Hypothetical performance of syndrome-based management of acute paediatric admissions of children aged more than 60 days in a Kenyan district hospital

Mike English,[1,2] James Berkley,[1,3] Isiah Mwangi,[1] Shebbe Mohammed,[1] Maimuna Ahmed,[1] Faith Osier,[1] Neema Muturi,[1] Bernhards Ogutu,[1,4] Kevin Marsh,[1,3] & Charles R.J.C. Newton[1,5]

Objective To investigate whether the outpatient, syndrome-based approach of the Integrated Management of Childhood Illness (IMCI) protocol could be extended to the inpatient arena to give clear and simple minimum standards of care for poorly resourced facilities.
Methods A prospective, one-year admission cohort retrospectively compared hypothetical performance of syndrome-based management with paediatrician-defined final diagnosis. Admission syndrome definitions were based on local adaptations to the IMCI protocol that encompassed 20 clinical features, measurement of oxygen saturation, and malaria microscopy.
Findings After 315 children with clinically obvious diagnoses (e.g. sickle cell disease and burns) were excluded, 3705 admission episodes were studied. Of these, 2334 (63%) met criteria for at least one severe syndrome (mortality 8% vs <1% for ''non-severe'' cases), and half of these had features of two or more severe syndromes. No cases of measles were seen. Syndrome-based treatment would have been appropriate (sensitivity >95%) for severe pneumonia, severe malaria, and diarrhoea with severe dehydration, and probably for severe malnutrition (sensitivity 71%). Syndrome-directed treatment suggested the use of broad-spectrum antibiotics in 75/133 (56% sensitivity) children with bacteraemic and 63/71 (89% sensitivity) children with meningitis.
Conclusions Twenty clinical features, oxygen saturation measurements, and results of malaria blood slides could be used for inpatient, syndrome-based management of acute paediatric admissions. The addition of microscopy of the cerebrospinal fluid and haemoglobin measurements would improve syndrome-directed treatment considerably. This approach might rationalize admission policy and standardize inpatient paediatric care in resource-poor countries, although the clinical detection of bacteraemia remains a problem.

Keywords Acute disease/therapy; Critical illness/therapy; Syndrome; Pneumonia/diagnosis/drug therapy; Malaria/diagnosis/drug therapy; Diarrhea/diagnosis/drug therapy; Child nutrition disorders/diagnosis/therapy; Meningitis/diagnosis/drug therapy; Bacteremia/diagnosis/drug therapy; Infant; Child, Preschool; Models, Theoretical; Prospective studies; Kenya (*source: MeSH, NLM*).

Mots clés Maladie aiguë/thérapeutique; Maladie grave/thérapeutique; Syndrome; Pneumonie/diagnostic/chimiothérapie; Paludisme/diagnostic/chimiothérapie; Diarrhée/diagnostic/chimiothérapie; Troubles nutrition enfant/diagnostic/thérapeutique; Méningite/diagnostic/chimiothérapie; Bactériémie/diagnostic/chimiothérapie; Nourrisson; Enfant âge pré-scolaire; Modèle théorique; Kenya (*source: MeSH, INSERM*).

Palabras clave Enfermedad aguda/terapia; Enfermedad crítica/terapia; Síndrome; Estudio prospectivo Neumonía/diagnóstico/quimioterapia; Paludismo/diagnóstico/quimioterapia; Diarrea/diagnóstico/quimioterapia; Trastornos de la nutrición del niño/diagnóstico/terapia/quimioterapia; Meningitis/diagnóstico/quimioterapia; Bacteremia/diagnóstico/quimioterapia; Lactante; Infante; Modelos teóricos; Estudios prospectivos; Kenya (*fuente: DeCS, BIREME*).

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Introduction

Over the last ten years, considerable effort has been put into developing the Integrated Management of Childhood Illness (IMCI) initiative, a generic, but adaptable, approach to the assessment and management of sick children when they present to first-level health facilities in resource-poor countries. Under the IMCI initiative, algorithms define illness severity and make recommendations about treatment and hospital referral (*1*). Target facilities often are run by community nurses or medical assistants. To complement the referral strategy, a manual that addresses inpatient management was produced recently (*2*). A number of studies have examined the assessment and referral components of IMCI (*3–8*), but the possible impact on inpatient management has not been addressed. In many government district hospitals in sub-Saharan Africa, however, the health workers who manage inpatients have similar qualifications to those who make referrals. Often supervision from senior staff is limited and

[1] Centre for Geographic Medicine Research, Coast, Kenya Medical Research Institute (KEMRI)/Wellcome Trust Research Laboratories, PO Box 230, Kilifi, Kenya (email: menglish@kilifi.mimcom.net). Correspondence should be sent to Dr English at this address.
[2] Department of Paediatrics, University of Oxford and Oxford Radcliffe Hospitals Trust, John Radcliffe Hospital, Headington, Oxford, England.
[3] Centre for Tropical Medicine, University of Oxford, John Radcliffe Hospital, Headington, Oxford, England.
[4] Department of Paediatrics, University of Nairobi, Kenya.
[5] Institute of Child Health, Wolfson Centre, Mecklenburgh Square, London, England.
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there is little or no access to a reliable, laboratory-based diagnostic service, which makes diagnosis difficult even in the referral facility. Syndromic management according to IMCI therefore may become the de facto approach to initial medical management for inpatients.

