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Predicting Outcome of Childhood Bacterial Meningitis With a Single Measurement of C-Reactive Protein

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Introduction: C-reactive protein (CRP), a marker of inflammation, shows high serum levels in invasive bacterial infections. We investigated the potential of a single CRP measurement at different phases of acute childhood bacterial meningitis to predict outcomes.

Methods: Using whole-blood finger-prick samples with no centrifugation, CRP was measured quantitatively on arrival and on day 3 or 4 in children participating in 2 prospective, randomized, double-blind treatment studies conducted in Latin America or Angola. The results were compared with patient outcomes.

Results: Although initial CRP values from 669 children gave useful prognostic information, the 3rd or 4th day measurements taken from 275 children associated significantly with seizures, slow recovery and low scores on the Glasgow Outcome Scale, with odds ratios for CRP values above the median (62 mg/L) ranging from 2 to 6, 2 to 5, and 3 to 5 (Latin America–Angola), respectively. Hearing impairment, although not full deafness, was 3 to 7 times more likely if CRP was above the median soon after hospitalization.

Conclusions: Especially in resource-poor settings, clinicians have few simple-enough tools to identify the child with meningitis who requires maximum attention. CRP is a worthy addition.

Key Words: C-reactive protein, bacterial meningitis, childhood, developing countries, prognosis

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The value of quantitatively measuring the serum level of C-reactive protein (CRP) to distinguish viral versus bacterial meningitis (BM) of childhood was shown 3 decades ago.[1,2] Less clear is the extent to which a single CRP determination may predict outcomes of BM. If it were to perform as well as in the acute osteoarticular infections,[3,4] we would gain a simple, fairly cheap and rapid method[5–8] suitable also for resource-poor settings which, with some exceptions,[9,10] are still awaiting large-scale implementation of conjugate vaccines.

Although performing 2 extensive treatment trials on childhood BM in Latin American (LatAm)[11] countries and 1 centre in Angola,[12] we included a preplanned collection of CRP data, measured on arrival to hospital and during treatment. This exceptionally large dataset allowed us to address the question posed in this study.

METHODS

Patients

The details of the setup of the LatAm and Angolan studies are explained elsewhere.[11,12] All patients fulfilled strict criteria for BM. The LatAm series[11] included 654 children aged 2 months through 16 years from Argentina, Brazil, Dominican Republic, Ecuador, Paraguay and Venezuela in 1996 to 2003. Ceftriaxone was given to all children, who were randomized also to receive intravenous dexamethasone, oral glycerol, both, or neither (a placebo preparation) as adjuvant medication. In Luanda,[12] 723 children aged 2 months to 13 years were treated with cefotaxime, but randomized to take it either as a slow continuous infusion or traditionally as 6-hourly boluses for the first 24 hours. In addition, the patients received high-dose paracetamol or placebo orally for the first 48 hours. Both study protocols were approved by the relevant Ethics Committees, and all participants were enrolled only after consent by a legal guardian. This study discusses the information obtained from single CRP measurements made during days 1 to 4 of treatment. The main characteristics and differences of the LatAm and Luanda children who had or not CRP measured are summarized in Table, Supplemental Digital Content 1, http://links.lww.com/INF/C421.

On arrival at the hospital, a thorough clinical investigation was carried out by the attending pediatrician, who performed the spinal tap and ordered all sample taking. He/she also completed the questionnaires specially designed for these studies, giving us uniform data from patients representing 2 languages and 2 continents. At discharge, a thorough clinical investigation was again performed, with special attention to the neurological outcome, and the results were added to the questionnaire. "Severe neurological sequelae" were defined as blindness, severe psychomotor retardation, quadriplegia or hydrocephalus needing a shunt, whereas "any neurological sequelae" included those entities along with moderate psychomotor retardation, hemiparesis, monoparesis or ataxia.

Hearing was measured shortly after discharge in LatAm, but on day 7 in hospital in Angola. Mostly, Brainstem Evoked Response Audiometry was used, unless the child was cooperative enough for conventional audiometry. Deafness was defined as the better ear's inability to detect sounds ≤80 dB, whereas "any hearing impairment" meant inability to distinguish sounds <60 dB.

