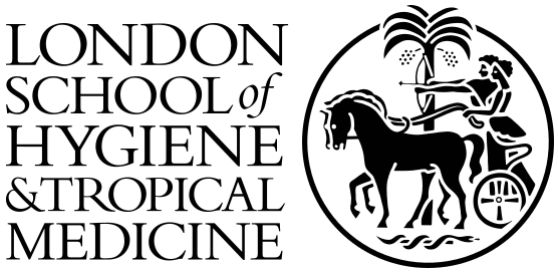

Pallor as a clinical sign of severe anaemia in children: an investigation in the Gambia

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Anaemia associated with malaria is a major public health problem in African countries. Since most primary health facilities have to rely on physical signs and not laboratory tests to detect anaemic patients who need referral for blood transfusion, we have assessed the reliability of simple clinical signs to predict severe anaemia.

A trained field assistant examined 368 children admitted to a tertiary care hospital, assessing the pallor of their eyelids (conjunctiva), palms and nailbeds, counting the respiratory rate, and looking for signs of respiratory distress. After the children's admission, their packed cell volume (PCV) was measured, and the need for transfusion and the outcomes were noted. A second observer examined 173 of these children so that interobserver variability in the detection of clinical signs could be assessed.

A total of 27% of the 368 children had a PCV of <15%. In a multiple regression analysis, definite pallor of the conjunctiva, definite pallor of the palms, and a "sick" appearance of the child were identified as independent significant predictors of a PCV of <15%. The best predictor was a combination of definite pallor of the conjunctiva and *pallor of the palms, with a sensitivity of 80% and a specificity of 85%. Inclusion of signs of respiratory distress did not improve the prediction. Pallor was a reproducible sign (weighted kappa statistic for the comparison between two observers: $\kappa = 0.6$ for conjunctival pallor). We conclude that pallor can be used as a sign for referring children who may require blood transfusion.*

Introduction

Anaemia is a major health problem in the Gambia and many other African countries (*1*), most cases in children being related to malaria. Although the pathogenesis of malarial anaemia is complex, there are two distinct types: (1) a chronic, low-grade anaemia associated with persistent parasitaemia; and (2) an acute malarial infection with haemolysis and a rapid drop in haemoglobin (*2*). The latter is especially dangerous when it occurs against a background of chronic anaemia, and can quickly lead to life threateningly low levels of haemoglobin.

In the Gambia, anaemia in children is strongly associated with the main malaria transmission season, which peaks in October and November (*1*). At the Royal Victoria Hospital (RVH) in Banjul, the only paediatric referral hospital in the country, the number of children receiving blood transfusions during the past few years because of malarial anaemia rose from 195 in 1991 to 567 in 1995, an annual increase of 24% (RVH, unpublished data, 1996). It is likely that this is due to increasing resistance of Gambian strains of *Plasmodium falciparum* to chloroquine, the first-line antimalarial drug (*1*, *3*). Because blood is scarce and there is a risk of transmission of blood-borne infections (*3–5*), children admitted to the RVH are transfused only if it is considered life-saving. A study from Kenya (*4*) has shown that transfusion is only beneficial in children with a haemoglobin (Hb) level ≤3.8 g/dl. Accordingly, the routine management guidelines in the RVH are to transfuse children only if their haematocrit (packed cell volume, PCV) is <12% or if they are in heart failure.

In developing countries, blood transfusion is available in only selected hospitals and severely anaemic patients who present at a peripheral health centre or peripheral hospital must be referred. Because it is frequently impossible to measure the PCV in peripheral health centres, decisions on referral for possible transfusion must be based on physical signs which can be detected by health professionals with limited training. The present study was carried out to evaluate the reliability of simple clinical signs to predict anaemia in children.

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Patients and methods

The study was carried out in the children's ward of the RVH in Banjul between July and December 1994. The climate is typical of the West African sub-Sahelian savanna with two distinct seasons: a wet season from June to November, and a dry season from December to June. Transmission of malaria occurs throughout most of the year, but is highest from August to November.

