Outpatient management of children at low risk for bacterial meningitis

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ABSTRACT

Objective To determine the outcome of children aged 2–14 years with cerebrospinal fluid (CSF) pleocytosis and at very low risk for bacterial meningitis managed as outpatients without antibiotics.

Methods Multicentre, prospective, observational study conducted at nine Spanish paediatric EDs. Patients were diagnosed with meningitis based on clinical suspicion of meningitis and CSF pleocytosis when evaluated in the ED. Children between 2 and 14 years of age with pleocytosis and very low-risk criteria for bacterial meningitis (well appearing, Bacterial Meningitis Score (BMS)=0, procalcitonin (PCT)<0.5 ng/mL and observation without deterioration for less than 24 hours in the ED) were treated as outpatients without antibiotics pending CSF cultures. The primary composite outcome was a final diagnosis of bacterial meningitis or return to the ED for clinical deterioration.

Results Of 182 children between 2 and 14 years old diagnosed with meningitis, 56 met the very low-risk criteria and 45 were managed as outpatients. None was diagnosed with bacterial meningitis or returned due to clinical deterioration. Another 31 patients with BMS=1 (due to a peripheral absolute neutrophil count (ANC)>10 000/mm^3) and PCT <0.5 ng/mL were managed as outpatients, diagnosed with aseptic meningitis and did well. BMS using PCT had the same sensitivity but greater specificity than classic BMS.

Conclusions This set of low-risk criteria appears safe for the outpatient management without antibiotics of children with CSF pleocytosis. Larger studies are needed to evaluate the predictive values of replacing peripheral ANC with PCT in the BMS.

Key messages

What is already known on this subject

- Most meningitis in children are aseptic. Identifying these children may prevent unnecessary hospitalisations and antibiotic treatments. Different scores have been developed to distinguish children with aseptic and bacterial meningitis, being the most useful the Bacterial Meningitis Score.

What this study adds

- This prospective, multicentre study in nine Spanish paediatric EDs found that the combination of clinical criteria, the Bacterial Meningitis Score and low procalcitonin allows safe outpatient management without antibiotics for around 20% of children 2 years or older diagnosed with meningitis. Procalcitonin may improve the performance of the Bacterial Meningitis Score.

INTRODUCTION

Meningitis is an inflammation of the membranes surrounding the central nervous system infection caused by different pathogens. Most meningitis cases are aseptic and, when the cause is identified, enteroviruses are involved in over 90% of the cases.[1 2] In recent years, there has been a decrease in bacterial meningitis cases as a result of the success of the conjugate childhood immunisation programmes.[3 4] Nevertheless, bacterial pathogens still are responsible for around 5% of the meningitis in children.[5–7]

Distinguishing bacterial meningitis from aseptic meningitis is necessary to manage adequately children with meningitis. Accurate and rapid diagnosis of acute bacterial meningitis is essential as early initiation of antibiotic improves patient's outcome. On the other hand, identifying children with viral meningitis can prevent unnecessary hospitalisations and antibiotic treatments. Different scores have been developed, including clinical data and rapidly available parameters, such as the peripheral white blood cell count and the cerebrospinal fluid (CSF) white cell count.[6 8] The Bacterial Meningitis Score (BMS) is a validated clinical prediction rule to identify children at low risk for bacterial meningitis.[6] The BMS includes five dichotomous predictors (the presence of convulsions, the absolute neutrophil count in peripheral blood and in CSF, CSF protein and CSF Gram stain), giving a possible score of 0 to 6 points. The authors also defined a subset of children in which BMS is not applicable (younger than 2 months old, those critically ill, those with purpura, children not previously healthy or treated with antibiotics 72 hours prior to the lumbar puncture). A subset of patients with BMS=0 (those well appearing, well hydrated, and without any signs of neurological or haemodynamic compromise) may be followed as outpatients, perhaps after the administration of a long-acting parenteral antibiotic.[6] Selected febrile children with pleocytosis are occasionally managed as outpatients without receiving antibiotic treatment, although the selection criteria are not always specified.[7 9 10]

