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Papers

Use of clinical syndromes to target antibiotic prescribing in seriously ill children in malaria endemic area: observational study

James A Berkley, Kathryn Maitland, Isaiah Mwangi, Caroline Ngetsa, Saleem Mwarumba, Brett S Lowe, Charles R J C Newton, Kevin Marsh, J Anthony G Scott, Mike English

Abstract

Objectives To determine how well antibiotic treatment is targeted by simple clinical syndromes and to what extent drug resistance threatens affordable antibiotics.
Design Observational study involving a priori definition of a hierarchy of syndromic indications for antibiotic therapy derived from World Health Organization integrated management of childhood illness and inpatient guidelines and application of these rules to a prospectively collected dataset.
Setting Kilifi District Hospital, Kenya.
Participants 11 847 acute paediatric admissions.
Main outcome measures Presence of invasive bacterial infection (bacteraemia or meningitis) or *Plasmodium falciparum* parasitaemia; antimicrobial sensitivities of isolated bacteria.
Results 6254 (53%) admissions met criteria for syndromes requiring antibiotics (sick young infants; meningitis/encephalopathy; severe malnutrition; very severe, severe, or mild pneumonia; skin or soft tissue infection): 672 (11%) had an invasive bacterial infection (80% of all invasive bacterial infections identified), and 753 (12%) died (93% of all inpatient deaths). Among *P falciparum* infected children with a syndromic indication for parenteral antibiotics, an invasive bacterial infection was detected in 4.0-8.8%. For the syndrome of meningitis/encephalopathy, 96/123 (76%) isolates were fully sensitive in vitro to penicillin or chloramphenicol.
Conclusions Simple clinical syndromes effectively target children admitted with invasive bacterial infection and those at risk of death. Malaria parasitaemia does not justify withholding empirical parenteral antibiotics. Lumbar puncture is critical to the rational use of antibiotics.

Introduction

Invasive bacterial infections are an important cause of childhood illness and death worldwide. To develop effective guidelines for initial antimicrobial treatment, knowledge of the likely cause of illness and the pattern of antibiotic resistance are fundamental. However, many resource poor countries lack local data and look to the World Health Organization for guidance. Advice on the management of common conditions has recently been summarised in the context of the integrated management of childhood illness approach.[1] Diagnosis in such settings usually depends on the identification of a small number of clinical syndromes. Seriously ill children often meet criteria for several clinical syndromes, however, and different diseases may cause the same clinical syndrome.[2] In malaria endemic areas uncertainty may exist because the clinical manifestations of malaria overlap with those of pneumonia, bacteraemia, and meningitis.[3–12]

We aimed to determine how well antibiotic treatment is targeted by simple rules based on current WHO guidelines, how application of such rules is affected by malaria parasitaemia in an endemic area, and to what extent antibiotic resistance threatens the use of cheap antibiotics. These analyses aim to reflect the practical decisions faced by clinicians, rather than simply describing the antimicrobial sensitivities of individual bacterial species or the bacterial aetiology of diseases defined at discharge.

Methods

Location and clinical methods

Kilifi District Hospital is located in a rural area on the Kenyan coast; a Kenya Medical Research Institute centre is based at the hospital. Children receive up to 50 mosquito bites infective for *Plasmodium falciparum* annually, with two transmission seasons.[13] Ten per cent of women attending the hospital antenatal clinic in 2000 were infected with HIV.[14] *Haemophilus influenzae* type b conjugate vaccination had not begun at the time of the study. Government employed clinical officers, without training in the integrated management of childhood illness, referred children to the paediatric wards.