In essence, much clinical medicine is syndrome based. Characteristic combinations of symptoms, signs, and investigations often define a disease state. The emphasis in medical training and texts is still to use clinical skills to maximize the sensitivity and specificity of diagnosis within the paradigm of treating the single most probable cause of illness. However, this reductionist approach may be costly (in terms of mortality and morbidity) in situations in which the precision of classification is limited by the availability and quality of symptoms, signs, and results of investigations (lowering sensitivity, specificity, or both), in which illnesses are particularly severe (high case fatality), and in which true mixed pathology is more frequent. The latter two conditions apply in many resource-poor countries, notably areas where malaria is endemic. Tacit acknowledgement of this situation means that many health workers treat children for more than one possible disease — a feature also implicit in a syndromic approach to management. As a syndromic approach may offer advantages, such as simplifying training and standardizing inpatient clinical care, and because IMCI may prompt such a move anyway, we examined its potential in children admitted to a Kenyan district hospital.

Methods

The study was undertaken at Kilifi District Hospital, which is located in the Coast Province of Kenya, and is the main government inpatient facility for a district of approximately 500 000 people (although 80% of admissions are drawn from a more proximate population of 200 000). Most of the population consists of subsistence farmers who live in scattered rural homesteads, and mortality in children aged <5 years is likely to be close to the national average of 111 per 1000 live births (*9*). Malaria is endemic in the area, with two annual peaks of transmission and subsequent disease in June to August, and December to January. Acutely ill children who present to the hospital are assessed in the outpatient department by government clinical officers (health professionals with a minimum of three years' training, who are not members of the research team). These staff provide night and day cover and decide upon admission or discharge. Children aged $\geqslant$13 years are not admitted to the paediatric ward.

The study ran prospectively from 1 September 1999 to 31 August 2000. A standardized proforma was produced to record symptoms included in IMCI assessments and signs of proven local value (*10*). This proforma was completed by a clinical member of the research staff as soon as children were admitted (24-hour cover was provided). The main modifications of the IMCI assessment were the use of prostration as a clinical definition of lethargy and replacement of the clinical sign cyanosis by a measured oxygen saturation <90% (NPB 40, Nellcor, CA, USA). Prostration is identified by the direct observation of an inability to breastfeed in a child aged <1 year or the inability to maintain a sitting position in older children. Prostration has previously been shown to indicate a high risk of mortality locally (*10*), and we have found that it is easier to teach how to assess it than the less objective characteristic of lethargy recommended by IMCI (*1*). After the proforma was completed, and before any results from investigations were available, the admitting clinician recorded his or her principal, presumptive diagnosis. Laboratory investigations (a Giemsa-stained blood film for detection and quantification of malaria parasites, full blood count, and blood culture) were performed for all children whose parents gave consent (over 95% of those with a possible febrile illness) as part of a separate study (to be described elsewhere) and otherwise as clinically indicated. Micrococci, *Staphylococcus epidermidis*, *Bacillus* spp., *Flavobacterium* spp., and *Acinetobacter* spp. were considered to be contaminants. Additional investigations available, and performed according to locally agreed clinical management protocols, included the following: blood glucose, electrolytes, creatinine, chest X-ray, and examination of the cerebrospinal fluid. Inpatient clinical care comprised at least daily review and was supervised by a consultant paediatrician (*M.E.*). All changes in the clinical condition or management were recorded in the case notes, as were the results of investigations that were repeated or augmented when clinically indicated.

At discharge, the case notes and results of all investigations were reviewed by one of four senior clinical investigators (*M.E., J.B., C.N.*, and *I.M.*), and a final diagnosis was assigned. In cases where there was doubt, the final diagnosis was assigned after discussion between the investigators, but no formal assessment was made of the agreement between decisions about the final diagnosis. Where the child had more than one problem, the primary final diagnosis was defined as that which accounted for the admission and the subsequent hospital stay, and the secondary diagnosis as a problem that also required treatment. Final diagnoses were graded as severe or not severe by using the clinical criteria used for the syndromic diagnoses. Data recorded on the questionnaires were entered in duplicate by different data entry clerks and verified throughout the study period with FoxPro 2.1 software. Weight-for-height *Z*-scores were calculated with WHO/National Center for Health Statistics standards by using EpiInfo 2000 software (Centers for Disease Control and Prevention, Atlanta, GA, USA). Analyses were performed with Stata 6 software (Stata Corporation, College Station, TX, USA). At the end of the data collection period, syndrome diagnoses were computer generated with a series of logical operands derived from the admission questionnaire data and the malaria parasite slide only. Syndromic diagnosis thus was not used for clinical management.