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A meta-analysis of BMS validation studies found very few children with bacterial meningitis were misclassified.[11] Those misclassified were under 1 year old or had meningococcal meningitis. However, the specificity of the BMS is around 50% and some variables, like the peripheral absolute neutrophil count, show overlapping areas in patients with bacterial and aseptic meningitis.[3] Procalcitonin (PCT) has a better performance than other acute-phase reactants in identifying patients with an invasive infection[12–14] and, specifically, those due to *Neisseria meningitidis*.[15] Values of PCT higher than 0.5 ng/mL show a sensitivity of 99% (95% CI 97% to 100%) and a specificity of 83% (95% CI 76% to 90%) in identifying patients with bacterial meningitis.[12 16] It seems that a low PCT may be helpful to identify children with presumed viral meningitis suitable for outpatient management.

Our hypothesis is that selected children with very low-risk criteria for bacterial meningitis can be safely managed as outpatients without receiving antibiotics. The main objective of this study is to determine the outcome of patients aged 2 to 14 years old at very low-risk criteria for bacterial meningitis managed as outpatients without antibiotics.

The secondary objectives are:

- To analyse the impact of this approach in the management of children with acute meningitis.
- To analyse the value of replacing the peripheral absolute neutrophil count with PCT in the performance of the BMS (PCT modified BMS, BMS-PCT).

METHOD

We carried out a multicentre, prospective, observational study including children between 2 and 14 years of age diagnosed with meningitis in nine paediatric EDs for a period of 3 years (October 2012 to September 2015). The study was endorsed by the Spanish Paediatric Emergency Research Group (RISEUP-SPERG).

Selection of patients

We included children aged 2 to 14 years old with pleocytosis in the CSF examination when evaluated in the ED in which BMS was applicable and all the following tests were performed: white blood cell count, C reactive protein, PCT, blood culture, CSF examination (including bacterial and enteroviral culture, and enteroviral and bacterial PCR).

CSF examination was performed at the discretion of the physician in charge.

Exclusion criteria

- Children in which BMS is not applicable: critically ill children, those with purpura, children not previously healthy or treated with antibiotics 72 hours prior to the lumbar puncture.[6]
- Children younger than 2 years of age, due to the fact that in this age group clinical symptoms and signs are frequently overlapped between bacterial and aseptic meningitis.

The patient had to fulfil all the following to be considered at very low-risk criteria for bacterial meningitis: aged 2 to 14 years old, well appearing, no sign of neurological compromise, BMS=0, PCT <0.5 ng/mL and no deterioration while staying in the Observation Unit of the ED (always less than 24 hours). Finally, in order to consider outpatient management for a child at very low risk for bacterial meningitis, follow-up had to be available by the primary care paediatrician in the following 24 hours.

Main outcome measures

Children with very low-risk criteria for bacterial meningitis were managed as outpatients without antibiotics finally diagnosed with bacterial meningitis or who returned to the ED due to clinical deterioration.

Definitions

Bacterial meningitis: detection of a bacterial pathogen in the CSF (positive bacterial culture and/or positive Gram stain and/or bacterial genomic detection) or in the blood culture with associated pleocytosis.

Aseptic meningitis: children diagnosed with aseptic meningitis included:

- Viral meningitis: positive enteroviral culture or positive enteroviral PCR in CSF.
- Non-specific meningitis: pleocytosis and no detection of a bacterial pathogen or enterovirus in CSF and blood.

Positive blood or CSF culture: isolation in blood or CSF of true pathogens such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Enterococci*, *group A and B Streptococci*, *Listeria* or *Salmonella* species. Isolation of coagulase-negative *Staphylococci*, *Propionibacterium*, *Streptococcus viridans* and *Corynebacteria* in previously healthy immunocompetent children (no history of heart disease, ventriculoperitoneal shunt, catheters, prostheses or others) were considered as contaminants.

