Acute bacterial meningitis (BM) accounts globally for 2% of deaths in children younger than 5 years (1). BM triggers a strong inflammatory reaction in the central nervous system (CNS), and the extent of this reaction is associated with adverse outcomes (2, 3). Cathelicidins make up an antimicrobial peptide family, which plays an important role in innate and adaptive host defense. The only human cathelicidin, LL-37, is best known for its antimicrobial properties, although it also exerts multiple immunomodulatory effects (4). In cathelin-related antimicrobial peptide (CRAMP) knockout mice, induced pneumococcal meningitis increased the numbers of bacteria and decreased neutrophil infiltration in the CNS, which led to a mortality rate higher than that in wild-type mice (5). Moreover, intrathecally administered CRAMP reduced the meningitis-related mortality rate in wild-type mice, suggesting cathelicidin as a possible adjuvant medication (6). Elevated cerebrospinal fluid (CSF) cathelicidin levels have been reported in patients with tuberculous meningitis and BM (7, 8), but no studies so far have assessed the dynamics of CSF cathelicidin in BM in response to treatment.

We investigated cerebrospinal fluid (CSF) cathelicidin concentrations in childhood bacterial meningitis on admission and during antimicrobial treatment. CSF cathelicidin concentrations on admission correlated with CSF white cell counts and protein levels but not with bacterial etiology. A greater decrease in the concentration in response to treatment was associated with a better outcome. Since the CSF cathelicidin concentration reflects the degree of central nervous system (CNS) inflammation, it may be used as a novel biomarker in childhood bacterial meningitis. An early decrease during treatment likely signals more rapid mitigation of the disease process and thus a better outcome.

Laboratory measurements and statistical analysis. Cathelicidin concentrations in CSF were assessed by using a commercial enzyme-linked immunosorbent assay kit (USCN Life Science, Wuhan, China) (8). All values below 0.1 ng/ml were given a predefined value of 0.05 ng/ml. The data were analyzed with StatView software, version 5.0.1 (SAS Institute, Cary, NC). The Wilcoxon signed-rank test, Spearman’s rank correlation, the Mann-Whitney U test, the Kruskal Wallis test, and logistic regression were used when appropriate.

Patient demographics. A total of 99 patients (median age, 8 months) fulfilled the inclusion criteria. The most common causative agent was Haemophilus influenzae type b (n = 40) followed by Streptococcus pneumoniae (n = 26) and Neisseria meningitidis (n = 7). Four patients with Gram-negative enteric bacilli were identified, one patient with Streptococcus agalactiae was identified, and one patient had H. influenzae type a meningitis. The etiology for 20 patients remained unknown, but they all fulfilled the strict criteria for BM set in the original trial (9). As for the adjuvant treatment, 20 patients received dexamethasone, 25 received glycercol, 32 received both agents, and 22 received a placebo. The case fatality rate in our series was 14%, severe neurologic sequelae on discharge were detected in 4%, and deafness was detected in 18%.

Cathelicidin concentrations versus other findings. The CSF cathelicidin concentrations varied overall from 0.05 to 1,258 ng/ml, with medians of 27.9 ng/ml for CSF1 (n = 77; IQR, 43.4 ng/ml). A significant difference existed between the CSF1 and CSF2 cathelicidin concentrations (P = 0.006). The CSF cathelicidin concentrations on admission did not differ in terms of patient age (Table 1) or causative agent. However, patients who presented...
with a lower GCS score tended to show higher CSF cathelicidin concentrations in both samples (Table 1). CSF1 concentrations correlated with the CSF1 white cell count and protein level, whereas the CSF2 cathelicidin levels were associated with the CSF2 protein level but not with the leukocyte count of the same sample (Table 1).

No differences emerged between the CSF2 cathelicidin concentrations and the specific adjuvant used in treatment (P > 0.05).

**Prognostic value.** Although no statistical significance was reached, higher CSF1 cathelicidin concentrations on admission were typically associated with better outcomes (higher GOS score at discharge from hospital) (Table 1). That said, lower ratios of CSF2 to CSF1 cathelicidin correlated with higher GOS scores, suggesting that a clear decrease in the CSF1 cathelicidin concentration during treatment predicted a better outcome (Table 1). No similar correlation between outcome and the ratio of CSF white cell counts was observed. In addition, a decrease in CSF1 cathelicidin concentration (44 patients), compared with either no change (3 patients) or an increase (18 patients), predicted a better recovery (GOS score 5) (odds ratio [OR], 3.75; 95% confidence interval, 1.19 to 11.81; P = 0.001).

In this retrospective analysis of 99 children with BM, we demonstrated that an early decrease in the CSF1 cathelicidin concentration during the first 12 to 24 hours of antimicrobial treatment was associated with a better outcome. To our knowledge, this is the first study in which CSF cathelicidin, measured twice during the course of BM, is related to the outcome in patients with this severe disease. Furthermore, the CSF1 cathelicidin concentration on admission reflected the degree of CNS inflammation in BM, correlating very clearly (P < 0.001) with the CSF white cell count and protein level.

There were limitations of this study. The samples were stored frozen for several years before cathelicidin was measured, and CSF samples were not available from all the patients. However, because all the samples were treated and stored similarly, a possible degradation process would presumably have had a minor effect on the ratio of CSF2 to CSF1 cathelicidin. While we acknowledge these problems, our findings are consistent with previously reported research results.

Our study’s findings indicate that CSF cathelicidin can be used as a novel biomarker of the inflammatory process in BM, since its dynamics in the early course of the disease predict the outcome.

### Table 1: Correlations between CSF cathelicidin, patient characteristics and outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>CSF1 Cathelicidin</th>
<th>CSF2 Cathelicidin</th>
<th>CSF2/CSF1 Cathelicidin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ρ</td>
<td>P value</td>
<td>ρ</td>
</tr>
<tr>
<td>CSF1 cathelicidin</td>
<td>0.543</td>
<td>&lt;0.001</td>
<td>0.405</td>
</tr>
<tr>
<td>Age</td>
<td>-0.158</td>
<td>0.14</td>
<td>-0.063</td>
</tr>
<tr>
<td>GCS score on admission</td>
<td>-0.192</td>
<td>0.08</td>
<td>-0.301</td>
</tr>
<tr>
<td>CSF1 white cell count</td>
<td>0.528</td>
<td>&lt;0.001</td>
<td>0.278</td>
</tr>
<tr>
<td>CSF1 protein level</td>
<td>0.618</td>
<td>&lt;0.001</td>
<td>0.600</td>
</tr>
<tr>
<td>CSF2 white cell count</td>
<td>0.342</td>
<td>0.009</td>
<td>0.206</td>
</tr>
<tr>
<td>CSF2 protein level</td>
<td>0.346</td>
<td>0.006</td>
<td>0.466</td>
</tr>
<tr>
<td>GOS score on discharge</td>
<td>0.209</td>
<td>0.05</td>
<td>-0.092</td>
</tr>
</tbody>
</table>

However, further studies are needed to uncover the mechanisms behind these interesting observations.

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**REFERENCES**