Analysis of oral antibiotic treatment that failed to prevent the development of Haemophilus influenzae meningitis: consequences on mortality

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One hundred and four children suffering from Haemophilus influenzae meningitis were studied in a multi-centre study in France between October 1991 and June 1993. The clinical and bacteriological findings were similar to those usually found in this condition. Fifty three per cent of the H. influenzae strains cultured produced β-lactamase and 98% were of type b. Forty-six children who had been prescribed oral antibiotics before hospitalisation were analysed in this study. This analysis took into account the nature of the antibiotic and whether it was prescribed as the treatment of first or second intention. Treatment failures, defined according to pre-established criteria, were found to be independent of whether or not the incriminated strain was β-lactamase producing and whether or not it was sensitive in vitro to the antibiotic prescribed. None of the 46 children who had received pre-hospital oral antibiotics died while three of the 58 who had not received pre-hospital oral antibiotics died. However, it is difficult to establish in our study a clear relationship between the reduction of mortality and previous oral antibiotic treatment in bacteriologically proven cases of H. influenzae meningitis.

Introduction

Before the introduction of vaccination, Haemophilus influenzae was the most frequent cause of bacterial meningitis in children. The incidence of H. influenzae meningitis has been estimated in France to be about 15 to 18 cases for every 100,000 children aged between 0 and 5 years (median 17 months), with the highest incidence occurring in children between 6 and 18 months old (Boucher et al., 1992). It is sometimes fatal and can be associated with serious sequelae (Taylor et al., 1990).

Meningitis is sometimes preceded by symptoms suggesting an upper respiratory tract infection (URTI) for which antibiotics are frequently prescribed at home. The efficacy of the antibiotic prescribed against the initial infection and its ability to prevent complications depend on several factors, including the strength and number of doses, patient compliance with treatment, period of infection before commencement of...

Many comparative and non-comparative clinical studies have tried to assess the efficacy of antibiotics in the treatment of common intercurrent infections in children by measuring the resolution of symptoms and the prevention of complications. However, as these complications are rare, it is seldom possible to analyse them adequately, thus reducing such studies to simple descriptions of isolated, or a small number of, cases of treatment failures (Pesnel et al., 1983; Phillips, 1986).

The objective of the present study was to measure the efficacy of initial antibiotic therapy in the prevention of *H. influenzae* meningitis by noting the circumstances in which meningitis developed and assessing whether or not there was a failure of treatment with the given antibiotic against the acute infection.

**Materials and methods**

Case histories were collected in a multi-centre study involving 23 teaching and general hospitals located throughout France. The study was retrospective for the cases diagnosed between October 1991 and April 1992, and prospective for those diagnosed between May 1992 and June 1993. A total of 104 children were included in the study.

All cases were children less than 15 years from whom the bacteriology laboratory identified an *H. influenzae* meningitis according to the following criteria: presence of *H. influenzae* or its soluble antigens in the cerebrospinal fluid (CSF); or presence of *H. influenzae* or its soluble antigens in at least one blood culture together with a CSF showing at least two of the following three criteria: more than 5 cells/mm³, proteins greater than 0.45 g/L, glucose <2.5 mmol/L or a CSF/blood glucose ratio <0.5.

The organism isolated from each case was typed and studied for production of β-lactamase.

Data were collected using questionnaires addressed to bacteriologists and clinicians in charge of each patient, and compiled at the Centre National de Référence pour *H. influenzae* (CHU of Purpan, Toulouse, France).

The following demographic data were recorded from each patient’s clinical file: past medical history, history of the presenting illness before hospitalisation, whether or not antibiotics were started at home, existence of an apparent initial focus of infection, whether this focus was probable (elicited from child’s entourage) or definite (confirmed upon clinical examination in hospital).

No specific diagnostic criteria was established to define an apparent initial focus of infection (i.e. otoscopy for acute otitis media, chest X-ray for pneumonia, etc.)

To establish a relationship between the two pathological processes, a maximum period of 21 days was allowed between the beginning of symptoms and diagnosis of meningitis.

Some items in the questionnaire and the conclusion in each case file were reviewed by one of the authors (JA) as an independent assessor. The conclusions of the assessor took precedence over those made by the treating centre.