We recruited all children admitted from February 1999 to December 2001, unless a clinically obvious disorder was present that was unlikely to cause diagnostic uncertainty, such as elective surgery, trauma, sickle cell crisis, congenital anomalies, tetanus, or nephrotic syndrome.[2] We collected clinical data, a malaria slide, full blood count, and blood culture on admission.[15 16] Table 1 gives clinical definitions. Our lumbar puncture policy included any of the following at any time during admission: meningism; impaired consciousness (delayed until neurologically stable); prostration in children aged under 3 years; and seizures, other than simple febrile seizures or as a septic screen in young infants.[17] Inpatient treatment followed WHO and local guidelines, including recommended protocols for severe malnutrition.[1]

Laboratory methods

We used a BACTEC 9050 instrument (Becton Dickinson, USA) to process blood cultures, and further processed them by standard methods. We regarded *Staphylococcus epidermidis*, *Streptococcus viridans*, *Bacillus*, or *Micrococcus* species as contaminants. We counted the leucocytes in cerebrospinal fluid (CSF) in a modified Neubauer chamber and did Gram stain and latex agglutination for *Haemophilus influenzae* type b and *Streptococcus pneumoniae* (Murex Diagnostics, UK) if >10 leucocytes/μl were present. We

Table 1 Definition of clinical syndromes and currently recommended antibiotic treatment

Syndrome	Definition	Recommended antibiotic treatment*
Sick young infants	Any child <60 days old sick enough to warrant admission to hospital	Gentamicin with either penicillin or ampicillin
Meningitis/encephalopathy	Neck stiffness, bulging fontanel, or impaired consciousness†	Penicillin with chloramphenicol
Severe malnutrition	Severe wasting‡ or kwashiorkor	Gentamicin with either penicillin or ampicillin
Very severe pneumonia	Respiratory distress§ plus one or more of prostration¶, cyanosis, or hypoxia**	Chloramphenicol
Severe pneumonia	Respiratory distress§	Penicillin
Mild pneumonia	Tachypnoea†† plus a history of either cough or difficulty breathing	Oral amoxicillin
Skin or soft tissue infection	Cellulitis, abscess, pyomyositis	Cloxacillin

*Parenteral unless otherwise indicated.
†Blantyre coma score ≤2.[5]
‡Weight for age z score <–4 by NCHS standards (Epi Info 2000, CDC, Atlanta, USA).
§Lower chest wall indrawing or abnormally deep breathing.
¶Inability to sit unassisted if aged ≥1 year or inability to drink or breastfeed if aged <1 year.[6]
**SaO_2<90% in air by pulse oximetry (Nellcor, USA).
††≥50 breaths per minute if aged 60 days to 1 year; ≥40 breaths per minute if ≥1 year old.[1]

assayed glucose in CSF and a concurrent blood sample (Analox Ltd, UK). We defined bacterial meningitis as positive CSF culture, positive CSF latex agglutination test, organisms on Gram stain, CSF leucocytes ≥ 50/µl, or CSF:blood glucose ratio < 0.1.[17] Antibiotic susceptibilities were determined at the end of the study (E-test, AB Biodisk, Sweden) at the manufacturer's laboratory and interpreted using National Committee for Clinical Laboratory Standards guidelines.[18] We defined in vitro sensitivity as "fully sensitive" for children with meningitis and "fully sensitive" or "intermediately sensitive" for children without meningitis. Isolates from children aged 60 days or older with confirmed meningitis were classified as resistant to gentamicin because of poor CSF penetration. Isolates were tested against individual antibiotics, and sensitivity to an antibiotic combination was defined as sensitivity to either of the antibiotics alone. Blood counts were automated (Beckman/Coulter Inc, USA). For malaria diagnosis, we stained a thick and thin blood slide with Giemsa and examined it at x1000. Laboratory procedures were internally and externally quality controlled (www.neqas.com).

