



Editorial

## **Should antibiotics be given before admission when meningococcal disease is suspected?**

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## Should antibiotics be given before admission when meningococcal disease is suspected?

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Invasive meningococcal disease is the most destructive acute infection in children. In spite of the progress in prevention with the immunisation with a conjugate vaccine against *Neisseria meningitidis* serogroup C, the overall mortality for meningococcal septic shock was found to be around 10%<sup>1</sup>, in severe meningococcal disease, with important consequences as tissue necrosis requiring excision or amputation and neurological disease.

Meningococcal disease is a rapidly progressive childhood infection, specially for young children, and it can produce death in very few hours. Early recognition, and therefore early appropriate management of the disease, is important. Validated risk of mortality/severity scoring systems are used to discriminate between different levels of disease severity and prognosis at admission. They allow to discriminate the severity of the disease and to start an early aggressive treatment<sup>2,3</sup>. Despite that, a significant number of children with meningococcal disease are misdiagnosed at the beginning, and the treatment starts too late.

A recent study in the United Kingdom analysed retrospectively the course of illness before admission to hospital in 448 children with meningococcal disease<sup>4</sup>. Most children had only non-specific symptoms in the first 4-6 h. The classic features of haemorrhagic rash, meningism, and impaired consciousness developed late (median onset 12-24 h). However, 72% of children had early symptoms of sepsis (legs pain, cold hands and feet, abnormal skin colour) that first developed at a median time of 8 h. Only 51% children were sent to hospital after the first consultation being the median time, between the beginning of symptoms and hospital admission, of 19 hours. Although validity of this study is limited because data were obtained from questionnaires answered by parents and from primary-care records, the results emphasize the low utility of classic clinical features of meningococcal disease to the early diagnosis of the illness. Recognising early symptoms (legs pain, cold hands and feet, abnormal skin colour) of sepsis could increase the proportion of children identified by primary-care clinicians and shorten the time to hospital admission. Unfortunately, these symptoms are unspecific and they can be present in less severe infectious diseases, specially when the fever is increasing. Experimental and clinical studies of severe sepsis support the concept that early resuscitation with fluid and antibiotic therapy improves survival in a time-dependent manner<sup>5</sup>. Because that, international campaigns have been developed to increase awareness and to improve outcome in severe sepsis<sup>5</sup>.

However few studies have analysed the efficacy of treatment before admission in meningococcal diseases. A retrospective cohort study of infants and children

with sepsis found that aggressive fluid resuscitation of pediatric septic shock, by community physicians, was associated with an improved outcome<sup>6</sup>. As early antibiotic therapy is an important prognosis factor in sepsis, it seems natural that patients diagnosed in primary care received antibiotics before the transfer to hospital. However there is not enough scientific evidence that support the utility of this treatment. Randomised controlled trials investigating the effect of antibiotic treatment before admission on outcome of meningococcal disease would be required to examine this question. Such studies may never be done in view of the anticipated logistical and ethical difficulties.

The systematic review by Hahné et al<sup>7</sup>, critically appraised in this issue of "Evidencias en Pediatría"<sup>8</sup>, found only observational cohort studies whose results are surprising. Oral antibiotic treatment given before admission was associated with reduced mortality whereas the association between parenteral antibiotics before admission and outcome was uncertain<sup>9-12</sup>.

In some publications, as the one recently published by Harnden et al<sup>9</sup>, children who were given parenteral penicillin by a general practitioner, had an increased mortality. This could be because of a bias towards giving parenteral penicillin to the most severely ill children, so that oral penicillin was received only by those who had a less severe disease. Moreover most of the studies do not include nor analyse the effect of many variables that can modify the prognosis of meningococcal sepsis, such as the characteristics of the organism, the meningococcal serotype, the age of the patient, the case management, the aggressive treatment of complications, the early diagnostic, etc.

In view of the lack of scientific evidence it is important to conduct a critical appraisal of the benefits and risks of the early antibiotic treatment.

Benefits of treatment with antibiotics before admission are potentially important because, as has been told previously, early antibiotic treatment improves the prognosis of patients with sepsis, and the earlier the treatment, the better the prognosis.

Concerns have been raised arguing that antibiotic treatment before admission may: lower the proportion of patients who can subsequently be diagnosed by microbiological tests, delay the start of appropriate treatment in hospital and contribute to spread antibiotic use.

Treatment of children before admission to hospital with suspected meningococcal disease should not produce any delay in hospital admission, and therefore it is necessary to evaluate, in every case, the time necessary to

give the antibiotic and the time of delay to the hospital. It is evident that we can not use the same criteria in a urban primary care centre, with a well organised emergency transport, that a primary care centre that has not a hospital nearby.

If the patient has received antibiotics before admission, the microbiological cultures will be frequently negative. However the damage of making impossible a microbiological diagnosis is not as important as the benefit. Meningococcal sepsis diagnosis is mostly clinical and the evolution does not change with the bacterial identification. Otherwise, as meningococcal sensitivity to penicillin and cephalosporins keeps being high, it does not exist a real risk to delay the specific treatment, as in other infections.

At present we live in a time of excessive prescription of antibiotics in infections, probably caused by virus and with low severity. By and large Spanish pediatricians are aware of the importance of not using commonly antibiotics, that increase the risk of resistances and health expenditure. However, the incidence of meningococcal disease is relatively low and its resistance to antibiotics is scarce. Because of these reasons, ambulatory antibiotic treatment in children with suspected meningococcal disease probably would neither contribute to the indiscriminate use of antibiotics during the childhood nor to the increase of antibiotic resistance.

If it is decided to administer an antibiotic, which one should be used and how? The appropriate antibiotic treatment in meningococcal sepsis is penicillin, or third generation cephalosporins if there is a doubt of whether the responsible agent can be *Haemophilus influenzae*. Antibiotic should be given intravenous because of its fast action. However, in primary care and in a severely ill child this could be difficult. In these cases intramuscular antibiotics could be given, though the absorption could be delayed in septic shock. If the transport time to the hospital is delayed, and while waiting the emergency transport, a peripheral venous line should be attempted to give appropriate fluid therapy and antibiotics. If this were not possible, intramuscular antibiotic should be considered. Oral antibiotic treatment should only be used in those cases when parenteral antibiotic could not be given.

In conclusion, although there is a lack of scientific evidence in favour of giving antibiotics to all patients with suspected meningococcal disease, before transfer to hospital, taking into account the severity and the rapid progress of the disease, and that treatment does no produce harm, parenteral antibiotics should be started in primary care to all children with suspected meningococcal disease. This therapy should delay neither the transport to hospital nor the appropriate treatment.

Finally, it is important to emphasize the importance that early diagnosis has on the prognosis. We have to insist on health education of general population, family practitioners and pediatricians in primary care and

hospital. They should be aware of the early symptoms of sepsis, and recognise and tell it from another benign causes of fever. In any case, contrarily to most fever diseases in childhood, for which we can have an expectant attitude, in the suspicion of meningococcal disease the best attitude is to be careful and to transfer urgently the child to hospital.

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