungus ($n = 1$). Children with and without BSI were similar according to gender, age, vital signs, HIV status and mortality rates (Table 1). Positivity rates were not significantly greater in the very young. Admission blood cultures were positive in 6 of 28 (21%) of those <3 months old, 2 of 20 (10%) of those 3 to <6 months old, 3 of 42 (7%) of those 6 months old to <12 months old and 24 of 135 (18%) of those 1 to <13 years old. One 3-month-old boy with a BSI also had a positive malaria smear. No blood cultures were positive for *Mycobacterium* spp.

TABLE 1. Characteristics of participants, by blood culture status

Characteristic*	Blood Culture Results		P†
	Positive ($n = 35$)	Negative ($n = 190$)	
Male (%)	57	55	NS
Age (yr)			
Mean	2.4	2.5	
Median	1.3	1.4	NS
Range	0.1–12	0.1–12	
Vital signs (median)			
Pulse (beats/min)	148	147	NS
Respiratory rate (breaths/minute)	48	48	NS
Temperature (°C)	37.3	37.5	NS
Temperature range	33.9–39.7	35.0–41.0	
Died (%)	17	12	NS
Malaria-positive (%)	3	6	NS
HIV-positive (%)	37	26	NS
Chronic cough (%)	34	16	0.019
History of acute lethargy (%)	20	6	0.015
Lethargic at examination (%)	14	4	0.035
Malnutrition (%)	34	12	0.002
Oral thrush (%)	11	2	0.012
Chronic cough or malnutrition (%)	51	23	0.002
Lethargy by history or examination (%)	29	8	0.001
Any 1 symptom‡ (%)	69	31	<0.001
Any 2 symptoms‡ (%)	23	2	<0.001

* Data incomplete for various individuals: temperature (12 missing), mortality status (52 missing), malaria status (1 missing) and HIV status (6 missing).

† Wilcoxon rank sum test or Fisher's exact test.

‡ Of malnutrition or chronic cough, lethargy by history or on examination and oral thrush.

NS, not significant.

Children with or without BSI differed significantly with regard to the presence or absence of chronic cough, a history of lethargy, lethargy on physical examination, oral thrush and/or malnutrition on physical examination (Table 1). A history of lethargy and lethargy on physical examination were highly related ($P < 0.001$) with a 92% rate of concordance with one another. For 3% of children, both characteristics were present; for 3% lethargy was present on physical examination but not noted in history; for 5% lethargy was noted in history but not on examination; for 89% neither characteristic was present. The only other significant interrelationship among these five variables was between malnutrition and chronic cough ($P < 0.001$). Because of these relationships the related variables were never both included in a single logistic regression analysis but rather combined into a new variable, i.e. one new variable defined as the presence of lethargy by history or lethargy on examination; a second variable defined as the presence of chronic cough or malnutrition. In a series of univariate and logistic regression analyses, these two derived variables were more powerful statistically than any combination of individual variables (data not shown). These two derived variables groups along with the independent profile, oral thrush, were identified as the three symptom clusters significantly related to BSI.

Calculations concerning statistically significant combinations of the five clinical profiles associated with BSI are provided in Table 2. We have included data for profiles and combinations of profiles that were present in ≥5 children and for those that had the three highest values in each of percentage correct, sensitivity, specificity, PPV and NPV. All combinations had relatively low sensitivities, with the highest being 69%, for the presence of at least one of the five clinical profiles or at least one of the three symptom clusters (i.e. malnutrition or chronic cough; lethargy by history or lethargy on examination; and oral thrush). These combinations also had the highest NPV, 92%, and the highest number of patients exhibiting the symptom(s), 83. Specificities were as high as 98% for the presence of oral thrush ($n = 7$) or the presence of at least two of the three symptom clusters ($n = 11$). These also were the combinations with the highest PPV, at 57 and 73%. In logistic multivariate regression analyses, the presence of malnutrition or chronic cough [parameter estimate (b) = +1.3; odds ratio (OR), 3.8; 95% confidence interval (CI), 1.7 to 8.6; $P < 0.001$], lethargy by history or lethargy on examination ($b = +1.8$; OR 5.8; CI 2.2 to 15.4; $P < 0.001$) and oral thrush ($b = +1.9$; OR 6.4; CI 1.3 to 36.8; $P = 0.010$) were most strongly associated with blood culture positivity.

