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EDITORIAL

Fever without source in infants less than 3 months of age. What's new?☆

Fiebre sin foco en lactantes menores de 3 meses. ¿Qué hay de nuevo?

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The approach to a febrile infant aged less than 3 months continues to be a challenge. The key issue is how to recognise when we are facing a potentially severe infection. In recent years, there have been changes in both the aetiology of severe infections and in the tools that are or are going to be at our disposal to approach their aetiological diagnosis.

When it comes to infections of a bacterial aetiology in young infants, two facts have changed the situation in Spain in recent years. The first one is the policy for the prevention of early-onset neonatal sepsis adopted by obstetricians, which has led to a clear decrease in the incidence of infection by *Streptococcus agalactiae*. However, it is unclear whether the incidence of late-onset sepsis has decreased in equal measure, so we must remain to be aware of these infections past the first week of life.[1] On the other hand, the nearly universal vaccination against pneumococcus in Spain has produced a marked decrease in invasive disease due to *Streptococcus pneumoniae* in every age group. A study by de la Torre et al.[2] confirmed these changing trends in the aetiology of bacterial infections in young infants, and emphasised the importance of *Escherichia coli* as the leading causative agent of severe bacterial infections in this age group, and therefore in the differential diagnosis of urinary tract infections, its most frequent form of disease, consistent with what has been described in other countries.[3]

But bacterial infections aside, viruses, which many do not associate with our patients, are emerging as the causative agents of severe illness in this age group. On one hand, and mostly based on the North American literature, there is infection by herpes simplex viruses, which given its severity and the availability of an effective treatment—acyclovir—should be taken into consideration, especially in the first month of life. While the incidence in the United States is of 33 cases per 100 000 live births, in some countries neighbouring Spain, such as the United Kingdom, the incidence is of 1.65 cases per 100 000 births. We do not have data on the incidence of neonatal herpes infections in Spain. This means that we have no clear policy on whether or not to empirically treat herpes infections in the youngest infants with manifestations of sepsis, and underscores the need to conduct studies on the subject. De la Torre[2] reported the detection of only 3 cases of herpes infection out of 3400 assessed infants (0.08%), although the study had not been designed to determine the incidence of herpes infections and thus the results must be interpreted with caution. The other groups of viruses that are involved in severe illness in this age group are enterovirus and parechovirus, and the latter in particular. Human parechovirus, especially type 3, has been recently recognised as a relatively frequent causative agent of fever without source and sepsis in young infants, usually aged less than 2 months,[4] often requiring admission to intensive care units. Although the short-term outcome of

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these infections is good (usually within a few hours), these infants are treated as if they had a bacterial infection, with administration of broad-spectrum antibiotics and often prolonged hospitalisations. Both enterovirus and parechovirus can be detected in cerebrospinal fluid (CSF), but it is also possible to detect them in blood, faeces or throat swab samples using polymerase chain reaction (PCR). One characteristic feature of parechovirus infection is the absence of pleocytosis even when the virus has been detected in CSF.

All of the above requires that we reconsider our approach to the aetiological diagnosis of infants with fever without source. Whether a lumbar puncture is necessary or not, and in which patients, is currently being debated. The importance of ruling out a urinary tract infection seems unquestionable, as this is the most common site of bacterial infection in Spain. Also, molecular virological tests for the rapid diagnosis of infection by herpes simplex virus, enterovirus and parechovirus are clearly an invaluable tool in the evaluation of fever without source and suspected sepsis in this age group. Once their routine use is widespread in microbiology laboratories of Spanish hospitals, we will not only be able to make accurate diagnoses, but also to avoid unnecessary treatments and protracted hospitalisations.

I cannot conclude this reflection without a discussion of a seemingly near future in the search for techniques that will allow us to know whether we are facing a viral or a bacterial infection. At present, none of the currently used biological markers, like C-reactive protein, procalcitonin or other that are not as widespread, have been shown to be able to discriminate bacterial infections with sufficient sensitivity and specificity. The multiple scores combining clinical and laboratory data that have been developed have also failed to achieve this, although they are useful for the management of patients. To further complicate matters, the coexistence of bacterial and viral infections is being described with increasing frequency. There have been enormous advances in virological diagnostic techniques, and today we are able to quickly and easily detect infections by various viruses at the bedside or within a few hours, although this does not allow us to rule out the presence of bacterial infection with certainty, especially in cases in which classical markers such as C-reactive protein are outside their normal range.

Research in recent years has focused on the fields of genomics and metabolomics, and nanotechnology-based approaches for detecting host responses to infection and discriminating between viral and bacterial infections are being explored. Various molecules and cytokines, and even the possibility of developing simultaneous assay panels for several markers, are currently being investigated. Using transcriptomic, proteomic or metabolomic techniques, researchers are analysing the various responses of individuals to infection. Gene expression profiling using microarray technology can simultaneously measure the messenger RNA of thousands of transcriptions. This offers a rapid method for screening thousands of molecular species with a single assay. Our goal would be to identify gene expression profiles in specific infections relative to others in order to determine whether the underlying infection is of viral, bacterial or mixed aetiology.

Studies of this kind are being conducted in children of different ages. We ought to comment on the study conducted by Mahajan et al,[5] who used this technology to identify bacterial infections in febrile infants aged less than 60 days. They identified 66 genes whose expression allowed the detection of bacterial infection with a sensitivity of 87% and a specificity of 89%. In children with bacteraemia, a 10-gene transcriptional profile had a sensitivity of 94% and a specificity of 95%, improving on the yield of the Yale Observation Scale. They also demonstrated that this technology could be used successfully in hospital emergency departments with samples of as little as 1 mL of blood. Although these studies have limitations and their findings have yet to be confirmed, the ground that is left to cover is steadily decreasing, and in the not-so-distant future we may be able to determine whether our patients have—or not—a bacterial infection.

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