Severe syndromes were classified as those that warranted parenteral treatment (*1, 2, 10*). The IMCI classification does not distinguish between severe malaria, possible severe sepsis, and possible meningitis, because it aims to ensure appropriate initial treatment before further investigation at a referral centre. We therefore based the syndrome diagnosis of severe malaria on previous work (*10*) and that for meningitis on recommendations in the IMCI inpatient care manual (*2*) and local experience, with the proviso that only signs already part of the IMCI algorithms should be included in a first definition (hence assessment of the fontanelle was not included routinely). As a stiff neck may be found less commonly in younger children, an alternative set of defining features was included for children aged <2 years. Although the definitions for meningitis essentially are "nested" within the definition of severe febrile disease, we felt it was worth examining them both individually as a diagnosis of meningitis might have different implications

for the choice and duration of treatment. We did not attempt to define a syndrome of primary bacteraemia or septicaemia, but instead adopted the IMCI-defined "very severe febrile disease" as one syndrome. Table 1 gives a full description of severe syndrome definitions applied in this analysis.

Results

Overall, 4026 children aged ⩾60 days were admitted during the study period; 221 (5.5%) of them died. Three children died before they were assessed, and data from three further children were inadequate for use, which left 4020 records in the dataset. Although 550 (13.7%) were aged >5 years — a group not covered by IMCI — these cases were included in the analysis because any syndromic approach is likely to be applied to all children. Table 2 gives the final diagnoses that accounted for ⩾0.5% of admissions. Clinical disorders highly unlikely to cause diagnostic uncertainty were found in 315 (7.8%) children (Box 1). As the primary role of syndromic management is likely to be to define appropriate care when there is diagnostic difficulty, data on these children were excluded. A dataset that comprised records from 3705 children referred to as "admissions requiring diagnosis" was the subject of all analyses.

Table 3 gives data on the total number of specific "severe" syndromes that would have been identified, as well as indicating the extent to which these overlapped. No cases of severe, complicated measles were seen, and only 12 cases fulfilled syndrome criteria of mastoiditis (these are excluded from Table 3). Overall, 2318 (62.6%) admissions requiring diagnosis fulfilled at least one severe syndrome definition; mortality in this group was 7.8% (181/2318). In the 1378 children without a severe syndrome, the most common final diagnoses were malaria (661, 48%), pneumonia (179, 13%), and gastroenteritis (262, 19%). Case-fatality rates among these treated "non-severely ill" children were 0.6%, 0%, and 0.7%, respectively, and 1% overall. If an entirely clinical definition of very severe pneumonia, in which clinically detected cyanosis had replaced a measured oxygen saturation <90%, had been used, the total number of children with a classification of severe or very severe pneumonia syndrome would have been only 662: 62/724 (8.6%) children would have been "misclassified" as having mild pneumonia. The general pattern of overlap with other syndromes (Table 3) would not have been affected significantly by use of this clinical definition.

The acute management of severe syndromes suggests six immediate and distinct therapeutic strategies: parenteral antibiotics; parenteral antimalarials; intravenous fluid resuscitation; specific nutritional support; oxygen; and, potentially, blood transfusion.

For three children, all six strategies would have been indicated by the symptoms and signs on admission (Table 4). Mortality decreased as the number of interventions the children's conditions warranted decreased, although 67% of

Table 1. **Definitions of severe syndromes**[a]

Syndrome diagnosis	Defining clinical features	Recommended treatment
Meningitis[b]	Stiff neck + any of fits, fever, or prostration (or worse neurological status) at any age Fever + any fits + prostration and age <2 years	Broad spectrum antibiotics (chloramphenicol and benzylpenicillin)
Lower respiratory infection pneumonia	History of cough or difficulty breathing plus:	
Mild[c]	respiratory rate ⩾50 if <1 year, ⩾40 if ⩾1 years	Oral antibiotic (amoxycillin)
Severe	indrawing	Benzylpenicillin
Very severe	prostration or oxygen saturation <90%, or both	Chloramphenicol + oxygen
Gastroenteritis (GE) with severe dehydration	Diarrhoea (watery stool ⩾ three times/day) with both sunken eyes and reduced skin turgor or prostration alone	Intravenous rehydration
Severe persistent diarrhoea with dehydration[b]	Diarrhoea (watery stool ⩾ three times/day) >14 days and any of: sunken eyes, reduced skin turgor or prostration	Intravenous rehydration if also meets criteria for GE with severe dehydration
Very severe febrile disease	Fever (as part of history or on examination) + stiff neck or any general danger sign (modified from Integrated Management of Childhood Illness): prostration, vomiting everything, any convulsions in the history, and unconsciousness	Broad-spectrum antibiotic – Chloramphenicol (parenteral antimalarial in the absence of a severe malaria definition)
Mastoiditis	History of ear problem + tender swelling behind the ear	NR[d]
Severe anaemia	Severe palmar pallor	Blood transfusion
Malnutrition (severe)	Visible severe wasting or oedema of both feet	Nutritional support Broad-spectrum antibiotics (benzylpenicillin and gentamicin)
Severe malaria	Prostration (or worse neurological status) and/or deep breathing and/or indrawing plus positive blood slide *or* unconsciousness irrespective of parasitaemia	Parenteral antimalarial (quinine) Broad-spectrum antibiotics (benzylpenicillin and chloramphenicol)