Pleocytosis: 10 leucocytes/mm^3 or greater in CSF.[7]

In haemorrhagic lumbar punctures, we used the following correction factor: CSF white blood cell count (WBC) corrected=CSF WBC–(CSF red blood cell count (RBC) × peripheral WBC/peripheral RBC).

Previously healthy children: patients without any of the following risk factors: (1) immunosuppression (oncological illness, chronic renal failure, transplant patient, sickle cell disease), (2) the presence of a mechanical device (indwelling catheter, ventriculoperitoneal shunt, auditory prostheses) and (3) an invasive diagnostic or therapeutic procedure in the previous 10 days.

Well-appearing patients: defined by a normal paediatric assessment triangle after being evaluated by a paediatric emergency physician during the first hour after attending the paediatric ED. The paediatric assessment triangle is a simple, rapid and useful tool recommended by the American Academy of Paediatrics for health professionals to develop their first impression of the appearance of children. It assesses three aspects (appearance, work of breathing, and circulation to the skin) describing their physiological status and guiding the initial approach to their care, with no need to examine patients or measure their vital signs. Appearance, respiratory and circulatory items had to be classified as normal for infants to be classified as well appearing, and data had to be reflected on the patient's charts.

Critically ill children: severe mental disturbance, evidence of cerebral herniation or need for respiratory or haemodynamic support.

Data collection

We received endorsement from the Research Network of SEUP (Spanish Paediatric Emergency Research Group—RISEUP-SPERG) in April 2012. After that, prior to the initiation of the study, one of the main investigators (SG) distributed via email the electronic questionnaire to the site investigators of the EDs in order to confirm understanding of text, suitability of data collection at all participating sites and to ensure clarity of final data collection. All queries regarding data collection were dealt with by the main investigator in order to maintain consistency of data collection.

Patients were identified by ED physicians and collected demographic, clinical and management data: age, gender, personal history, any treatment administered before arriving to the ED, duration of the fever, symptoms, physical examination, tests,

diagnosis, treatments administered, length of stay in the hospital and evolution of the patient. A telephone follow-up at 1 month post-discharge was conducted for children managed as outpatients. During the telephone interview, we asked about additional medical assessments, admission to other hospitals, administration of antibiotics after discharge and clinical status. An electronic questionnaire via Google Drive for each patient was fulfilled by the physician in charge and sent to the main investigator.

Ethics committee

The study was approved by the Ethics Committee of the Basque Country. Informed consent was obtained from the parents/legal guardians of these patients.

Statistical analysis

The statistical analysis was carried out with IBM SPSS Statistics for Windows (V.22, Armonk, New York, USA). The data were expressed as means, CIs and SD for the quantitative variables and as numbers and percentages for the categorical variables. The continuous variables were compared with Student's t-test and the categorical variables with the χ^2 test and Fisher's exact test. The significance level was established at $P < 0.05$.

RESULTS

During the study period, we registered 461 220 episodes corresponding to children younger than 14 years of age in the included paediatric EDs. Of these, 233 were finally diagnosed with meningitis (0.05%, 95% CI 0.04 to 0.06). Forty-four children were under 2 and 15 (34.1%) were diagnosed with bacterial meningitis. Finally, 182 were older than 2 years and showed pleocytosis in the CSF examination and were included in the study (figure 1): 173 aseptic meningitis (95.1%, 95% CI 91.6 to 98.2) and 9 bacterial meningitis (4.9%, 95% CI 1.76 to 8.04) (table 1).