The subjects were chosen from among children admitted to the children's ward during working hours, a maximum of 10 a day being enrolled in order of presentation. As most admissions during the time of the year of this study were related to malaria, a large number of study children were anaemic. A field assistant was trained to perform a limited physical examination of the patients on admission, before a PCV was carried out, without knowledge of the admission diagnosis. This examination included an assessment of pallor of the conjunctiva, the palms and the nailbeds using a semiquantitative scale (0 = no pallor, 1 = possible pallor, 2 = definite pallor, 3 = definite severe pallor). The respiratory rate was counted, the temperature and body weight were recorded, and the arterial oxygen saturation and heart rate were determined using a pulse oximeter. The presence or absence of nasal flaring and grunting was noted, and any enlargement of the liver and spleen was determined by palpation. It was also recorded whether the child looked "sick". To investigate interobserver variability, up to 5 children a day, already seen by the field assistant, were examined by one of the physicians (*M. W. W.*). This second observation, undertaken without access to the field assistant's records, was carried out in the hospital ward within approximately 2 hours of the first observation.

Children admitted to the ward were looked after by the hospital physicians, who made all further decisions concerning treatment, including transfusion. Since blood for preparation of malaria films and determination of the PCV was taken only if considered clinically appropriate, not all the children examined by the field assistant had their PCV measured. The result of the PCV, the decision on transfusion, and the final diagnosis and outcome were all recorded by the field assistant.

Verbal consent was obtained from the child's carer by the field assistant who explained the nature of the study in the local language. The study was approved by the Gambian government Medical Research Council Ethical Committee.

Statistical methods

Summary statistics were calculated for each measurement: correlation between variables using Spearman's rank correlation coefficient, predictors of anaemia using multiple logistic regression models, and comparisons between models using a likelihood ratio test. Sensitivity and specificity were calculated for different cut-off points of PCV and for different combinations of signs, and modified receiver-operator characteristics (ROC) curves were plotted from these, using different degrees of pallor to predict anaemia with shifting cut-off points of PCV taken as "true anaemia".

Weighted kappa statistics, which measure the agreement between observers beyond random agreement and take the degree of disagreement into account, were calculated for the comparison between the two observers (*6*). Analyses were performed using SPSS for Windows, SAS for Windows, and Epi Info software packages.

Results

A total of 563 children underwent a physical examination on admission, but the PCV was measured for only 368. All further analyses refer to these 368 children. Their median age was 28 months (interquartile range: 14, 48 months); 49% were female and 10% had received treatment for malaria in the previous month (mean length of time since this treatment, 22 ± 9 days).

On physical examination, only 3% of the children appeared normal, 61% looked sick and 36% very sick. On examination of the conjunctiva, 52% did not have pallor, 11% had possible pallor, 16% had definite pallor, and 22% had definite, severe pallor. On examination of the palms, 41% did not have pallor, 14% had possible, 19% had definite, and 26% had definite, severe pallor. On examination of the nailbeds, 50% did not have pallor, 13% had possible, 17% had definite, and 20% had definite, severe pallor. While 61% of the children had nasal flaring, grunting was heard occasionally in 7% and with every breath in 10%. The median respiratory rate was 46 (interquartile range: 36, 58) breaths per minute; 17% of the children had mild and 7% had moderate indrawing of the lower chest wall. A total of 75% of the children had a palpable liver >1 cm (median 3 cm and interquartile range: 2–4 cm); 42% had palpable spleens. The median heart rate, measured by pulse oximeter, was 148 beats per minute (interquartile range: 133, 162).

A positive blood film for *P. falciparum* was obtained in 70% of the children, with a median parasite density of 25000/μl (interquartile range: 5000, 750000). The packed cell volume ranged from 8%

Table 1: **Median packed cell volume (PCV), by different degrees of pallor on examination of the conjunctiva, palms and nailbeds**

Site	Pallor: None	Possible	Definite	Definite, severe
Conjunctiva	27 (21, 32)[a]	19 (15, 25)	15 (13, 18)	13 (11, 15)
Palms	29 (22, 34)	21 (17, 27)	16 (13, 20)	13 (11, 15)
Nailbeds	27 (22, 32)	17 (14, 22)	15 (13, 18)	13 (10, 15)

[a] Figures in parentheses are the interquartile range.

to 54%, with a median of 20% (interquartile range: 14%, 29%); 11% had a PCV of <12%, 27% a PCV of <15%, and 60% a PCV of <24%. Blood transfusions were given to 34% of the children, and 13% of the study children died. The median PCV by degree of pallor is shown in Table 1; Fig. 1 indicates the degree of overlap in the detection of pallor at different sites for a PCV cut-off value of 15%.