Mortality results and clinical predictors. At completion of the study, 24 participants were still hospitalized, 7 had signed out against medical advice,

TABLE 2. Clinical history and symptoms present in ≥5 children and most highly associated with positive blood cultures

Clinical Signs	Correct (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Oral thrush (n = 7)*	85	11	98	57	86
Lethargy on examination (n = 13)	83	14	96	38	86
Malnutrition or chronic cough (n = 62)	73	51	77	29	90
Malnutrition and chronic cough (n = 15)	83	17	95	40	86
Malnutrition, chronic cough, or oral thrush (n = 65)	72	54	76	29	90
Presence of ≥1 of the 5 clinical profiles† (n = 83) or ≥1 of the 3 symptom clusters (n = 83)‡	69	69	69	29	92
Presence of ≥2 of the 5 clinical profiles (n = 30)	83	37	91	43	89
Presence of 2 of the 3 symptom clusters‡ (n = 11)	87	23	98	73	87

* n, the number of children having the specified symptom.

† The 5 clinical profiles found significant were oral thrush, malnutrition, chronic cough, lethargy by history and lethargy on examination.

‡ Because they were significantly related to one another, malnutrition or chronic cough were treated as one symptom cluster, and lethargy by history or lethargy on examination were treated as a second system cluster. Oral thrush was the third profile in these analyses. No child had symptoms from all three symptom clusters.

152 were discharged and 21 had died; outcome was unrecorded for 21 patients. As with BSI mortality was not associated with demographic characteristics, including age and HIV serostatus, or with admission vital signs. Mortality rates were 19% for children <3 months old, 7% for those 3 to <6 months old, 8% for those 6 to <12 months old and 14% for those 1 to <13 years old. The presence or absence of a BSI also was not related to mortality. For children with known outcomes, four findings were significantly more common in children who subsequently died than in those who survived: acute decreased feeding (67% *vs.* 38%, P = 0.018, n = 72 with symptom); malnutrition (38% *vs.* 5%, $P < 0.001$, n = 16); lethargy on examination (19% *vs.* 2%, P = 0.005, n = 7); and preadmission antimalarial use (52% *vs.* 20%, P = 0.002, n = 41).

Malnourished children were older than adequately nourished children (median age of 2 years *vs.* 1 year, P = 0.004) and more likely to be HIV-seropositive (26% *vs.* 11%, P = 0.010). However, neither age nor HIV statuses were themselves significantly associated with mortality. Nourishment was significantly related to survival irrespective of BSI status: 60% (3 of 5) of malnourished children with BSI died *vs.* 0% (0 of 13) of normally nourished children with BSI (P = 0.010). Among those with negative blood cultures, 45% (5 of 11) of those with clinical malnutrition died, compared with only 9% (13 of 144) of those not malnourished (P = 0.004). Prior receipt of antimalarials was not related to the presenting complaint, results of malaria smears or prior symptoms other than vomiting (P = 0.020) (data not shown). Children who had received antimalarials were more likely to be HIV-seropositive (P = 0.030) and to have a Calmette-Guérin bacillus vaccine scar (P = 0.006), the latter suggesting greater use of/access to medical care.

Of these four variables antimalarial use before admission and acute decreased feeding were significantly related to one another (P = 0.018, 62% concordance); these were therefore combined into one variable (antimalarial use before admission or acute decreased feeding) for some univariate and logistic regression analyses. The criteria for being included in the analyses outlined in Table 3 were the same as those for inclusion in the Table 2 analyses (see above). The sensitivities of some of these combinations were 80%; PPVs ranged from 19 to 71%. Specificities were as high as 99%, and NPVs were >90% (Table 3).

In logistic regression analyses, mortality was most strongly associated with malnutrition (b = +2.4; OR 11.2; CI 3.3 to 39.7; $P < 0.001$), lethargy on examination (b = +2.8; OR 16.0; CI 2.8 to 105.3; $P < 0.001$) and preadmission antimalarial drug usage or acute de-

TABLE 3. Clinical history and symptoms present in ≥5 children and most highly associated with mortality

Clinical Signs	Correct (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Lethargy on examination (n = 7)*	88	19	98	57	90
Lethargy on examination or preadmission antimalarial use (n = 46)	76	62	78	28	94
Lethargy on examination or acute decreased feeding (n = 75)	62	71	61	20	94
Malnutrition or preadmission antimalarial use (n = 50)	75	67	76	28	94
Malnutrition and preadmission antimalarial use (n = 7)	90	24	99	71	90
Malnutrition or acute decreased feeding (n = 81)	61	81	58	21	96
Malnutrition and acute decreased feeding (n = 7)	90	24	99	71	90
Preadmission antimalarial use or acute decreased feeding (n = 89)	56	81	53	19	95
Presence of ≥1 of the 4 clinical profiles† or ≥1 of the 3 clustered profiles (n = 96)‡	53	86	49	19	96
Presence of ≥2 of the 4 clinical profiles‡ (n = 35)	84	67	86	40	95
Presence of ≥2 of the 3 clustered profiles (n = 16)‡	91	52	97	69	94

* n, the number of children having the specified symptom.