[a] Severe and complicated measles was not included as there were no measles outbreaks during the study period.
[b] On average there are <2 cases per annum of meningococcal disease, so purpura is not included as a suggestive sign of meningitis.
[c] Mild pneumonia was not included as a ''severe syndrome'', the definition is included here as it is an indication for antibiotic prescription.
[d] So few cases were seen that recommended treatment was not relevant.

Table 2. **Prevalence of final diagnoses among 4020 admissions of children aged ⩾60 days**

Final diagnosis	No. of cases	% of admissions	Case fatality rate (%)
Malaria (any severity)	1688	42.0	2.0
Lower respiratory tract infection (+ bronchiolitis)	527	13.1	2.5
Gastroenteritis	462	11.5	2.8
Protein calorie malnutrition	272	6.8	24.5[a]
Anaemia (blood slide negative for malaria)	132	3.3	8.3
Febrile convulsions (blood slide negative for malaria)	73	1.8	0
Meningitis	71	1.8	26.7
Burns	53	1.3	9.4
Severe skin or soft-tissue infection	51	1.3	0
Trauma	47	1.2	0
Upper respiratory tract infection	47	1.2	0
Sickle cell disease	46	1.1	6.5
Epilepsy	41	1.0	0
Asthma	40	1.0	0
Septicaemia or bacteraemia	35	0.9	40.0
Elective surgery	21	0.5	0
Nephrotic and nephritic syndromes and renal failure	21	0.5	23.8
Other	393	9.7	NA[b]

[a] The relatively high case fatality rate is attributed in part to the severity of the disease among children who presented to this hospital and in part to the likely contribution of underlying HIV infection.
[b] Not applicable.

Box 1. **Some disorders highly unlikely to cause diagnostic uncertainty**

- Sickle cell crisis
- Trauma
- Emergency and elective surgery
- Nephrotic and nephritic syndromes
- Arthritides
- Congenital abnormalities
- Tetanus

all deaths in the severe syndrome group occurred in those who warranted two or three interventions.

The indications for and choice of antibiotics are variable, but the potential performance of syndrome-directed antibiotic prescribing with respect to the presence of bacteraemia and a final diagnosis of meningitis is described in Table 5. Severe soft-tissue infection is included as an indication for antibiotic treatment in general, and, in line with WHO guidelines on inpatients, severe malnutrition is considered to be an indication for broad-spectrum treatment (*2*). The predominant organisms detected in the 58 bacteraemic children without a syndromic indication for broad-spectrum antibiotics were *S. pneumoniae* ($n = 21, 36\%$) and *Salmonella* spp. ($n = 19, 33\%$). In children with pneumococcal bacteraemia who did not have a syndromic indication for broad-spectrum antibiotics, five had syndrome diagnoses that indicated the use of benzylpenicillin (severe pneumonia) and nine had an indication for oral amoxicillin (pneumonia). Salmonella bacteraemia in children without a syndromic indication for broad-spectrum antibiotics was associated with diarrhoeal disease in two cases only.

Table 3. **Overlap between "severe" clinical syndromes among acute paediatric admissions excluding mastoiditis and measles, by total number identified**

Syndrome		No. with overlapping syndrome						
	n	Diarrhoea with severe dehydration (*n* = 161)	Very severe febrile illness (*n* = 1252)	Malnutrition (*n* = 384)	Severe pallor or severe anaemia (*n* = 529)	Severe persistent diarrhoea (*n* = 28)	Meningitis (*n* = 182)	Severe malaria (*n* = 534)
Severe or very severe pneumonia	724 (39)[a]	37 [23][b], *5*[c]	231 [18], *32*	71 [18], *10*	157 [30], *22*	3 [11], *0.5*	79 [43], *11*	282 [53], *39*
Diarrhoea with severe dehydration	161 (31)		71 [6], *44*	44 [11], *27*	17 [3], *11*	10 [36], *6*	10 [5], *6*	42 [8], *26*
Very severe febrile illness	1252 (51)			48 [13], *4*	196 [37], *16*	4 [14], *0.3*	182 [100], *15*	370 [69], *30*
Malnutrition	384 (50)				84 [16], *22*	23 [82], *6*	8 [4], *2*	29 [8], *5*
Severe pallor/severe anaemia	529 (37)					3 [11], *0.6*	42 [23], *8*	164, [31], *31*
Severe persistent diarrhoea	28 (4)						0	2 [0.4], *7*
Meningitis	182 (1)							119 [22], *65*

[a] Figures in parentheses are the % with no overlapping syndrome.
[b] Figures in square brackets are the % of the total number for the overlapping syndrome shown for each column.
[c] Figures in italics are the % of the total for the syndrome shown for each row.