Serum CRP was measured immunoturbidimetrically[5–7] using a special analyzer (Quikread, Orion Diagnostica, Espoo, Finland). The initial samples for CRP were taken at presentation, and resources permitting, on subsequent days on the ward in conjunction with other blood samples. Where a CRP level exceeded 160 mg/L, the specimen in LatAm was diluted and reanalyzed. In Luanda, this was impossible and all CRP values exceeding this level were recorded as 161 mg/L.

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I. Roine is one of the owners of a Chilean company that distributes laboratory reagents and equipment, including CRP reagents and the Quikread instrument. The author have no other conflicts of interest to disclose.

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Statistical Analysis

CRP results were expressed as medians with interquartile range (IQR). Single CRP results from day 1 or 2 and from day 3 or 4 of treatment were compared with other data, all prospectively collected, on the patient, their clinical evolution and outcome using Spearmann correlation, Mann–Whitney *U* test, or Kruskall–Wallis, as appropriate. If CRP had been measured on both days 1 and 2 or 3 and 4, we used the higher value. The odds ratios (OR) with 95% confidence intervals (95% CI) of an association between CRP above median value on day 3 or 4 and the clinical course of disease was calculated by logistic regression. This model was also used to calculate the odds of specific adverse outcomes associated with (1) CRP above median on day 3 or 4, (2) a Glasgow Coma Score <13 (below median) at presentation and (3) both (1) and (2) combined. The diagnostic usefulness of a CRP value above median on day 3 or 4 for predicting adverse outcomes was estimated by calculating its sensitivity, specificity and positive and negative predictive values for each outcome. *P* values below 0.05 were deemed significant.

RESULTS

Predictive Value of Initial CRP Measurement

The performance of CRP versus the presenting status, and the etiology of BM are summarized in Tables 1 and 2. During the first or second day of treatment CRP was determined from 285 patients in LatAm and 384 patients in Luanda, the median values being 159 (IQR, 107) mg/L and 161 (IQR, 62) mg/L, respectively. The level of CRP was not related to the child's age or gender but was influenced by etiology: in LatAm and Luanda, meningococcal meningitis produced the highest and lowest values ($P = 0.03$ vs. $P = 0.004$, respectively). In both places, higher CRP correlated with a lower cerebrospinal fluid glucose concentration (ρ, −0.13; $P = 0.04$ and ρ, −0.19; $P = 0.0003$ in LatAm and Luanda, respectively). In Angola, increased CRP also associated with the Glasgow Outcome Score (ρ, −0.11; $P = 0.04$), initial cerebrospinal fluid matrix metalloproteinase-9 concentration[13,14] (ρ, 0.15; $P = 0.03$), and recovery with neurological sequelae ($P = 0.03$).

Predictive Value of CRP on Day 3 or 4

During day 3 or 4 of treatment, CRP was determined from 218 patients in LatAm and 57 in Luanda, the median values being 62 mg/L (IQR, 76) and 117 mg/L (IQR, 112), respectively (Tables 1 and 2). Although CRP level did not relate to etiology or the treatment modalities (data not shown), an indisputable association was found with several indices of the clinical course and outcome. Both in LatAm and in Luanda (Table 1), higher CRP associated with more days scored below 15 on the Glasgow Coma Scale ($P = 0.005$ and $P = 0.0006$, respectively), with longer stay in hospital ($P = 0.02$ and $P < 0.0001$, respectively), and with lower Glasgow Outcome Score ($P = 0.01$ and $P = 0.004$, respectively). Likewise, in both places (Table 2), higher CRP on day 3 or 4 identified the patients developing seizures ($P = 0.001$ and $P = 0.002$, respectively), those scoring below 5 on the Glasgow Outcome Scale ($P = 0.002$ and $P = 0.0006$, respectively) and children with impaired hearing ($P = 0.0007$ and $P = 0.005$, respectively).