Multiple logistic regression modelling. Multiple regression was performed to identify clinical findings that predicted severe anaemia. Two cut-off points were used to define severe anaemia — a PCV of 12% and a PCV of 15%. If a PCV of <12% was considered to represent severe anaemia, pallor of the conjunctiva and heart rate were significant independent predictors of anaemia. For a cut-off of 15%, pallor of the conjunctiva, pallor of the palms, and appearance ("sick") were independent predictors. The odds ratios for a child being anaemic, defined as a PCV of <12% and <15%, respectively, in relation to the degree of pallor of the conjunctiva are presented in Table 2. Definite severe pallor of the palms had an additional significant odds ratio of 6.82 (95% CI: 1.64, 28.39), compared to children with no pallor of the palms.

Receiver–operator characteristics curves. Receiver–operator characteristics curves were calculated for all combinations of significant variables in the regression analysis, using PCV as a continuous variable between a value of 9% and a value of 16%. Definite pallor of the palms, definite pallor of the conjunctiva, and a combination of the two achieved the best sensitivity and

Fig. 1. **Venn diagrams of the overlap of pallor at the three sites (conjunctiva, palm, nailbed).** Diagram A shows definite pallor at the sites for a cut-off in PCV of 12%; B shows definite severe pallor for a cut-off of 15%.

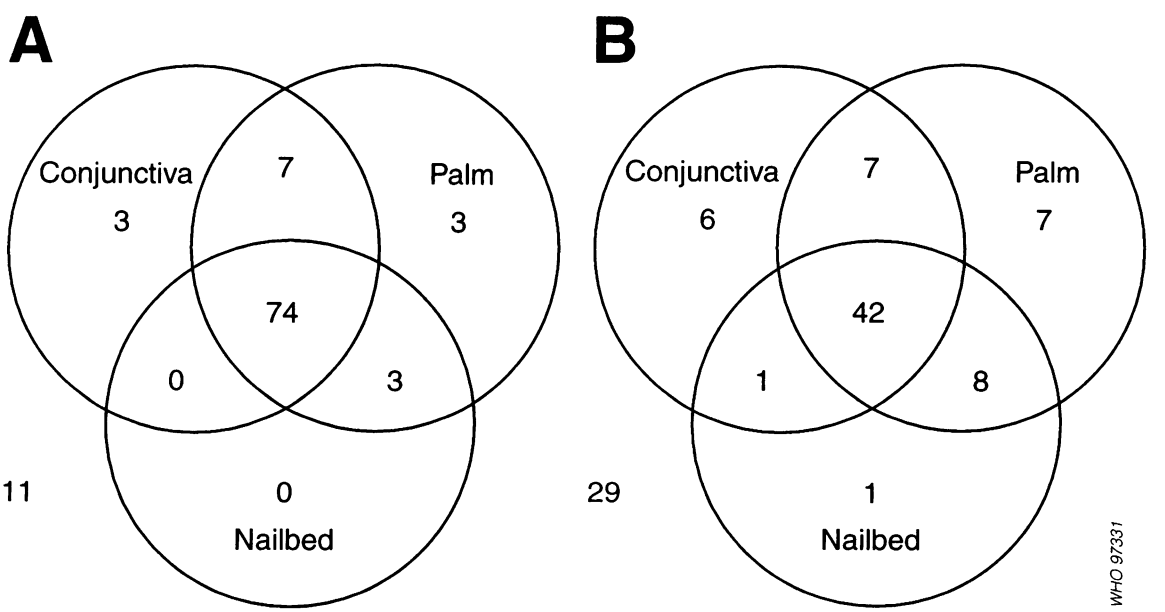


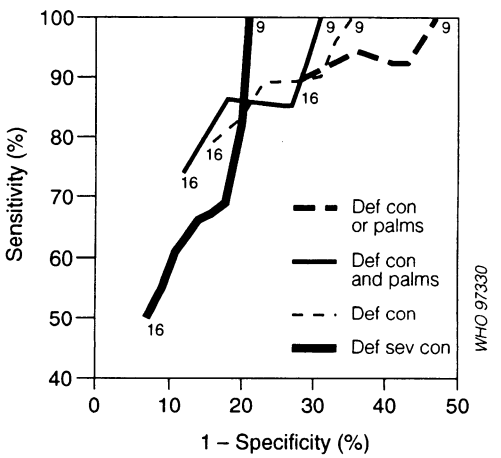
Table 2: **Odds ratios of anaemia defined as a PCV of <12% or <15% in relation to degree of pallor of the conjunctiva**