Table 4. **Number of treatment strategies warranted on admission of children and mortality rates**

No. of treatment strategies warranted	No. of children	Mortality (%)
6	3	–
5	14	31[a]
4	95	–
3	308	18
2	696	11
1	1162	1

[a] In children who warranted four or more interventions.

Table 6 shows the performance of syndrome diagnosis compared with the final diagnosis (a composite of primary and secondary diagnoses where appropriate). The use of the same clinical signs to define severity of final diagnosis and to define syndromes explains the high sensitivities in the cases of severe malaria, pneumonia, and gastroenteritis. The positive predictive values indicate the degree of possible overtreatment attributable to a syndromic approach. With the same approach, the clinician's initial diagnoses were defined as severe or non-severe. A clinician's initial diagnosis of diarrhoea with severe dehydration, before laboratory results were available, had a positive predictive value of 80% (sensitivity 94%) for a final diagnosis of diarrhoea with severe dehydration. In the same way, a clinician's admission diagnosis of severe or very severe pneumonia had a positive predictive value of 78% (sensitivity 88%) when identifying children with severe or very severe pneumonia as a final diagnosis. For meningitis, however, clinicians correctly identified only 27/71 (30%, positive predictive value 52%) cases on admission (this assumed that no second diagnosis was permitted). This mirrored the poor performance of our specific syndrome-based diagnosis (sensitivity 56%, positive predictive value 22%, Table 6).

Discussion

The IMCI algorithms were designed as first assessment tools for sick children in developing countries in the hope that optimizing their management would improve outcome. We adapted this approach to assess the potential for formalized, syndrome-based inpatient management in poorly resourced environments. For children admitted without a highly characteristic symptom or sign complex (e.g. sickle cell disease or acute nephritis), 63% of admissions requiring diagnosis had features compatible with at least one severe syndrome classification. Those not captured by a severe syndrome definition had clinically milder disease, with low overall mortality (1%) and short inpatient stays (median, 2 days). Definitions of severe syndromes used as admission criteria might considerably reduce admission rates. These crude data, however, would overlook more subtle clinical indicators that prompt admission, and less severely ill children may have had lower mortality because they were most helped by inpatient treatment. Without further information therefore, it is difficult to balance the risk of not admitting lower risk children with the benefit in terms of quality of care that might accrue from having fewer admissions.

Might a syndromic approach for children with signs of severe illness usefully guide treatment?

Our gold standard was the final diagnosis. Disease progression during an inpatient stay might, through misclassification, tend to weaken the apparent performance of syndromic diagnosis. On the other hand, the use of the same clinical signs to define severity of final diagnosis and syndrome diagnosis will tend to improve sensitivity. Notwithstanding these considerations, positive predictive values for three of the severe syndromes (pneumonia, diarrhoea, and malaria) ranged from 46% to 70%, with sensitivities for identifying the gold standard diagnosis of at least 96%; this suggests that a syndromic approach may at least provide a clear rationale for how to target treatment.

It increasingly is recognized that assignment of a single diagnosis is problematic (*4, 6, 8, 11*). The syndrome-based

Table 5. **Performance of syndromic indications for antibiotic therapy[a]**

Syndrome cluster	Positive blood culture (n = 133/3705)		Final diagnosis of meningitis (n = 71/3705)	
Any syndromic indication for oral or parenteral antibiotics (n = 2260): otitis media, pneumonia, severe soft-tissue infection, very severe febrile disease, severe malaria, clinical meningitis, and severe malnutrition	106/133	Sensitivity 75% PPV[b] 5% LR[c] 2.5	Not clinically relevant	Not clinically relevant
Syndromic indication for any parenteral antibiotic (benzylpenicillin alone, chloramphenicol ± benzylpenicillin or gentamicin and benzylpenicillin) (n = 1897): severe pneumonia, very severe febrile disease, severe malaria, clinical meningitis, and severe malnutrition	89/133	Sensitivity 67% PPV 5% LR 1.9	63	Sensitivity 89% PPV 4% LR 1.8
Syndromic indication for broad-spectrum regime (chloramphenicol ± benzylpenicillin or gentamicin and benzylpenicillin) (n = 1594): very severe pneumonia, very severe febrile disease, severe malaria, clinical meningitis, and severe malnutrition	75/133	Sensitivity 56% PPV 5% LR 1.7	63	Sensitivity 89% PPV 4% LR 2.2
Clinical meningitis alone (n = 184)	Not clinically relevant	Not clinically relevant	40	Sensitivity 56% PPV 22% LR 14

[a] In all cases, it is assumed that investigations not done were negative and in the case of blood cultures that ''contaminants'' were clinically unimportant.
[b] PPV = positive predictive value.
[c] LR = likelihood ratio.