Half of the children whose CRP on day 3 or 4 exceeded the median of 62 mg/L had seizures 2 to 6 times more frequently than the others. The trend was quite similar (2–3 to 5 times greater risk) for those with suboptimal clinical course, and for those who scored below 5 on the Glasgow Outcome Scale (Table 3). However, the

TABLE 1. Spearmann Correlations (Corrected for Ties) Between CRP Values (mg/L) Versus Patient Characteristics on Arrival, Course of Illness and Outcomes

	Latin American		Luanda	
Variable	Rho	*P* Value	Rho	*P* Value
CRP on day 1 or 2	n = 285		n = 384	
Age, mo	−0.04	0.49	0.04	0.40
Axillary temperature, °C	−0.04	0.53	0.05	0.34
Blood tests				
Sedimentation rate, mm/h	ND*		0.25	0.003
White cell, count/μL	−0.02	0.76	0.01	0.93
Hemoglobin, g/dL	−0.04	0.56	−0.07	0.18
Platelet, count/μL	−0.14	0.03	−0.07	0.24
Cerebrospinal fluid				
White cell, count/μL	0.15	0.02	0.02	0.67
Glucose, mg/dL	−0.13	0.04	−0.19	0.0003
Protein, g/dL	0.07	0.24	ND	
Matrix metalloproteinase-9, ng/mL	ND		0.15	0.03
Tissue inhibitor of metalloproteinase-1, ng/mL	ND		0.03	0.63
Glasgow Coma Score†	0.02	0.70	−0.02	0.71
Time to death from admission, hrs	−0.61	0.05	−0.14	0.11
Days of temperature ≥37.5°C	−0.19	0.002	−0.02	0.67
Days Glasgow Coma Score <15	−0.01	0.93	0.05	0.38
Days of hospital stay	0.14	0.06	0.11	0.07
Glasgow Outcome Score‡	0.02	0.77	−0.11	0.04
CRP on day 3 or 4	n = 218		n = 57	
Days of temperature >37.5°C	0.01	0.93	0.28	0.04
Days Glasgow Coma Score <15	0.19	0.005	0.46	0.0006
Days of seizures	ND		0.44	0.001
Days of hospital stay	0.21	0.02	0.65	<0.0001
Glasgow Outcome Score	−0.21	0.01	−0.41	0.004

*Not determined.
†Range 3 (worst)–15 (best).
‡Range 1 (worst)–5 (best).

TABLE 2. Differences Between CRP Values (mg/L) and Qualitative Variables on Admission Versus During Course of Illness, and Outcomes, Using Mann–Whitney and Kruskall–Wallis test

	Latin American			Luanda		
Variable	Yes	No	*P* Value	Yes	No	*P* Value
CRP on day 1 or 2	n = 285			n = 384		
Female	160 (99)*	150 (110)	0.07	152 (86)	140 (104)	0.92
Etiology						
Streptococcus pneumoniae	160 (68)		0.03	160 (70)		0.004
Haemophilus influenzae	160 (73)			161 (27)		
Neisseria meningitidis	189 (159)			134 (98)		
Glasgow Outcome Score† <5	169 (72)	155 (57)	0.83	161 (51)	155 (79)	0.04
Any neurologic sequelae‡	160 (105)	156 (114)	0.67	161 (49)	151 (86)	0.03
Any hearing impairment§	169 (70)	151 (118)	0.08	161 (59)	158 (74)	0.77
Death	160 (128)	157 (114)	0.36	161 (45)	158 (71)	0.08
CRP on day 3 or 4	n = 218			n = 57		
Seizures during stay	90 (73)	57 (76)	0.001	160 (61)	60 (98)	0.002
Glasgow Outcome Score <5	92 (72)	57 (72)	0.002	161 (28)	63 (87)	0.0006
Any neurologic sequelae	100 (88)	58 (75)	0.0003	103 (117)	107 (112)	0.92
Any hearing impairment	95 (72)	57 (70)	0.0007	161 (14)	74 (118)	0.005
Death	54 (78)	64 (76)	0.70	154 (49)	103 (113)	0.28

*In parentheses, interquartile range.

†Range from 1 (worst) to 5 (best).

‡Blindness, severe or moderate psychomotor retardation, tetraplegia, hemiparesis, monoparesis and hydrocephalus needing a shunt or ataxia.

§Hearing threshold >40 dB.