Oral antibiotic treatment which commenced before hospitalisation was considered to be a failure when it was prescribed according to its full recommended schedule for treating the apparent initial focus of infection and it still did not prevent meningitis. Treatment failures were divided into 3 categories (1) confirmed failure, when treatment was administrated >48 h before admission to hospital, with knowledge of the daily dose
schedule of administration and compliance (refered by parents or based on the referral letters) or when the antibiotic was inactive against *H. influenzae*, regardless of the therapeutic schedule used; (2) possible failure, when the treatment was administered >48 h before admission to hospital, with knowledge either of the daily dose and schedule of administration or of the compliance of treatment (refered by parents or based on the referral letters); (3) efficacy not evaluable, when the duration of treatment was <48 h or patient compliance was doubtful (no information available in the hospital records).

There was no requirement in the study protocol to measure plasma and/or urinary antibiotic levels. Similarly, a count of the number of tablets actually consumed by the patient was not recorded.

**Statistical analysis**

The case report forms were analysed using the statistical software SAS Institute Inc. Cary, NC, USA version 6.08, on a PC Compaq 486, Compaq LTD, Houston, TX, USA. The quantitative variables were recorded by their number, means, and standard deviations. The qualitative variables were represented by their frequencies and percentages.

A certain number of sub-groups were described, to make comparisons using the chi-square test, e.g. children previously receiving antibiotics, versus those not receiving antibiotics, β-lactamase producing strains versus non-β-lactamase producing strains. Items for which physicians did not give answers were considered as missing data and were not included in denominators to make comparisons.

A detailed descriptive analysis was conducted on the failures of antibiotic therapy, taking into account the antibiotic used and whether the treatment was prescribed in the first or second intention.

**Results**

*Findings before hospitalisation*

The main characteristics of the study population are shown in Table I. Males predominated (62% boys); there was a mean age of 17.3 months (range 1–55). The age group in which the largest number of infections was seen was between 6 and 12 months (30.7%, 32 out of 104 children); 87% of the children were aged less than 3 years and 77% less than 2 years. The methods of child care at the time of contracting the infection were: 66% at home, 13.5% in a day-care centre, 9.5% by a child-minder and 11% attended school. Forty five out of 102 children (44%) had a past history of an URTI (27%, 28 out of 102 children) and bronchopulmonary (13%, 13 out of 102 children) infections (data missing for two children). Only one child had been (incompletely) vaccinated against *H. influenzae* b.

*Clinical findings at hospitalisation*

At hospitalisation 55 out of 101 children (54%) had, in the opinion of the physician, a clearly identifiable infectious focus (data missing for three children). In 45% of cases (*n* = 44) this was an URTI, in 8% it was bronchopulmonary infection (*n* = 8) and in 5% (*n* = 3) both URTI and bronchopulmonary infection. The time interval between the
appearance of symptoms and hospitalisation was on average 2.35 days (range 0–15).
A summary of the clinical picture at hospitalisation is shown in Table II.

**Bacteriological results**

In 99 children (95%), the CSF culture grew *H. influenzae*. In the other cases, the bacteriological diagnosis was confirmed by a positive blood culture (four cases), or a positive soluble antigen test in the CSF (one case). Blood cultures were positive in 63 out of 76 cases.

Fifty-five out of 103 (53%) isolates were β-lactamase producing; 102 strains were of type b (including the case of positive soluble antigen in the CSF), one was of type f, and one was not typable. Meningitis due to type f *H. influenzae* was seen in a child who had been incompletely vaccinated (only one injection).
Table II. Comparison of children with and without antibiotic treatment: effects of previous antibiotic therapy