Table 6. **Comparison of syndrome diagnosis with final "gold-standard" diagnosis**

Syndrome diagnosis	Gold standard diagnosis	Sensitivity	Specificity	Positive predictive value
Severe or very severe pneumonia	Final diagnosis of severe or very severe pneumonia[a]	330/333 (99)[b]	2978/3372 (88)	330/724 (46)
Diarrhoea with severe dehydration	Final diagnosis of gastroenteritis with signs of severe dehydration[a]	92/96 (96)	3540/3609 (98)	92/161 (57)
Severe malnutrition	Final diagnosis of kwashiorkor or admission weight-for-height *Z*-score <–3	235/331 (71)	3227/3374 (96)	235/382 (62)
Meningitis	Final diagnosis of meningitis	40/71 (56)	3490/3634 (96)	40/184 (22)
Severe malaria	Final diagnosis of severe malaria[a]	374/377 (99)	3148/3279 (95)	374/534 (70)
Severe anaemia	Severe anaemia requiring urgent transfusion: haemoglobin <4 g/dl, haemoglogbin 4–5 g/dl with acidotic breathing, indrawing, or prostration (*25*)	264/315 (84)	3120/3390 (92)	264/534 (49)

[a] The clinical criteria for determining severity of final diagnosis were the same as the criteria in the admission syndrome.
[b] Figures in parentheses are percentages.

approach provides a structured format for prescribing multiple treatments to severely ill children — a situation that, in our clinical experience, is often appropriate. It remains unclear, however, how the management of such children should be prioritized. Would it be appropriate to begin aggressive crystalloid fluid resuscitation of a child with severe pneumonia and signs of dehydration? The prospect of adding further syndromic diagnoses, notably for HIV infection, makes the issue of syndrome hierarchy important.

The relatively poor performance of the clinical syndrome of meningitis (sensitivity 56%, positive predictive value 22%) and the physician's presumptive clinical diagnosis (sensitivity 30%, positive predictive value 56%) for a final diagnosis of meningitis warrants some discussion. We set a relatively low clinical threshold for performing a lumbar puncture, which maximizes case ascertainment (reducing systematic misclassification) and tends to reduce measured sensitivity. In our setting, therefore, where most episodes of febrile illness with convulsions are attributable to malaria (*12*), only 1 in 20 lumbar punctures resulted in a diagnosis of meningitis. Reliable data from lumbar punctures serve two purposes: to detect true cases and to limit unnecessary, prolonged antibiotic therapy. Although modifying the definition of meningitis syndrome improved sensitivity to 85% when children with a history of seizures were included, and to 77% when a more stringent history of more than two convulsions or a single seizure lasting more than 30 minutes was needed, the positive predictive values of these expanded definitions would fall to 6% and 11%, respectively, resulting in much unnecessary treatment.

A well-functioning laboratory service also is important in the treatment of malaria and in decision-making about transfusions. Such a laboratory might prevent exposure of almost 50% of children with severe pallor to the risk of transfusion, as well as preserving a very valuable resource.

The combination of malaria microscopy and a syndrome definition of severe malaria is capable of reducing quinine use by more than 65% compared with the recommended initial outpatient approach of treatment based on the syndrome of "very severe febrile disease" (*1*). This latter syndrome, not surprisingly, was the most prevalent severe syndrome (1252, 34%) admissions requiring diagnosis, with half of the group qualifying because of fever and convulsions), and it contributed significantly to summary indications for broad-spectrum, parenteral antibiotic use.

Overall, taking culture-proven invasive disease as the gold standard, severe syndrome criteria performed modestly as "tests" of true disease. Likelihood ratios of close to or less than two would not normally be considered of any great value in making decisions on diagnosis or treatment. In clinical practice, however, the problem is often to define a "no-treatment" group. The definition chosen should minimise the risk from failing to treat, promote the rational use of scarce resources and prevent unnecessary, painful injections. If only the severe syndrome criteria assessed in this analysis (almost identical to "outpatient" IMCI criteria for parenteral antibiotics) permitted use of any parenteral antibiotics, then one in 42 admitted children might be bacteraemic but not receive this form of treatment. Alternatively, one might need to treat 41 children for every truly bacteraemic child in the "non-severely ill" admitted group. As the latter pragmatic approach — the treatment of any admission with parenteral antibiotics — would result in almost 2000 additional treatments per annum in our setting, attempts to further optimize indications for treatment are required. As the predominant organisms isolated from "non-severely ill" cases of bacteraemia were *S. pneumoniae* and *Salmonella* spp. — both well-described causes of bacteraemia in the absence of specific symptoms (*13, 14*) — optimization of indications may, however, prove difficult.

Is a syndromic approach to diagnosis and treatment worth pursuing?