TABLE 3. Odds for Slow or Suboptimal Recovery of Patients With CRP Above the Median Value on Day 3 or 4 of Treatment

		Latin American CRP>62 mg/L*			Luanda CRP>62 mg/L*		Luanda CRP>117 mg/L†	
Variable	n	OR (95% CI)	*P* Value	n	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
GCS‡ below 15 for >2 d*	212	1.57 (0.90–2.75)	0.11	57	6.04 (1.65–22.0)	0.007	6.67 (2.09–21.3)	0.001
Length of stay >8 d*	132	1.41 (0.67–2.96)	0.36	44	9.00 (1.84–44.0)	0.007	10.1 (1.15–88.9)	0.04
Seizures during stay	215	2.44 (1.29–4.61)	0.006	57	6.34 (1.81–22.2)	0.004	3.69 (1.20–11.4)	0.02
Secondary fever	214	2.30 (1.33–3.98)	0.003	44	4.53 (0.86–23.9)	0.08	1.71 (0.50–5.92)	0.39
Suboptimal clinical course§	211	2.11 (1.18–3.76)	0.01	57	5.14 (1.07–24.8)	0.04	8.59 (0.98–75.2)	0.05
Glasgow Outcome Score <5¶	146	3.09 (1.55–6.15)	0.001	52	5.50 (1.48–20.5)	0.01	6.11 (1.84–20.3)	0.003
Any neurological sequelae‖	202	3.35 (1.61–6.99)	0.01	44	1.31 (0.37–4.67)	0.68	0.87 (0.26–2.89)	0.82
Any hearing impairment >40 dB**	132	2.88 (1.39–5.93)	0.004	38	7.00 (1.28–38.4)	0.03	4.44 (1.12–17.7)	0.03
Death	218	0.85 (0.28–2.61)	0.78	57	1.56 (0.37–6.55)	0.55	2.96 (0.79–11.1)	0.11

*Median value from Latin America.

†Median value from Luanda.

‡Glasgow Coma Score, range from 3 (worst) to 15 (best).

§Temperature >37.5°C or irritability for >5 days, or convulsions after day 3 of treatment.

¶Range from 1 (worst) to 5 (best).

‖Blindness, severe or moderate psychomotor retardation, tetraplegia, hemiparesis, monoparesis and hydrocephalus needing a shunt or ataxia.

**Hearing threshold >40 dB.

clearest association between CRP above median and adverse outcome was for any hearing impairment, which was 3 times more likely in LatAm and 7 times more likely in Angola. In LatAm, CRP above median also doubled the risk of secondary fever, and trebled the risk of neurological sequelae. In Luanda, CRP above median increased 6 times the risk of scoring more than 2 days under 15 on the Glasgow Coma Scale and elevated 9 times higher the likelihood of hospital stay longer than 8 days.

To put into perspective the strength of these associations, we examined the LatAm series that composed a statistically meaningful number of children (Table 4). Here we compared the 3rd or 4th day CRP versus the child's performance on the Glasgow Coma Scale at arrival, this covariate being the single most powerful predictor for dismal outcome in childhood BM.[15] Scoring below 13 proved superior to raised CRP in terms of severe neurological sequelae (OR, 14.2; 95% CI, 3.15–63.5; $P = 0.005$ vs. OR, 5.71; 95% CI, 1.60–20.4; $P = 0.007$, respectively), whereas no difference was found for any neurological sequelae (OR, 4.24 vs. 3.24, respectively), for scoring below 5 on the Glasgow Outcome Scale (OR, 4.18 vs. 3.11, respectively), or for being left with impaired hearing (OR, 2.33 vs. 2.89, respectively). When the child showed both a CRP above median level and a Glasgow Coma Score below 13, the odds for severe neurological squelae, any neurological sequelae, or any hearing impairment increased to 25.4, 7.9 and 5.3, respectively. Full deafness by itself was not predicted by either index.

Finally, we explored the power of raised (above median) CRP levels on day 3 or 4 to predict adverse outcomes (see Table, Supplemental Digital Content 2, http://links.lww.com/INF/C422). Although the sensitivity and specificity remained modest, raised CRP had a high negative predictive value of no less than 92% to

TABLE 4. Strength of Associations Between Different Adverse Outcomes and the Single CRP Measurement on Day 3 or 4, or the Initial Glasgow Coma Score, or the Combination of These 2 Parameters; Analysis Limited to the Latin American Patients With Both Measurements Done