Analysis

For the purposes of this analysis only, we classified children as meeting the definition of a syndrome warranting antibiotic treatment (table 1) or not by using data collected on admission. We constructed an a priori hierarchy of the syndromes, reflecting prioritisation in clinical practice (figure). We did not use the outpatient integrated management of childhood illness syndrome of "very severe febrile disease,"[19] as we would expect referral care to be further rationalised. We assigned individual children to their highest priority syndrome. We compared proportions by using Fisher's exact test and explored the possibility that antibiotic resistance increased the risk of inpatient death by using multiple logistic regression. We labelled individuals as "resistant to treatment" if the organism isolated was resistant in vitro to the antibiotics defined by their syndrome. Terms included in the multiple regression model included age (<7 or ≥7 days), sex, meningitis, malnutrition, and malaria. We used Stata version 8.0 for statistical analysis.

Results

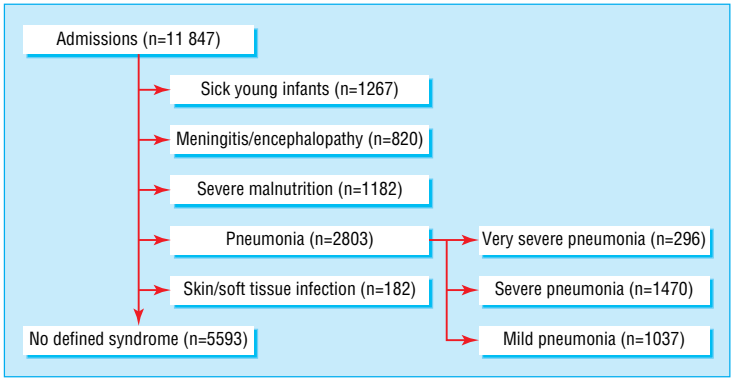
Among 14 987 admissions, we excluded 1254 (8.4%) with an obvious diagnosis, 134 (<1%) with missing data or refusal to consent, and 1752 (12%) with contaminated blood cultures, leaving 11 847 admissions (table 2). We detected an invasive bacterial infection in 843 (7.1%) admissions (table 3): 633 (5.3%) positive blood culture only, 9 (<0.1%) positive CSF culture only, 111 (0.9%) positive blood and CSF cultures, 21 (0.2%) positive blood culture with CSF evidence of meningitis, and 69 (0.6%) CSF evidence of meningitis but negative cultures. We detected *P falciparum* parasitaemia in 5270 (45%) admissions. A defined syndrome requiring antibiotics was present in 6254 (53%) admissions; of these, 672 (11%) had an invasive bacterial infection, representing 80% of all invasive bacterial infections, and 753 (12%) died in hospital, representing 93% of 813 inpatient deaths.

Sick young infants

Of 1267 young infants, 184 (15%) had an invasive bacterial infection (table 3), principally group B streptococci, *E coli*, *Acinetobacter*, and *Klebsiella* spp (table 4). The proportion of isolates susceptible in vitro to ampicillin-gentamicin was greater than that resistant to either penicillin-gentamicin or cefotaxime (both P = 0.001) (table 5).

Meningitis/encephalopathy syndrome

This clinical syndrome captured 101/160 (63%) cases of laboratory defined meningitis in children at least 60 days old; 21 (13%) other cases of meningitis outside this syndrome definition met another syndrome definition indicating parenteral antibiotics. The remaining 38 (24%) cases of meningitis would not have initially received parenteral antibiotics if syndromic treatment rules (that do not rely on lumbar puncture) had been followed



Hierarchical classification of defined syndromes requiring antibiotic treatment

Table 2 Clinical characteristics of study participants. Values are numbers (percentages) unless stated otherwise

Characteristic	Participants* (n=11 847)
Median (interquartile range) age (months)	17 (7 to 35)
Girls	5494 (46)
History of fever	9822/11 838 (83)
History of cough	5275/11 838 (45)
History of difficulty breathing	4065/11 838 (34)
History of diarrhoea	2545/11 838 (22)
History of convulsions	2719/11 837 (23)
Mean (SD) weight for age z score	−1.84 (1.50)
Kwashiorkor	766/11 833 (6.5)
Axillary temperature ≥37.5°C	7273/11 813 (62)
Impaired consciousness	734/11 835 (6.2)
Tachypnoea	4064/11 741 (35)
Subcostal indrawing	2317 /11 834 (20)
Deep breathing	737/11 836 (6.2)
Anaemia (Hb<8 g/dl)	4584/11 813 (39)
Severe anaemia (Hb<5 g/dl)	1173/11 813 (9.9)
Malaria parasitaemia	5 270/11 786 (45)