Of the 182 children aged 2–14 years old with pleocytosis, 56 fulfilled the inclusion criteria for outpatient management. Of these, 45 (80.3%) were managed as outpatients without antibiotics after a period of observation in the ED (13.3±7.1 hours). None of these 45 children was finally diagnosed with bacterial meningitis or returned due to clinical deterioration. An enterovirus was isolated in the CSF in 37 (82.2%) cases. All patients were reached in telephone follow-up, and all were well. Nine patients (20%) returned to the ED due to persistence of the symptoms, but none had clinical deterioration, and three were admitted. During their hospitalisation, they did not receive antibiotics and did well. Eleven patients with very low-risk criteria for bacterial meningitis were hospitalised due to not having an observation unit in the paediatric ED (6, 54.5%), persistence of headache or vomiting (4, 36.4%) or having difficult access to the hospital (1, 9.1%). All of them were diagnosed with viral meningitis; they did not receive antibiotics and did well (hospital length of stay, 40 ± 14.1 hours).

Sixty-one patients had BMS=1, exclusively due to the absolute neutrophil count higher than 10,000/mm^3. Of these, 52 had a PCT <0.5 ng/mL (BMS-PCT=0) and were diagnosed with aseptic meningitis. Of these, 31 (59.6%) were managed as

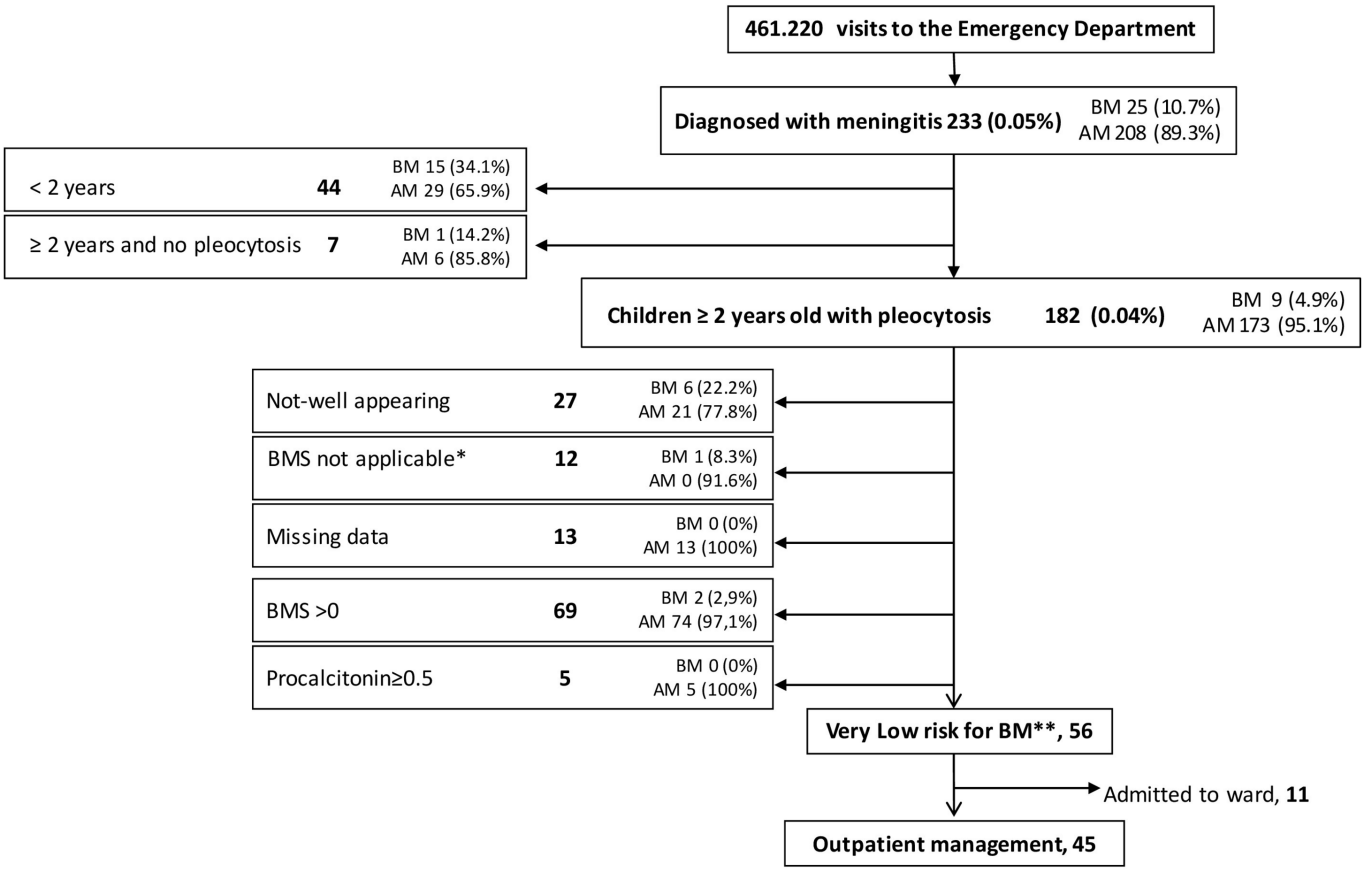

Figure 1 Flow chart of the patients. AM, septic meningitis; BM, bacterial meningitis; BMS, Bacterial Meningitis Score. *Critically ill children, those with purpura, children not previously healthy or treated with antibiotics 72 hours prior to the lumbar puncture. **The patient had to fulfil all the following to be considered at very low-risk criteria for bacterial meningitis: good general condition, no sign of neurological compromise, BMS=0, procalcitonin <0.5 ng/mL and no deterioration while staying in the Observation Unit of the ED (always less than 24 hours).