If routine inpatient care can be provided by well-trained personnel whose practice is supported and refined by high-quality basic laboratory services and senior supervision, syndromic care may have little to offer. This is rarely the situation in many African hospitals, however (*15, 16*). The syndromic approach evaluated here requires an answer to eight questions, examination for 12 physical signs (excluding measles and mastoiditis), measurement of oxygen saturation (clinical cyanosis had sensitivity <20% for an oxygen saturation <90%), and use of malaria microscopy. For the most part, these features are the same as those used in algorithms for

IMCI outpatient assessment and, as alluded to already, often little differentiates clinical staff employed in the inpatient or outpatient settings.

A focus on a limited number of features in both settings may increase the chance that a standardized approach to management, at least in the first 24 hours, could work under operational conditions. An appropriately organized recording form for these 21 features might be used to guide intervention with the six key modes of treatment in severe childhood illness in an area in which malaria is endemic. Two additional simple laboratory tests (microscopy of cerebrospinal fluid and measurement of haemoglobin) would considerably improve practice. In the context of an overburdened, under-resourced health system, appropriate syndrome-based management may allow a basic standard of care to be defined, treatment to be rationalized, outcomes to be audited, and performance to be assessed. Such an approach could be one way to improve the quality of care offered to children in hospital in many resource-poor countries. ■

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Résumé

Performance hypothétique de la prise en charge syndromique en cas d'hospitalisation pour affection pédiatrique aiguë chez les enfants de plus de 60 jours dans un hôpital de district du Kenya

Objectif Rechercher si l'approche syndromique adoptée pour les soins en ambulatoire dans le cadre du protocole de prise en charge intégrée des maladies de l'enfant (PCIME) peut être étendue aux cas hospitalisés en vue de définir des normes minimales de soins simples et claires pour les établissements pauvres en ressources.

Méthodes Une étude prospective d'un an portant sur une cohorte de cas hospitalisés a permis de comparer rétrospectivement la performance hypothétique de la prise en charge syndromique avec le diagnostic final établi par un pédiatre. La définition des syndromes observés à l'admission était basée sur une adaptation locale du protocole PCIME et comportait 20 critères cliniques, la mesure de la saturation en oxygène et l'examen microscopique à la recherche des parasites du paludisme.

Résultats Après exclusion de 315 enfants pour lesquels le diagnostic clinique était évident (par exemple drépanocytose ou brûlures), 3705 épisodes ayant conduit à une hospitalisation ont été étudiés. Parmi ces cas, 2334 (63 %) répondaient aux critères définissant au moins un syndrome grave (mortalité de 8 % contre moins de 1 % pour les cas « non graves »), et la moitié d'entre eux aux critères définissant deux syndromes graves ou plus. Aucun cas de rougeole n'a été observé. Le traitement syndromique aurait été approprié (sensibilité >95 %) pour les cas de pneumonie grave, paludisme grave et diarrhée avec forte déshydratation, et l'aurait probablement été pour les cas de malnutrition grave (sensibilité 71 %). Le traitement selon cette approche préconisait l'utilisation d'antibiotiques à large spectre chez 75 enfants présentant une bactériémie sur 133 (sensibilité 56 %) et 63 enfants atteints de méningite sur 71 (sensibilité 89 %).

Conclusion Il est possible d'utiliser 20 critères cliniques, la mesure de la saturation en oxygène et les résultats de l'examen de frottis sanguins pour la recherche du paludisme en vue de la prise en charge syndromique des enfants hospitalisés pour une affection pédiatrique aiguë. L'addition d'un examen microscopique du liquide céphalo-rachidien et d'une mesure de l'hémoglobine améliorerait considérablement le traitement. L'approche syndromique permettrait de rationaliser les politiques d'hospitalisation et de normaliser les soins aux enfants hospitalisés dans les pays pauvres en ressources, même si la détection clinique de la bactériémie reste problématique.

Resumen

Resultados hipotéticos del manejo sindrómico de los ingresos pediátricos agudos de niños de más de 60 días de edad en un hospital de distrito de Kenya

Objetivo Investigar si el enfoque sindrómico aplicado a los pacientes ambulatorios en el protocolo de la Atención Integrada a las Enfermedades Prevalentes de la Infancia (AIEPI) podría extenderse a los pacientes hospitalizados, a fin de proporcionar unas normas mínimas, claras y sencillas, para los centros con pocos recursos.

Métodos Se hizo un estudio prospectivo con una cohorte de ingresados a lo largo de un año a fin de comparar de forma retrospectiva los resultados hipotéticos del manejo sindrómico y el diagnóstico final de los pediatras. Las definiciones de los síndromes de ingreso se basaron en adaptaciones locales del protocolo de la AIEPI que abarcaban 20 características clínicas, la saturación de oxígeno y la microscopía del paludismo.