*Denominators less than 11 847 indicate missing data.

absolutely. The most common isolates were *S pneumoniae* and *H influenzae* (table 4). Four hundred and twenty two (52%) children with this syndrome had a positive malaria slide; 29 (6.9%) of these had an invasive bacterial infection compared with 117/397 (30%) children with negative slides ($P<0.001$, table 3). Case fatality did not vary significantly with malaria parasitaemia. Only 76% of isolates were fully sensitive in vitro to penicillin-chloramphenicol compared with 93% for cefotaxime ($P<0.001$, table 5). When we excluded *H influenzae*, 86% of isolates were sensitive to penicillin-chloramphenicol. Susceptibility results were similar when all meningitis cases missed by this syndrome definition were included.

Severe malnutrition syndrome

Severe malnutrition syndrome accounted for 141/659 (21%) of invasive bacterial infections and 200/533 (38%) of deaths in children aged at least 60 days (table 3). *S pneumoniae*, *E coli*, and non-typhoidal salmonellae were the most common isolates (table 4). Most (959, 81%) of these admissions did not meet criteria for another syndrome requiring antibiotics, making anthropometry or kwashiorkor the sole basis for antibiotic treatment. Of these,

Table 3 Number of admissions with defined syndromes, prevalence of invasive bacterial infections, malaria parasitaemia, and outcome. Values are numbers (percentages) unless stated otherwise

Syndrome	Median (IQR) age (months)	Invasive bacterial infection*	Meningitis	Deaths	Malaria slide positive	Invasive bacterial infection*	
						Malaria positive	Malaria negative
Sick young infants (n=1267)	7 (2-22) days	184 (15)	50 (4.0)	280 (22)	34 (2.7)	2/34 (5.9)	176/1213 (15)
Meningitis/encephalopathy (n=820)	27 (13-46)	147 (18)	101 (12)	150 (18)	422 (52)	29/422 (6.9)	117/397 (30)
Severe malnutrition (n=1182)	24 (15-39)	141 (12)	3 (0.3)	200 (17)	376 (32)	33/376 (8.8)	108/802 (13)
Very severe pneumonia (n=296)	13 (5-29)	33 (11)	8 (2.7)	56 (19)	124 (42)	5/124 (4.0)	28/172 (16)
Severe pneumonia (n=1470)	10 (5-20)	88 (6.0)	5 (0.3)	52 (3.5)	455 (31)	18/455 (4.0)	69/1004 (6.9)
Mild pneumonia (n=1037)	17 (10-29)	69 (6.7)	8 (0.8)	15 (1.5)	526 (51)	16/526 (3.0)	52/509 (10)
Skin/soft tissue infection (n=182)	19 (10-36)	10 (5.5)	0	0	86 (47)	1/86 (1.2)	9/95 (9.5)
No defined syndrome (n=5593)	23 (11-44)	171 (3.1)	35 (0.6)	60 (1.1)	3247 (58)	53/3247 (1.6)	118/2324 (5.1)
All admissions (n=11 847)	17 (7-35)	843 (7.1)	210 (1.8)	813 (6.9)	5270 (45)	157/5270 (3.0)	677/6516 (10)

IQR=interquartile range.
*Includes meningitis and bacteraemia.