Table 1 Characteristics of the 182 children older than 2 years with pleocytosis (N, 95% CI)

	Aseptic meningitis N (%) (95% CI)	Bacterial meningitis N (%) (95% CI)
Total	173 (95.1) (90.8 to 97.3)	9 (4.9) (2.6 to 9.1)
Previously unhealthy children	0 (0 to 2.1)	2 (22.2) (6.3 to 54.7)
Sex (male %)	121 (69.9) (62.7 to 76.2)	6 (66.6) (35.4 to 87.9)
Not well appearing	21 (12.1) (8.0 to 17.8)	6 (66.6)* (35.4 to 87.9)
Antibiotics in the previous 72 hours	14 (8.1) (4.8 to 13.1)	1 (11.1) (1.9 to 43.5)
Procalcitonin (ng/mL)†		
<0.5	144/165 (87.2) (81.3 to 91.5)	1/7 (14.3) (2.5 to 51.3)
0.5–2	19/165 (11.5) (7.5 to 17.3)	0 (0 to 35.4)
>2	2/165 (1.2) (0 to 4.3)	6/7 (85.7) (48.6 to 97.4)
Aetiology		
Enterovirus	134 (77.4) (70.7 to 83.3)	
Streptococcus pneumoniae		4 (44.4) (18.8 to 73.3)
Neisseria meningitidis		4 (44.4) (18.8 to 73.3)
Haemophilus influenzae		1 (11.1) (1.9 to 43.5)

*Two of these patients were critically ill (one of them also with purpura).
†In patients with procalcitonin performed.

outpatients and did well. The other nine had a PCT >0.5 ng/mL and six were put on antibiotics, seven were admitted for more than 24 hours and were ultimately diagnosed with aseptic meningitis.

Of the 182 children, 15 had incomplete data to build the BMS (none diagnosed with bacterial meningitis) and 19 were children in which BMS was not applicable (including five patients with bacterial meningitis). In 148 children older than 2 years old with pleocytosis, the BMS was applicable and had a PCT obtained. The performance of the BMS and BMS-PCT in the children in which the BMS is applicable is shown in tables 2 and 3.