† The 4 clinical profiles found significant were malnutrition, lethargy on examination, receipt of antimalarial medications before admission and acute decreased feeding.

‡ Because they were significantly related to one another, receipt of antimalarial medications before admission, and acute decreased feeding were treated as one symptom cluster in some univariate and logistic regression analyses.

creased feeding ($b = +1.6$; OR 5.1; CI 1.5 to 22.1; $P = 0.008$).

HIV results. In our study 173 patients were tested for HIV; of these 21 (12%) were positive. In additional analyses no statistically significant relationships between HIV and the presence or absence of a BSI were found. These analyses were as follows. First, because of maternal antibody transfer, children <1.5 years old testing HIV-seronegative were included in an analysis but those identified as HIV-seropositive were included only if they had plasma HIV-1 levels assessed and detectable virus found ($n = 10$). In this analysis categorization for children ≥1.5 years old remained based on HIV serostatus; 29% of those with BSI ($n = 31$) were HIV-seropositive compared with 20% of those without BSI ($n = 170$). Results were similar for two other analyses. For all HIV-seropositive children with viral levels assessed, those with detectable virus in plasma were not significantly more likely to have a positive blood culture (5 of 26) than were those without detectable virus (0 of 6), nor did plasma viral titers differ significantly between those with and without BSI (medians 1 246 556 copies/ml, $n = 5$ *vs.* 667 190 copies/ml, $n = 27$).

DISCUSSION

In one study examining emergency triage assessment and treatment of children in developing countries, it was noted that guidelines to identify low risk children are gravely needed if mortality rates in developing countries are to improve.[24] In our study of hospitalized Malawian children, we found that five indices, all readily evaluable at hospital admission, strongly distinguished blood culture-negative from culture-positive children: history of chronic cough; history of lethargy; lethargy on examination; oral thrush; and malnutrition. Ninety-two percent of the children lacking all five of these "BSI indices" subsequently were found to have negative blood cultures. Seventy-three percent of those with at least two of the following symptom clusters subsequently were found to have positive blood cultures: malnutrition or chronic cough; lethargy by history or lethargy on examination; and oral thrush. Similarly mortality was associated with four indices: lethargy on examination; malnutrition; acute decreased feeding; and prior antimalarial use. Ninety-six percent of children lacking all four of these "mortality indices" survived. More than 70% of those with malnutrition and at least one other symptom subsequently died. Both the BSI and the mortality indices can be obtained in minutes, require no laboratory equipment, cost nothing to obtain and have high NPVs.

Our findings differ from those of one major study[12] in that we did not find age or any vital signs directly related to either BSI status or mortality, although nourishment status was related to vital sign abnormalities at admission (data not shown). Further we did not find malnutrition associated with infections specifically or diarrhea in general (data not shown).[8, 9, 12] However, our findings are consistent with a recent South African study of BSI in children, in which age and HIV disease stage were not related to BSI status whereas wasting and lethargy were signs that a child should receive priority care.[7] Also similar to our findings, both malnutrition and lethargy were reported as being related to serious illness in children presenting for emergency care at one Malawi hospital.[13] Our findings that malnutrition was a strong risk factor for BSI and, independently, for mortality are consistent with decades of nutritional literature.[9, 13, 25–27]

Gram-negative pathogens were the preponderant cause of BSI in our study population. These organisms often predominate as causes of BSI in Malawi and other developing countries.[9–11, 21, 28] Gram-negative organisms can be highly invasive and thus are disproportionately important causes of morbidity and mortality.[4, 8, 10] In areas and seasons in which Gram-negative organisms predominate, we suggest that our indices may provide a useful approach to determining the initial care of children suspected of sepsis and without obvious localized infection: i.e. those children who can most safely be observed without antimicrobial therapy rather than immediately treated empirically; children who are most likely in need of immediate antimicrobial therapy; children who might safely receive medical care at a later time; or children who are in need of most intense observation.