Table 4 Bacterial isolates cultured. Values are numbers (percentages*)

Bacterial isolates	Sick young infants	Meningitis/ encephalitis	Severe malnutrition	Very severe pneumonia	Severe pneumonia	Mild pneumonia	Skin/soft tissue infection	No defined syndrome	Total
Gram positive									
Streptococcus pneumoniae	13 (8)	47 (37)	40 (27)	14 (44)	28 (31)	29 (43)	1 (10)	30 (19)	202
Staphylococcus aureus	16 (9)	5 (4)	5 (3)	1 (3)	2 (2)	3 (4)	4 (40)	18 (12)	54
Group A streptococci	13 (8)	5 (4)	3 (2)	2 (6)	0	1 (1)	1 (10)	5 (3)	30
Group B streptococci	20 (12)	0	0	0	0	0	0	0	20
Other Gram positives†	8 (5)	1 (1)	4 (3)	1 (3)	0	4 (6)	0	4 (3)	22
Gram negative									
Non-typhoidal salmonellae	3 (2)	9 (7)	25 (17)	2 (6)	18 (20)	16 (24)	0	44 (28)	117
Haemophilus influenzae	8 (5)	36 (29)	12 (8)	5 (16)	18 (20)	6 (9)	0	16 (10)	101
Escherichia coli	19 (11)	3 (2)	31 (21)	2 (6)	11 (12)	3 (4)	0	7 (5)	76
Acinetobacter sp	17 (10)	6 (5)	9 (6)	2 (6)	6 (7)	1 (1)	1 (10)	11 (7)	53
Klebsiella sp	17 (10)	1 (1)	4 (3)	0 (0)	2 (2)	0	1 (10)	2 (1)	27
Pseudomonas sp	9 (5)	6 (5)	2 (1)	1 (3)	2 (2)	1 (1)	1 (10)	4 (3)	26
Other Gram negatives†	30 (17)	7 (6)	13 (9)	2 (6)	2 (2)	4 (6)	1 (10)	14 (9)	73
Total	173	126	148	32	89	68	10	155	801

*Percentages refer to columns.
†Other common isolates in admissions ≥60 days included group D streptococci (10), *Campylobacter* sp (4), *Enterobacter* sp (3), and *Shigella* sp (3). Other common isolates in young infants included *Aeromonas* sp (7), *Enterobacter* sp (7), and group D streptococci (6).

Table 5 In vitro antimicrobial susceptibilities (E-test)*. Values are percentages

Antibiotics	Young infants (n=167)	Meningitis/ encephalitis (n=123)	Severe malnutrition (n=141)	Very severe pneumonia (n=30)	Severe pneumonia (n=84)	Mild pneumonia (n=64)	Skin/soft tissue infection (n=8)	No defined syndrome (n=141)
Amoxicillin/ampicillin	55	70	57	73	56	72	50	59
Co-trimoxazole	73	34	42	43	36	56	88	54
Benzyl penicillin	31	33	32	50	34	47	38	28
Chloramphenicol	76	76	77	83	74	83	100	81
Penicillin and gentamicin	88	51	81	68	73	83	88	77
Ampicillin and gentamicin	97	81	87	84	85	91	88	88
Penicillin and chloramphenicol	82	76	77	83	74	83	100	82
Cefotaxime	86	93	94	93	92	98	88	93

*E-test was done on 758 (95%) isolates. Percentages refer to the proportion of isolates sensitive to the antibiotic or combination. For admissions with confirmed meningitis, sensitivity is taken as the NCCLS "sensitive" breakpoint. For children aged ≥60 days with confirmed meningitis, isolates were classified as not susceptible to gentamicin because of poor penetration in cerebrospinal fluid. In admissions without meningitis, sensitivity is taken as NCCLS "intermediate" or "sensitive."

88 (9.2%) had an invasive bacterial infection and 153 (16%) died, compared with 53 (24%) and 47 (21%) of the 223 who met other syndrome definitions (both $P<0.001$). The prevalence of invasive bacterial infection was higher in children with negative malaria slides than in those with positive slides ($P=0.02$, table 3). Case fatality was lower in admissions with negative malaria slides (166/802, 21%) than in those with positive slides (34/376, 9.0%) ($P<0.001$). In vitro susceptibility to amoxicillin-gentamicin was greater than that to penicillin-gentamicin ($P<0.05$, table 5).