	Severe Neurological Sequelae*, n = 198		Any Neurological Sequelae†, n = 198		Any Audiological Sequelae‡, n = 130		Deafness§, n = 130		Glasgow Outcome Score¶ <5, n = 144	
Variable	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
CRP >62 mg/L‖	5.71 (1.60–20.4)	0.007	3.24 1.54–6.79)	0.002	2.89 1.39–5.98)	0.004	1.86 0.59–5.90)	0.29	3.11 1.56–6.21)	0.001
Glasgow Coma Score<13‖	14.2 3.15–63.5)	0.0005	4.24 2.06–8.75)	<0.0001	2.33 1.13–4.79)	0.02	1.10 0.36–3.38)	0.87	4.18 2.07–8.43)	<0.0001
Both against one or none	13.1 4.07–42.0)	<0.0001	5.78 2.77–12.1)	<0.0001	5.55 2.35–13.1)	<0.0001	2.36 0.75–7.38)	0.14	8.06 3.51–18.5)	<0.0001
Both against none	25.4 3.22–200)	0.002	7.91 3.04–20.6)	<0.0001	5.31 2.01–14.0)	0.0007	1.71 0.48–6.18)	0.41	9.07 3.44–23.9)	<0.0001

*Blindness, severe psychomotor retardation, tetraplegia or hydrocephalus needing a shunt.
†Any severe neurological sequelae or moderate psychomotor retardation, hemiparesis, monoparesis or ataxia.
‡Hearing threshold >40 dB in the better ear.
§Hearing threshold ≥80 dB in the better ear.
¶Range 1 (worst) to 5 (best).
‖Median values.

97% for death, severe neurological sequelae or deafness. Thus, children with a CRP below 62 mg/L on the 3rd or 4th day in hospital had a very small risk of succumbing, developing severe neurological problems or remaining left with impaired hearing. When initial Glasgow Coma Scores below 13 were combined with a raised median CRP value, the positive likelihood ratios increased slightly, but otherwise hardly improved the information obtained from the single CRP measurement.

DISCUSSION

Clinicians who attend children with BM have few laboratory indices to help them decide which patients deserve the closest attention. This is harrowingly true in resource-poor settings. CRP is a useful yardstick, especially if measured sequentially, and preferably daily, during the first week or so.[1,2] Frequent and sequential monitoring is not always possible, however, and a single measurement may be all that is obtainable. In such cases, a single CRP measurement on the 3rd or 4th day is most informative because it rather reliably identifies the patients with highest risk of seizures, slow recovery, hearing impairment and low scoring in the Glasgow Outcome Scale. We are not aware of any alternative laboratory or other investigation that equals serum CRP determination in simplicity and cheapness. Serum procalcitonin,[8,16–18] another index of inflammation, is much costlier, slower to measure, and requires expensive equipment. This is partly because serum procalcitonin concentration is only 1/1000th that of CRP.

CRP can be measured easily and rapidly, even at bedside. Only a whole-blood finger-prick sample is required, there is no need for centrifugation, and an automated analyzer gives the quantitative result within minutes.[5–7] Although the course of invasive bacterial infections is best followed up with daily determinations,[1–4] this study shows how well just a single measurement during the 3rd or 4th day of treatment performs in childhood BM. The predictive capacity of CRP almost paralleled the child's score on the Glasgow Coma Scale at presentation to hospital.[15] Combining the initial Glasgow Coma score with the CRP value from day 3 or 4 would double the predictive power. Both measures are inexpensive and simple enough to be utilized anywhere, in the world's wealthy and poor areas—good news for developing countries where the majority of pediatric BM is encountered.

We acknowledge limitations in our study. CRP was not measured from every single patient, and one may argue that the 2 series, one from Latin America and the other from Africa, were not necessarily comparable. However, the disease (meningitis) and the age groups were the same, the causative agents were mostly the same, the data were collected prospectively in a similar manner, both series were among the largest to date, the socioeconomic conditions were not drastically dissimilar, CRP was measured with the same method and the procedure was included in the routine protocols.

Although there were some differences in the predictive value of CRP between the 2 sites, there were far more similarities. The differences in the number of patients, which was greater in Luanda on day 1 to 2 and much smaller on day 3 to 4 may have contributed to the discrepancies, together with the much higher mortality rate and a possible co-infection by endemic malaria in Luanda. Very high-CRP values could not be diluted in Luanda, where malaria, which also increases CRP,[19] may also have somewhat distorted the results.

Despite these considerations, we believe the message is clear: serum CRP, even if not optimally measured daily,[1–4] provides useful information about outcomes of childhood BM. If resources allow only one measurement, this should be scheduled on the 3rd or 4th day of treatment. If the Glasgow Coma Scale is used to grade the child's presenting status, outcomes are predicted even more reliably by combining the CRP value with the Glasgow score.

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