Pallor	PCV: <12%	PCV: <15%
Possible	4.6 (0.6, 33.9)[a]	5.2 (1.5, 18.3)
Definite	19.2 (3.8, 96.5)	10.3 (3.1, 34.1)
Definite, severe	55.6 (12.5, 247.5)	14.7 (4.3, 50.8)

[a] Figures in parentheses are the 95% confidence intervals.

specificity (Fig. 2). Definite severe pallor of the conjunctiva quickly dropped to a low sensitivity even for low cut-off points of PCV. In combination, definite pallor of the palms and definite pallor of the conjunctiva had the best sensitivity and specificity for cut-off points between 14% and 16%. At all cut-off points, the sensitivity for definite pallor of the conjunctiva alone was always slightly higher than for definite pallor of conjunctiva *and* palms, but the specificity was slightly lower.

Fig. 2. **Modified receiver–operator characteristics curves of the sensitivity and specificity (in percent) of pallor observed at different sites and of different degrees for shifting cut-off points of the packed cell volume (PCV) between 9% and 16%.** The cut-off PCV chosen at that particular point is considered to be the limit of anaemia, for which sensitivity and specificity are depicted. Within one line, the cut-off defining anaemia thus shifts from 9% to 16%. Def con or palms = definite pallor of conjunctiva *or* palms; Def con and palms = definite pallor of conjunctiva *and* palms; Def con = definite pallor of the conjunctiva; Def sev con = definite severe pallor of the conjunctiva.



Simple combination models. A number of simple combination models based on the significant parameters from a regression model were explored for their sensitivity, specificity, and predictive values for a PCV cut-off point of 15%. This cut-off point was chosen clinically following review of the ROC curves described above. These models are shown in Table 3. Definite pallor of the conjunctiva was the single best parameter with a sensitivity of 83%, a specificity of 80%, and a positive predictive value of 62%. A combination of definite pallor of the conjunctiva *and* definite pallor of the palms decreased the sensitivity to 80% but improved the specificity and positive predictive value to 85% and 67%, respectively.

Inter-observer variability. A subgroup of 173 children was examined by a second examiner. The agreement between the observers for individual, discrete variables is shown in Table 4. For the variables with poor agreement, the side of the disagreement was investigated. For grunting, 14% of the children were considered better, whereas 8% were considered worse by the second observer (the physician). For a "sick" appearance, 24% were considered better and 12% worse; and for nasal flaring, 24% were considered better and 4% worse.

Discussion

This study shows that definite pallor of the conjunctiva alone or in combination with definite pallor of the palms, as recorded by a field assistant, predicts severe anaemia with high precision. Pallor of the conjunctiva was detected more reproducibly than pallor of the nailbeds or palms. In primary health facilities in African countries, a decision about referral for blood transfusion has to be made without laboratory facilities to measure blood haemoglobin or PCV, and the clinical criteria should therefore be as specific and sensitive as possible. If the sensitivity of the referral criteria is too low, possible life-threatening anaemia will be missed; if the specificity is too low, the system will be overburdened with unnecessary referrals, and, where the referral centre is far away, with unnecessary costs for the patient. Our study population had a high proportion of anaemic children (27%), leading to a high positive predictive value of 67% for the combined criteria of definite pallor of the conjunctiva and palms. This means that 2 out of 3 children with anaemia were identified correctly. Applying the same combination to a less selected population, the positive predictive value would drop considerably, and a higher number of children would be referred unnecessarily. We had previously performed a study in an outpatient de-

Table 3: **Sensitivity, specificity, and positive and negative predictive values for different signs and combinations of signs to predict anaemia, defined as a PCV of <15%**

Sign or combination of signs	Category	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Pallor of conjunctiva	Definite	83	80	62	93
	Severe	55	91	71	84
Pallor of palms	Definite	88	72	54	94
	Severe	63	89	68	86
Appearance	"Sick"	28	60	72	69
Pallor of conjunctiva and palms	Both sites definite	80	85	67	92
	Both sites severe	49	94	75	83
	Either site or both definite	91	68	48	95
	Either site or both severe	70	86	66	88
Pallor of conjunctiva and appearance	Definite pallor and "sick"	24	91	50	76
	Severe pallor and "sick"	19	97	68	76
Pallor of palms and appearance	Definite pallor and "sick"	25	90	47	76
	Severe pallor and "sick"	22	96	65	76
Pallor of conjunctiva and palms and appearance	Both sites definite and "sick"	23	93	56	76
	Both sites severe and "sick"	18	97	72	76
	Either site or both definite and "sick"	26	87	43	75
	Either site or both severe and "sick"	23	95	38	76