Pneumonia syndromes

Of 2803 (24%) children admitted with a pneumonia syndrome, 1470 (52%) had severe disease and 296 (11%) had very severe disease. The prevalence of invasive bacterial infection with severe pneumonia syndrome was similar to that with mild pneumonia syndrome, but case fatality was greater ($P=0.001$, table 3). *S pneumoniae* (38%), Enterobacteriaceae (30%), and *H influenzae* (15%) were the most common isolates (table 4). Three to four per cent of children with a positive malaria slide had an invasive bacterial infection compared with 6.9-16% in those with a negative slide (all $P<0.001$, table 3). Case fatality did not vary significantly with malaria parasitaemia. Isolates from children with severe or very severe pneumonia were more commonly susceptible to chloramphenicol alone than to penicillin alone ($P=0.05$) and to ampicillin-gentamicin than to penicillin-gentamicin ($P=0.04$, table 5).

Skin or soft tissue infection syndrome

Ten (5.5%) of 182 children with skin or soft tissue infections had an invasive bacterial infection. *Staphylococcus aureus* accounted for four (40%) invasive infections, and all these were sensitive to cloxacillin.

No defined syndrome requiring antibiotics

Of 5593 children without a syndrome requiring antibiotics, 171 (3.1%) had an invasive bacterial infection and 60 (1.1%) died. Non-typhoidal salmonellae, *S pneumoniae*, and *S aureus* were the most common isolates (table 4). Of 2324 malaria slide negative admissions, 118 (5.1%) had an invasive bacterial infection compared with 53/3247 (1.6%) slide positive admissions ($P<0.001$). Among children with an axillary temperature ≥39°C, invasive bacterial infection was present in 47/488 (9.6%) with a negative malaria slide compared with 22/1422 (1.6%) with a positive slide ($P<0.001$). We found no significant association between invasive bacterial infection and prostration, seizures, diarrhoea, vomiting, jaundice, or severe anaemia. Among children with an invasive bacterial infection, 0/53 children with a positive malaria slide died compared with 11/118 (9.3%) of those with a negative slide ($P=0.02$). In those without an invasive bacterial infection, 20/3194 (0.6%) children with a positive malaria slide died compared with 29/2216 (1.3%) with a negative slide ($P=0.009$).

Antimicrobial resistance and outcome

Antibiotic resistance to recommended treatment was associated with an odds ratio of 1.22 (95% confidence interval 0.78 to 1.92) for fatal outcome. If only deaths after 24 hours of admission were examined, the association with a fatal outcome strengthened (odds ratio = 1.90, 0.95 to 3.80), but the possibility of no association could not be absolutely excluded.

Discussion

Clinical officers and doctors at hospitals in sub-Saharan Africa face considerable challenges in managing seriously ill children, having few resources for diagnosis or treatment. Good early management is important because most deaths occur within 48 hours of admission. Initially, the management of seriously ill children is largely independent of the underlying cause. It includes resuscitation and correction of life threatening complications such as hypoxaemia, hypovolaemia, hypoglycaemia, convulsions, and severe anaemia. Antibiotics and antimalarials can be effective only if such complications are recognised and adequately treated.

Syndromic rules effectively target children with invasive bacterial infections

We have found that among acute paediatric admissions to a Kenyan district hospital, simple clinical syndromes based on WHO guidelines identified at admission 80% of children with an invasive bacterial infection and 93% of subsequent inpatient deaths. For every nine children with a defined syndrome indicating antibiotic treatment, one child had an identified invasive bacterial infection. Given the likely insensitivity of blood culture, we think this justifies empirical antibiotic treatment.