Table 2 Value of the Bacterial Meningitis Score and procalcitonin-modified Bacterial Meningitis Score related to the aetiology of the meningitis*

	Value of the BMS and BMS-PCT in regard to the aetiology of meningitis		
	0	1	>1
Score	N (%)	N (%)	N (%)
Bacterial meningitis, n=4			
BMS	0	0	4 (100%)
BMS-PCT	0	0	4 (100%)
Aseptic meningitis, n=144			
BMS	64 (44.4%)	73 (50.7%)	7 (4.9%)
BMS-PCT	121 (84.0%)	21 (14.6%)	2 (1.4%)

*For the 148 children who had complete data and for whom BMS was applicable.
BMS, Bacterial Meningitis Score; BMS-PCT, procalcitonin-modified BMS.

DISCUSSION

Our study suggests that a combination of clinical criteria, BMS and PCT enables safe outpatient management without antibiotics for around 20% of children aged 2 to 14 years with CSF pleocytosis in the paediatric ED. None of these patients was finally diagnosed with bacterial meningitis or returned due to clinical deterioration.

Although children with viral meningitis only require supportive treatment,[2] antibiotic therapy and admission of these patients is a generalised practice. However, a variable percentage of patients with suspected viral meningitis are managed as outpatients,[2 7 9 17] especially those over 3 years of age,[2] and between 15% and 50% of these patients did not receive antibiotics.[2 9 10 17] Hospitals with lower admission rates for meningitis did not show an increase in non-scheduled re-visits to the ED resulting in admission.[17] Except for a retrospective and single-centre study, none of these studies defined the criteria used to identify suitable patients for outpatient management.[9] Using strict criteria to identify children suitable for outpatient management should decrease the risk of misdiagnosing patients with bacterial meningitis.

Distinguishing bacterial meningitis from presumed aseptic meningitis is essential to the adequate management of children with meningitis. Nigrovic *et al* defined the criteria to identify patients at low risk for bacterial meningitis.[6] First of all, a series of patients at higher risk for having bacterial meningitis were excluded: critically ill children, those with purpura, previously non-healthy children or those receiving antibiotics 72 hours prior to the CSF examination. Our series supports these criteria, as the prevalence of bacterial meningitis in this group was around 25%. In a later validation study of the BMS, in patients in which the BMS was applicable, a value of 0 had a negative predictive value of 99.7% for bacterial meningitis.[11] In fact, of 2274 patients with BMS=0, 9 (0.4%) were finally diagnosed with bacterial meningitis. Of these, five were under 1 year old and the others were diagnosed with meningococcal meningitis. Bacterial meningitis is more difficult to distinguish from viral meningitis in children less than 2 years of age. In addition, several studies, including ours, have shown a higher prevalence of invasive bacterial infections, including meningitis, in these patients.[18 19] This is why we decided to exclude in our study young children and add PCT to identify suitable patients for outpatient management.

We added PCT because it is an excellent tool for identifying children with invasive bacterial infections,[13–15] including meningitis.[12 16] In fact, replacing the absolute neutrophil count for PCT in the BMS seems to increase the positive predictive value of the BMS. In our study, when compared with BMS, BMS-PCT showed a significant increase in the specificity with the same sensitivity. In addition, a group of patients was managed as outpatients without antibiotics although they had BMS=1, at the expense of the absolute neutrophil count. All these patients had a PCT <0.5 ng/mL and did well. As commented above, the absolute neutrophil count shows some overlapping in patients with bacterial and aseptic meningitis.[2]

Persistence of symptoms or accessibility to the ED should also be kept in mind to guarantee the safety of patients. For this reason, we also recommend to observe these patients in the ED before sending them home.

It is necessary to underline the importance of correctly applying these scores to the appropriate population. In our population, two children in which the BMS cannot be applied were diagnosed with bacterial meningitis. One of them was a 7-year-old critically ill girl without pleocytosis and the other one was a 5-month-old girl without pleocytosis. If calculated and mistakenly applied to these individuals, their BMS would have been 0. The BMS is a clinical prediction rule designed to apply in otherwise healthy and not critically ill children older than 2 months with CSF pleocytosis.