In the developing country setting, it must be remembered that blood cultures are a luxury, not a necessity, and realistically will not be available in the future. Unlike the situation in developed countries, physicians cannot begin empiric therapy on suspected sepsis patients with the expectation of discontinuing therapy within 72 h once blood culture negativity is confirmed. Our findings can be used by local physicians to determine the best clinical algorithm for their own patient population. Once this has been determined, instructions can be easily conveyed to even uneducated personnel. All options are simple to apply and do not require mathematical or statistical skills. For example if antimicrobials were routinely given to patients with at least two of the three BSI symptom clusters, then a high proportion of our study children (8 of 11) would have received antimicrobials appropriately; however, only a minority (<5%) of the children in our study fell into this category. If a hospital or clinic were in an area with high levels of antimicrobial resistance, children meeting these criteria might be those who should receive broader spectrum antibiotics. Alternatively if a hospital had only a few remaining vials of antibiotics, such children might be the best patients to receive

them empirically. On a larger scale if treatment had been given to children with any of the five symptoms, approximately one-third of the patients in our study would have received antimicrobials, but two-thirds of those with BSI would have been treated. Conversely 8% of those without these symptoms but with a BSI would not have received therapy at hospital presentation. However, that does not mean that they would not receive therapy later, postadmission. Thus treating a child with any of these symptoms but watching those without them might be a reasonable approach in many settings.

In areas with a high prevalence of resistance to available antimicrobials, a less empiric approach could be more appropriate. In these settings it may be preferable to withhold antimicrobials and observe children in larger subgroups defined by one or two of the above clinical profiles.

Our data should act as a powerful reminder that, despite the overwhelming problem of HIV infection in developing countries, malnutrition remains the most devastating health problem for children in these areas, at least in Malawi. Malnutrition is strongly related not only to BSI but also to mortality. Our findings of a >6-fold higher risk of dying among malnourished children than among adequately nourished children, with or without an associated BSI, suggest that intensive care facilities, if available, should be immediately or preferentially provided to malnourished children.[13, 29]

In summary, at least in developing countries where Gram-negative organisms predominate, these two sets of indices provide easily obtainable information indicating which children might be most in need of empiric antimicrobial therapy and/or intensive medical care and close observation. These indices are even more powerful in suggesting which children might be observed without antimicrobial therapy. Access to this information could decrease inappropriate antimicrobial use, slow the development of antimicrobial resistance and minimize overuse of sparse intensive care facilities.

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Commentary: Bacteremia in developing countries

Health care providers in resource-limited countries encounter a daunting challenge in facing excessive rates of serious infection-stimulated morbidity in combination with incomplete diagnostic testing and limited antibiotic options. It is no wonder that, in the face of overwhelming numbers of significantly ill patients and relatively few antibiotic choices, inappropriate antibiotic therapy is sometimes provided.[1] Some children die with infections that could have been effectively treated, and others are treated unnecessarily. Antibiotic resistance has been emerging at alarming rates fueled, in part, by overuse by health care providers. Despite the evidence that overuse of antibiotics has led to increased resistance patterns globally and that when usage is curbed antibiotic resistance rates decrease significantly,[2] only recently has inappropriate antibiotic use begun to decrease in some developed nations.[3] Around the world we need to use antibiotics appropriately and judiciously.

In resource limited settings, then, how can clinicians identify the patients who are most in need of systemic antibiotic therapy to prevent devastating consequences of serious infections? The World Health Organization's program of Integrated Management of Childhood Illness has sought to standardize and improve patient care in outpatient settings, and there is hope that similar clinically based inpatient protocols will help care for severely ill children in resource limited regions.[4] Thus several investigators have studied clinical factors that might be predictive of which ill children will have systemic bacterial infections and will stand to benefit most from appropriate antibiotic use. The premise is that these clinical predictors, in combination with known bacterial epidemiology and antibiotic resistance patterns, can then be used to construct local treatment protocols.

The outstanding article by Norton et al.[5] in this issue of the journal exemplifies the use of simple clinical criteria to identify children presenting with moderate to severe illness who would best stand to benefit from empiric use of antibiotics. The major clinical predictors of bacterial bloodstream infection identified in this prospective study were malnutrition or chronic cough, lethargy by history or lethargy on examination and oral thrush. In addition it was observed that malnutrition, but not HIV, was strongly related to bacterial bloodstream infections and to mortality. Although this was a well-performed study one must interpret the results carefully. Perhaps the major limitation of the study was the relatively small number of participants and positive cultures and, although not reported, a relatively weak power for some of the parameters examined. Secondly extrapolation to other populations, even in the tropics, must be done with caution because the study was conducted over a very short period (<1 month) and epidemiology, even within the population studied, will have great seasonal and yearly variations.[6] Finally this study identified only patients with bacteremia as an indication for antibiotic use, and it must be stressed that any protocol for appropriate use of antibiotics must include other clear indications of antibiotic use such as cellulitis, pyelonephritis and pneumonia. Clinical algorithms, such as suggested by the findings of this study, can be very useful in local settings. To broadly extrapolate criteria for clinical decision-making between countries, however, could be as inappropriate as suggesting that antibiotic selection

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