Does a positive malaria slide justify withholding antibiotics?

Overall, the presence of *P falciparum* parasitaemia was associated with a lower risk of invasive bacterial infection. However, where a syndrome requiring parenteral antibiotics (meningitis/ encephalopathy, malnutrition, very severe or severe pneumonia) was present, children with a positive malaria slide (by quality controlled microscopy in a research setting) still had a risk of detectable invasive bacterial infection between 1 in 25 and 1 in 11 and a risk of dying between 1 in 28 and 1 in 6 (table 3 and results section). We believe that these risks are too high to justify withholding parenteral antibiotics because a malaria slide is positive.

For children with the syndrome of mild pneumonia and a positive malaria slide, the case for withholding antibiotics strengthens: within this group, 1 in 33 had an identified invasive bacterial infection and 1 in 66 died. Given that blood cultures are less sensitive than other tests such as lung aspiration,[20 21] that treatment with oral amoxicillin is relatively inexpensive, and that the overall potential antibiotic pressure on resistance exerted by this group would be small, dual treatment of children in hospital, as is common in outpatient populations,[8] seems justified.

The accuracy of reading malaria slides in the region is an important concern. Recent reports suggest that this investigation is commonly unreliable, with frequent false positives.[22 23] Among children with a clinical syndrome compatible with cerebral malaria, such false positives would have a 1 in 3 chance of invasive bacterial infection. Children with the mild pneumonia syndrome and a false positive malaria slide would have a 1 in 10 chance. The unreliability of malaria microscopy in practice further considerably strengthens the case for following syndromic indications for antibiotic treatment, irrespective of the malaria slide result.

Among those with an axillary temperature ≥39°C but without a defined syndromic indication for antibiotics, an accurate malaria slide may be helpful in deciding on antibiotic treatment: 1 in 10 of those with a negative malaria slide had an "occult" invasive bacterial infection, whereas invasive bacterial infection was rare in children with positive slides and the outcome significantly better, although we did not establish how many of these children actually received antibiotics.

Does a syndrome indicating antibiotic treatment justify withholding antimalarials?

A third of children with a syndrome requiring antibiotics had a *P falciparum* parasitaemia, and 24% of the deaths in this group were due to malaria in the absence of invasive bacterial infection. Thus, among children admitted to hospital, suspected or microscopically confirmed malaria should be treated with antimalarials regardless of any antibiotic treatment. Where the results of a malaria slide are unreliable, children with features of severe malaria (impaired consciousness, deep breathing, or both) should receive both parenteral antimalarials and antibiotics. Oral antimalarials are likely to be adequate for those not classified as severe.

Meningitis: problems with clinical diagnosis and antimicrobial resistance

One in four cases of meningitis presented without a clinical syndrome indicating parenteral antibiotic treatment. Results were similar when more detailed clinical indicators of meningitis were studied in this hospital.[24] Meningitis was identified because our lumbar puncture protocol was broader than the syndrome definition, including suspicion of meningitis arising after admission. The pivotal role of lumbar puncture in rationalising treatment underlines the need to improve the use of this investigation[17]: 88% of children with the syndrome did not have meningitis. Lumbar puncture therefore permits considerable cost savings, especially where there is significant resistance to inexpensive antibiotics.[25] The high sensitivity to amoxicillin-gentamicin associated with this syndrome reflects the proportion of children with bacteraemia but not meningitis. Interestingly, *H influenzae* type b immunisation may reduce the need for more expensive antibiotics such as third generation cephalosporins.

Conclusions

We have shown that simple rules based on a hierarchical classification of WHO integrated management of childhood illness clinical syndromes can target admissions with invasive bacterial infections and those at risk of death. Our findings in this study, and previous studies,[2 15] indicate that the antibiotic management of children admitted to hospital in settings with no or few diagnostic resources should reflect a comprehensive assessment of the sick child and not focus on single diseases. A checklist illustrating such an approach is shown in the box. Our data are limited by being from one district hospital and using in vitro susceptibility testing (E-test). Similar studies are needed from other ecological zones in sub-Saharan Africa, especially areas with different prevalences of malaria and HIV. The potential impact on the aetiology of invasive bacterial infections of improved preventive strategies such as immunisation and changing patterns of resistance underscore the need for sustained surveillance in countries such as Kenya.