<table>
<thead>
<tr>
<th>Patients (n = 104)</th>
<th>Antibiotic (n = 46)</th>
<th>No antibiotic (n = 58)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial focus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>55/101 (54%)</td>
<td>27 (59%)</td>
<td>28 (48%)</td>
</tr>
<tr>
<td>URTI</td>
<td>46 (45%)</td>
<td>24 (52%)</td>
<td>23 (40%)</td>
</tr>
<tr>
<td>LRTI</td>
<td>11 (11%)</td>
<td>4 (8%)</td>
<td>7 (12%)</td>
</tr>
<tr>
<td><strong>Delay between symptoms and hospitalisation (days—mean 2.35, range 0—15)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>16 (35%)</td>
<td>39 (67%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>7 (15%)</td>
<td>9 (15%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>7 (15%)</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2 (4%)</td>
<td>4 (7%)</td>
<td></td>
</tr>
<tr>
<td>≥5</td>
<td>11 (24%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical picture at hospitalisation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean temperature (°C)</td>
<td>38.9 (36.0–40.7)</td>
<td>38.9 (36.5–40.7)</td>
<td>39.0 (36.0–40.5)</td>
</tr>
<tr>
<td>limits</td>
<td>16 (16%)</td>
<td>6 (13%)</td>
<td>10 (17.2%)</td>
</tr>
<tr>
<td>convulsions</td>
<td>9 (9%)</td>
<td>3 (6.5%)</td>
<td>6 (10.3%)</td>
</tr>
<tr>
<td>coma</td>
<td>63 (60.5%)</td>
<td>31 (67%)</td>
<td>32 (55%)</td>
</tr>
<tr>
<td>vomiting</td>
<td>78 (75%)</td>
<td>34 (74%)</td>
<td>44 (75%)</td>
</tr>
<tr>
<td>neck stiffness</td>
<td>20 (19.2%)</td>
<td>3 (6.5%)</td>
<td>17 (29.3%)</td>
</tr>
<tr>
<td>shock</td>
<td>2 (5%)</td>
<td>62/76 (82%)</td>
<td>41/47 (87%)</td>
</tr>
<tr>
<td>Laboratory test</td>
<td>99 (95%)</td>
<td>45 (98%)</td>
<td>54 (93%)</td>
</tr>
<tr>
<td>CSF positive</td>
<td>62/76 (82%)</td>
<td>21/29 (93%)</td>
<td>41/47 (87%)</td>
</tr>
<tr>
<td>blood culture</td>
<td>22 (22%)</td>
<td>12 (26%)</td>
<td>10 (18%)</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sequelae</td>
<td>3 (3%)</td>
<td>0</td>
<td>3 (5.1%)</td>
</tr>
</tbody>
</table>

*Three children had both URTI and LRTI focus.

*Three out of 104 children had incomplete data collected.

URTI, Upper respiratory tract infection; LRTI, lower respiratory tract infection; NS, difference not statistically significant; CSF, cerebrospinal fluid.

**Outcome**

In every case, a suitable and standard parenteral antibiotic was prescribed as soon as the diagnosis was suspected in hospital.

Three children died (2.8%) and 22 children (21%) developed neurological sequelae, ranging from a mild psychomotor deficit to severe neurological disease.

**Effects of pre-hospital oral antibiotic treatment**

51 prescriptions of antibiotics were given to 46 children (44%) before hospitalisation: aminopenicillins (15 cases), co-amoxiclav (18 cases), first generation cephalosporins (9 cases), macrolides (6 cases), penicillin V (1 case), erythromycin-sulphafurazole (1 case) and co-trimoxazole (1 case). In seven cases, the initial antibiotic prescribed was changed. No children had received parenteral antibiotics.

The data from the patients who received an antibiotic before hospitalisation (treated group) were compared with those from the untreated patients (Table II).
An apparent infectious focus was found more frequently in the treated group (59% versus 48%). This difference was not statistically significant (NS). Shock was reported significantly more frequently among the untreated children (32% versus 7%, \( P = 0.002 \)). The other clinical findings at hospitalisation were not different between the two groups.

The time interval between the beginning of symptoms and hospitalisation was shorter in the untreated group. The percentage of children with a delay of less than 2 days was significantly higher in this group (67% versus 35%, \( P > 0.001 \)).

Sequelae from the meningitis were observed in 26% \( (n = 12) \) of the children previously treated with antibiotics and in 18% \( (n = 10) \) of the children not treated with antibiotics \( (P = 0.34) \). The three deaths reported were all from the untreated group of children. The breakdown of treatment failures according to whether the treatment was of first or second intention is shown in the Figure. According to our criteria in the treated group of children there were 20 confirmed failures and eight possible failures.

In the 18 cases where the strain was \( \beta \)-lactamase producing and the patient was treated with an aminopenicillin, with or without an inhibitor, there were 14 failures. The use of co-amoxiclav did not prevent treatment failures. In those patients in whom the strain was not \( \beta \)-lactamase producing (15 cases), six failures were observed with the same drugs. When a first generation cephalosporin was used, two failures were observed, one due to a sensitive strain and the other due to a \( \beta \)-lactamase producing strain. With the macrolides, treatment failures were seen in all (six out of six) cases (Figure).