Table 3 Test characteristics of the Bacterial Meningitis Score and procalcitonin-modified Bacterial Meningitis Score for bacterial meningitis

Performance of the BMS and BMS-PCT for bacterial meningitis (95% CI)						
	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Likelihood ratio positive	Likelihood ratio negative*
BMS ≥1	100% (51.0 to 100)	44.4% (36.6 to 52.6)	4.7 (1.9 to 11.6)	100 (94.3 to 100)	1.8 (1.5 to 2)	0 (0—undefined)
BMS-PCT ≥1	100 (51.0 to 100)	84.0 (77.2 to 89.1)	14.8 (5.9 to 32.5)	100 (96.9 to 100)	6.2 (4.3 to 9.1)	0 (0—undefined)

*The upper limit of the CI for likelihood ratio negative cannot be calculated because the values entered include one instance of 0.
BMS, Bacterial Meningitis Score; BMS-PCT, procalcitonin-modified BMS.

Although the rate of bacterial meningitis among children older than 2 years is similar to those previously reported,[5–7] if one considers the entire group of 233 children diagnosed with meningitis at our centres, the prevalence of bacterial meningitis is higher than previously described. This may be a bit surprising as the proportion of aseptic meningitis is increasing due to the impact of conjugate childhood immunisation programmes.[20] This may be due to the fact that the CSF examination sometimes is not practised when a viral meningitis is suspected in previously healthy well-appearing children.[7 12] In our study, an enterovirus was isolated in the CSF in more than 80% of the patients with aseptic meningitis managed as outpatients. The PCR test has a better performance than the viral culture to detect enterovirus in the CSF (sensitivity, 90%–100% vs 65%–75%). In addition, it can provide results within a few hours and have the potential to significantly affect the clinical management of CSF pleocytosis in children.[21 22] In this way, PCR test helps clinicians to determine the optimum therapy, avoiding supplementary examinations and unnecessary admissions. In a recent study, in 735 patients with an enterovirus detected in the CSF using this test, none had bacterial meningitis, suggesting that these patients could be safely treated as outpatients.[23]

The main limitation of the study is the sample size, due mainly to the low prevalence of meningitis in the children coming to the ED, as well as the low number of patients who fulfilled the criteria for outpatient management. Indeed, larger studies are needed to confirm these results. Nevertheless, as this was a multicentre, prospective study, our results may be representative of a population with similar vaccination conditions and identify a population that is suitable for outpatient management without antibiotics. On the other hand, some patients were not included in the study because it was not possible to observe them in the ED during some hours. Although no patient showed deterioration while staying in the ED, the role of the observation in the ED needs to be clarified in larger studies.

We can conclude that outpatient management for patients between 2 and 14 years of age with CSF pleocytosis who fulfilled this set of low risk criteria appears safe. The replacement of the peripheral absolute neutrophil count with PCT in the BMS enables the outpatient management of another significant number of patients. Future larger studies are needed to evaluate the yield of replacing peripheral absolute neutrophil count with PCT in the BMS.

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Contributors SG conceptualised and designed the study, supervised data collection, analysed the data, wrote the initial draft of the manuscript and approved the final manuscript as submitted. JE supervised data collection, analysed the data and approved the final manuscript as submitted. EA-A collaborated in the design of the study, analysed the data and critically revised the manuscript. MS supervised data collection and approved the final manuscript as submitted. JB collaborated in the design of the study and critically revised the manuscript. SM collaborated in the design of the study, analysed the data, revised multiple versions of the initial manuscript and critically revised the final manuscript. All the members of the meningitis group of RISEUP-SPERG gave the final approval of the manuscript.

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Ethics approval Ethical Committee of the Basque Country.

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