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Contributors: JAB and ME designed the study, participated in patient care, interpreted the findings, and wrote the report. JAB also collected and analysed the data. KMaitland, IM, JAGS, KMarsh, and CRJCN participated in and supervised patient care and data collection and contributed to the interpretation of findings and writing of the report. BSL was responsible for all in house laboratory procedures and data collection and participated in interpretation of the data and the final report. SM and CN did the bacteriological analyses, including E-tests, and participated in the interpretation of these data and in writing the report. JAB is the guarantor.

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Checklist for a syndromic, non-single disease approach to the management of children admitted to hospital

All of these questions should be answered for all children ill enough to warrant admission to hospital

- Does this child need immediate cardiopulmonary resuscitation (airway, breathing, circulation), including oxygen, fluid resuscitation, urgent blood transfusion*, glucose, or anticonvulsants?[26–28]
- Does this child meet criteria for a clinical syndrome(s) requiring antibiotic treatment? The types of antibiotic and route of administration will depend on the clinical syndrome—treat the most severe classification
- Does this child have a clinical syndrome indicating antimalarial treatment? The need for antimalarials will depend on a history of fever (presumptive treatment) or having reliable microscopy. The type of drug and route of administration will depend on whether or not signs of severe malaria (impaired consciousness, deep "acidotic" breathing, or both) are present[1 29]
- Is this child severely malnourished? WHO recommends that protocols for drugs, fluids, and nutritional support should be followed for children with severe malnutrition, even if treatments for malaria or bacterial syndromes are being given[1]
- Does this child have another obvious diagnosis?
- Does this child need a lumbar puncture to diagnose or exclude meningitis?[24]
- What maintenance oxygen, fluids, glucose, anticonvulsants, haematinics, or other drugs are needed?
- What level of observation or monitoring does this child need?
- When should this child be reviewed?

*Fluid resuscitation and blood transfusion protocols vary with the presence or absence of severe malnutrition

What is already known on this topic

Local data on bacterial aetiology and antimicrobial susceptibilities of childhood diseases are sparse in sub-Saharan Africa

Treatment guidelines for children in this setting tend to focus on individual diseases, which may lead to uncertainty where several causes of illness are possible

The clinical manifestations of severe malaria overlap with those of invasive bacterial infection, and malaria microscopy may be unreliable, causing further uncertainty

What this study adds

A simple hierarchical classification of clinical syndromes seems to effectively target admissions with invasive bacterial infection and those at risk of death

A positive malaria slide does not seem to justify withholding parenteral antibiotic treatment where it is indicated by a syndrome requiring antibiotics

A practical approach is to make separate decisions regarding antibiotic, antimalarial, and other treatments on the basis of the presence of defined clinical syndromes and the results of any reliable laboratory investigations

Competing interests: None declared.

Ethical approval: The Kenya Medical Research Institute national ethical and scientific review committees approved the study.

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Centre for Geographic Medicine Research (coast), PO Box 230, Kilifi, Kenya
James A Berkley *clinical research fellow*
Kathryn Maitland *clinical research fellow*
Isaiah Mwangi *clinical researcher*
Caroline Ngetsa *laboratory technologist*
Saleem Mwarumba *laboratory technologist*
Brett S Lowe *laboratory manager*
Charles RJC Newton *senior clinical research fellow*
Kevin Marsh *professor*
J Anthony G Scott *clinical research fellow*
Mike English *clinical research fellow*
Correspondence to: J A Berkley jberkley@kilifi.mimcom.net