Table 4: **Inter-observer variability between the paediatrician and the field worker, expressed as weighted kappa values for the individual discrete variables observed**

Variable	κ values	Agreement[a]
Grunting	0.21	Poor
Nasal flaring	0.35	Poor
Appearance	0.36	Poor
Liver palpable (>1 cm)	0.46	Good
Lower chest wall indrawing	0.51	Good
Pallor of the palms	0.54	Good
Pallor of the nailbed	0.59	Good
Pallor of the conjunctiva	0.60	Good
Spleen palpable	0.80	Excellent

[a] The agreement is according to Fleiss (*6*).

partment, in which only 1.1% of all children were severely anaemic (*7*). The positive predictive values of pallor of conjunctiva and palms for the prediction of anaemia were 22% and 21%, respectively. This indicates that pallor as a physical sign performs relatively better in settings with a lower frequency of the sign. The negative predictive value will be high in both settings.

It was unexpected that signs of respiratory distress, indicating possible heart failure, did not have much predictive power, and that grunting and nasal flaring were not reproducible clinical signs. A higher proportion of children had less severe signs on the second examination by the physician, perhaps because they were more agitated when first examined by the field assistant during admission. An alternative explanation is that the less experienced field assistant may have overdiagnosed signs such as grunting.

To decide on a cut-off point for possible referral is difficult, as the dynamics of development of anaemia depend on the level of malarial parasitaemia. According to the receiver-operator characteristics curves, a cut-off between 14% and 16% has the best combination of sensitivity and specificity. Such a cut-off would provide some safety for children whose haemoglobin level was still falling, but it is unnecessarily high for children who have stabilized their haemoglobin level. We chose not to take the need for transfusion as an outcome measure, as children might have been transfused several days after admission, when their haemoglobin had dropped secondarily. Other severely anaemic children died before being transfused, whereas some children died of causes other than anaemia, making death or transfusion unsuitable outcome measures.

Before the study, the field assistant was trained

in the detection of pallor, comparing degrees of pallor with the measured PCV. She received further feedback during the study when she recorded the PCV, after making her own clinical observations. This feedback might have contributed to the precision of "pallor" as a sign. Pallor of the conjunctiva was the single best sign in the Gambia, but pallor of the palms is similar in sensitivity. In settings with high indoor air pollution where conjunctival inflammation is common, pallor of the palms might be superior to that of the conjunctiva. Further studies are required on this matter.

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Résumé

La pâleur utilisée comme signe clinique d'anémie sévère chez l'enfant: une étude réalisée en Gambie

L'anémie associée au paludisme est un problème de santé publique majeur dans les pays africains. La plupart des centres de santé doivent s'appuyer sur des signes physiques et non sur des tests de laboratoire pour identifier les patients qui ont besoin d'être transférés et transfusés, et nous avons donc évalué la fiabilité de signes cliniques simples pour prévoir l'anémie sévère.

Un assistant de terrain formé a examiné 368 enfants admis dans un établissement hospitalier de troisième niveau, pour évaluer la pâleur des conjonctives, des paumes et du lit des ongles, la fréquence respiratoire et rechercher des signes de détresse respiratoire. Une fois les enfants hospitalisés, on a mesuré l'hématocrite, et enregistré le besoin de transfusion et divers critères. Un deuxième observateur a examiné 173 de ces enfants, de façon à pouvoir déterminer la variabilité interobservateur pour la détection des signes cliniques.

Sur l'ensemble des 368 enfants, 27% avaient un hématocrite <15%. L'analyse par régression logistique multiple a montré que des critères comme la pâleur nette des conjonctives ou des paumes et l'apparence «malade» de l'enfant étaient des prédicteurs indépendants *et* importants d'hématocrite <15%. Le meilleur prédicteur était obtenu en associant la pâleur des conjonctives *et* celle des paumes, avec une sensibilité de 80% et une spécificité de 85%. La prise en compte des signes de détresse respiratoire n'améliore pas la prévision. La pâleur était un signe reproductible (coefficient kappa pondéré qui mesure l'accord entre deux observateurs: $\kappa = 0,6$). En conclusion, la pâleur peut être considérée comme un signe permettant d'identifier les enfants pouvant nécessiter une transfusion.

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