**Discussion**

This study was conducted before the widespread vaccination of children against *H. influenzae* type b in France, and so it is probably one of the last to study this question on such a large scale. The object of the study was to analyse, over a limited period of time and using a large number of cases, the development of *H. influenzae* meningitis
as a function of initial oral antibiotic therapy prescribed in general practice for an apparent mild infection.

Clinical studies conducted to test antibiotics in mild infections such as otitis media or pharyngitis are usually designed to measure the favourable progress of patients. Such methods do not take into account spontaneous cures after common intercurrent infections (Marchant et al., 1992; Norrby, 1991). Another approach is to consider treatment failures, resulting in a severe illness after the prescription of an antibiotic. Such studies could be less difficult to carry out and may give clearer results. *H. influenzae* meningitis was chosen as the model to study because of its epidemiological and pathophysiological characteristics. The population at risk is homogeneous, and before the use of vaccination the outcome is well-known and constant over time (Swartz & Dodge, 1965a,b; Canton et al., 1980). The pathophysiology of the condition is well characterised by an invasion of the respiratory mucosa and, in approximately 40% of cases, a local focus of infection which can be associated with a bacteraemia and subsequent meningitis (Dabernat, 1985; Quagliarello & Scheld, 1992). The preventive or curative role of antibiotics lies in the period between the initial invasion and the bacteraemic phase.

The epidemiological patterns we observed (median age, sex ratio, mortality and sequelae) are in keeping with those of the previous study establishing the incidence of *H. influenzae* meningitis in France (Boucher et al., 1992) and those reported by Tudor-Williams et al. (1989) and Autret & Aujard (1993). Therefore, we have good reason to assume that there was no significant bias in the recruitment of our cases.

In our study the accuracy of establishing the past medical history or the diagnosis of an apparent initial focus of infection could be controversial because of the lack of specific clinical or radiographic criteria. However, the results reported here provide interesting information and reflect the way diagnosis is made in common clinical practice.

Our study revealed that a severe clinical presentation at hospitalisation was more frequently seen in patients who had not already received pre-hospital oral antibiotics (Table II). There was a significant difference in the speed of hospitalisation and severity of the illness depending on whether or not the child had received antibiotics at home. In fact, this difference could be explained more by the severity of the initial illness than by any effect of oral antibiotics: i.e. a more severe illness leads to immediate hospitalisation without indication for oral antibiotic treatment at home. Moreover, oral antibiotics did not prevent the presence of *H. influenzae* in the CSF culture of our patients although we did not study the concentration of *H. influenzae* in CSF. Therefore we cannot exclude an indirect beneficial effect of oral antibiotics related to a possible reduction in the concentration of bacteria thereby decreasing the severity of the illness (Feldman, 1978; Feldman et al., 1982). Children in whom treatment had been started before hospitalisation showed a longer period of pre-hospitalisation symptoms and a clinical picture on admission which was less severe than that seen in children hospitalised without previous antibiotic treatment. Similarly, the three fatal cases occurred in children who were not previously treated.

This study was not able to record precise data on patient compliance and respect of the dosage schedule because of the difficulty of collecting and checking this type of information (counting tablets ingested, assay of active substance in blood) in routine medical practice. About 60% of patients had a history of vomiting at the time of hospitalisation (Table II). One can suppose that vomiting could contribute to the failure
of a treatment if present at the time of the onset of the illness for which an oral antibiotic was prescribed. On the other hand vomiting is reported as a common symptom of children with acute otitis media or other mild infections treated with oral antibiotics. (Froom et al., 1990; Klein, 1994; Niemela et al., 1994) as well as an adverse event of oral antibiotics not leading to a treatment failure or severe complications (Arguedas et al., 1991; Jacobsson et al., 1993).

The only other factors we were able to take into account to explain the antibiotic therapy failures concerned the choice of antibiotic and bacteriological findings such as susceptibility of the strain. This limited the scope of the analysis of these failures even though they occurred in a series of bacteriologically documented meningitis. These difficulties represented the main stumbling block in our analysis of treatment failures. Furthermore, as in any study analysing failures, it is always very difficult to collect a sufficiently large number of cases to carry out an adequate statistical analysis.