Resultados Tras excluir a 315 niños con diagnósticos clínicos obvios (p. ej., anemia de células falciformes o quemaduras), se estudiaron 3705 episodios causantes de ingreso. De ellos, 2334 (63%) satisficieron los criterios definitorios de por lo menos un síndrome grave (mortalidad del 8%, frente a < 1% para los casos ''no graves''), y en la mitad de éstos coincidían características de dos o más síndromes graves. No se observaron casos de sarampión. El tratamiento sindrómico habría sido apropiado (sensibilidad > 95%) para la neumonía grave, el paludismo grave y la diarrea con deshidratación severa, y probablemente para la malnutrición grave (sensibilidad del 71%). El tratamiento centrado en los síndromes proponía usar antibióticos de amplio espectro en 75/133 (sensibilidad del 56%) niños con bacteriemia y 63/71 (sensibilidad del 89%) niños con meningitis.

Conclusión Las veinte características clínicas utilizadas, las mediciones de la saturación de oxígeno y tres pruebas sencillas de laboratorio podrían emplearse para el manejo sindrómico de los niños hospitalizados con problemas agudos de pediatría. El uso adicional de la microscopía del líquido cefalorraquídeo y de las concentraciones de hemoglobina mejoraría considerablemente el tratamiento centrado en los síndromes. Este enfoque permitiría racionalizar la política de ingresos y normalizar la atención pediátrica de los enfermos hospitalizados en los países con pocos recursos, si bien la detección clínica de la bacteriemia sigue planteando dificultades.

References

1. *Handbook: Integrated Management of Childhood Illness*. Geneva: World Health Organization; 2000**.** WHO document WHO/FCH/CAH/00.12. Available from: URL: http://whqlibdoc.who.int/hq/2000/WHO_FCH_CAH_00.12_pp1-82.pdf and http://whqlibdoc.who.int/hq/2000/WHO_FCH_CAH_00.12_pp.83-163.pdf
2. *Management of the child with a serious infection or severe malnutrition.* Geneva: World Health Organization; 2000. WHO document WHO/FCH/CAH/00.1.
3. Weber MW, Mulholland EK, Jaffar S, Troedsson H, Gove S, Greenwood BM. Evaluation of an algorithm for the integrated management of childhood illness in an area with seasonal malaria in the Gambia. *Bulletin of the World Health Organization* 1997;75 Suppl 1:25-32.
4. Perkins B, Zucker A, Otieno JR, Jafari J, Paxton HS, Redd L, et al. Evaluation of an algorithm for the integrated management of childhood illness in an area of Kenya with high malaria transmission. *Bulletin of the World Health Organization* 1997;75 Suppl 1:33-42.
5. Simoes E, Desta AF, Tessema T, Gerbresellassie T, Dagnew M, Gove S. Performance of health workers after training in integrated management of childhood illness in Gondar, Ethiopia. *Bulletin of the World Health Organization* 1997;75 Suppl 1:43-53.
6. Kalter HD, Schillinger JA, Hossain M, Burnham G, Saha S, deWit U, et al. Identifying sick children requiring referral to hospital in Bangladesh. *Bulletin of the World Health Organization* 1997;75 Suppl 1:65-75.
7. Kolstad PR, Burnham G, Kalter HD, Kenya-Mugisha N, Black RE. The integrated management of childhood illness in western Uganda. *Bulletin of the World Health Organization* 1997;75 Suppl 1:77-85.
8. Shah D, Sachdev H, Evaluation of the WHO/UNICEF algorithm for integrated management of childhood illness between the ages of two months and five years. *Indian Pediatrics* 1999;36:767-78.
9. *Demographic and Health Survey.* Nairobi: National Council for Population and Development, Central Bureau of Statistics & Office of the Vice-President, and Ministry of Planning and National Development, Republic of Kenya; 1999.
10. Marsh K, Forster D, Waruiru C, Mwangi I, Winstanley M, Marsh V, et al. Indicators of life-threatening malaria in African children. *New England Journal of Medicine* 1995;332:1399-404.
11. English M, Punt J, Mwangi I, McHugh K, Marsh K. Clinical overlap between malaria and severe pneumonia in African children in hospital. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1996;90:658-62.
12. Waruiru CM, Newton CRJC, Forster D, New L, Winstanley P, Mwangi I, et al. Epileptic seizures and malaria in Kenyan children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1996;90:2-155.
13. Graham SM, Walsh AL, Molyneux EM, Phiri AJ, Molyneux ME. Clinical presentation of non-typhoidal Salmonella bacteraemia in Malawian children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2000;94:310-4.
14. Korones D, Shapiro E. Occult pneumococcal bacteremia: what happens to the child who appears well at reevaluation? *Pediatric Infectious Disease Journal* 1994;13:382-6.
15. Nolan TAP, Cunha AJ, Muhe L, Qazi S, Simoes EA, Tamburlini G, et al. Quality of hospital care for seriously ill children in less-developed countries. *Lancet* 2000;357:106-10.
16. *Ministry of Health, Government of Kenya and ORC-Macro. Kenya Service Provision Assessment Survey.* Nairobi: Ministry of Health of Kenya & National Council for Population and Development Ministry of Finance and Planning; 1999.