In this study, the main antibiotic families commonly used for the treatment of URTI and bronchopulmonary infections in children were present, and to various degrees all were associated with therapeutic failures. The number of 'treatment failures' observed with any antibiotic against a given infection should be appreciated bearing in mind the extent to which these antibiotics are used against common infections in general practice. For example between November 1991 and June 1993, for a total of approximately 20 million prescriptions for URTI infections in children in France, the breakdown by indication of antibiotics prescribed including only otitis media and tonsillitis was as follows: amoxicillin: 6% otitis media, 37% tonsillitis; co-amoxiclav 34% otitis media, 10% tonsillitis; first generation cephalosporins: 18% otitis media, 29% tonsillitis; macrolides: 1% otitis media, 9% tonsillitis; erythromycin-sulphafurazole: 12% otitis media, 1% tonsillitis. However, detailed analysis of antibiotic treatment failures was limited because it proved almost impossible, given the conditions under which this study was conducted, to collect data concerning the actual consumption of antibiotics. This difficulty was encountered in both the retrospective and prospective cases analysed.

The activity of the antibiotic against the infecting bacterium did not seem to be a discriminating factor in the development of meningitis (Figure). It has been suggested that the delay between the primary infection and the development of meningitis is inversely related to the size of the inoculum reaching the CSF during the bacteraemic phase (Grenier & Marchand, 1983). Children receiving antibiotics after several days of apparently mild infection may already be in the bacteraemic phase and the start of meningitis. In such situations, the lack of efficacy of oral antibiotics perhaps should not be considered to be a therapeutic failure.

Among the studies published on meningitis very few analyse antibiotic treatment administered before the diagnosis of meningitis was suspected. Others which record preceding antibiotic therapy do not attempt to define objective criteria for therapeutic failure (Swartz & Dodge, 1965a,b; Winkelstein, 1970; Canton et al., 1980; Ispahani, 1983). Recent series have studied the effect on mortality of parenteral antibiotics administered by general practitioners before hospital admission for suspected meningitis (Cartwright et al., 1992; Gossain, Constantine & Webberly, 1992; Sorensen et al., 1992; Strang & Pugh, 1992).

Romer (1977) reported a series of 104 children and adults with bacterial meningitis, 30% of who had been previously treated. The mortality rate was higher and the
duration of symptoms before hospitalisation shorter in the previously untreated group of patients (Romer, 1977). These findings were confirmed in other large series (Winkelstein 1970; Jarvis & Saxena, 1972; Goldacre, 1977). However, as in the other series, the pre-hospital oral antibiotic therapy used for an unsuspected meningitis was not analysed.

The findings of the four recent studies to evaluate the effect of early parenteral penicillin in meningococcal meningitis were controversial (Cartwright et al., 1992; Gossain et al., 1992; Sorensen et al., 1992; Strang & Pugh, 1992). In three out of four studies with a total of 487 evaluated children and adults from five health districts in the UK, the authors found a substantial reduction in mortality (4.7% vs 11.5%) when antibiotics had been given before hospitalisation. The effect of a previous treatment with oral antibiotics was not analysed (Cartwright et al., 1992; Gossain et al., 1992; Strang & Pugh, 1992). However, Sorensen et al. (1992) in a Danish study that included 170 children and adults observed a higher rate of mortality in the 25 patients who received pre-hospital parenteral treatment (24% vs 3.8%) probably because of the severity of the infection. Interestingly as in our series, none died among the 20 who had received pre-hospital oral antibiotics for unsuspected meningitis.

The mortality rate in our study shows the same trend as previous data from the UK (Cartwright et al., 1992; Gossain et al., 1992; Strang & Pugh, 1992) although these results have to be analysed cautiously because of the many important differences between these studies.

In conclusion, a study of the efficacy of antibiotics prescribed to children before hospitalisation by analysing treatment failures, defined as the development of a severe infection after the prescription of the relevant antibiotic, is complicated by certain methodological difficulties. These concern the collection of patient compliance data and identification of the principal factors which may explain treatment failures. Nevertheless, such an approach seems to be necessary to properly evaluate the antibiotics used. The ideal method to undertake such an evaluation remains to be defined, although, it certainly would need to involve prospective studies. In the case of meningitis, such studies are even more difficult to conduct now, given the near disappearance of systemic infections due to \textit{H. influenzae}.

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