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EDITORIAL

Invasive infections due to group a streptococci and meningococci☆

Infecciones invasivas por estreptococo del grupo a y por meningococo: incertidumbres y certezas

Jesús Ruiz-Contreras*

Servicio de Pediatría del Hospital Universitario 12 de Octubre, Facultad de Medicina. Universidad Complutense, Madrid, Spain

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Two studies published in the current issue of *Anales de Pediatría* analyse the clinical experience with 2 infrequent diseases in a hospital in Madrid: invasive group A streptococcus (GAS) disease[1] and invasive meningococcal disease (IMD).[2] Both (although more frequently in case of IMD) can lead to shock, multiple organ failure and even death. The most severe form of invasive GAS disease, streptococcal toxic-shock syndrome (STSS) is mediated by bacterial exotoxins that act as superantigens and trigger a cytokine storm responsible that is responsible for this clinical picture. In opposition, fulminant meningococcaemia is an endotoxin-mediated shock. Early diagnosis is crucial in both of these diseases, but apart from this and the severity of disease, they share few other features. In fact, the approach to each of these diseases is different. Thus, in invasive GAS disease, the sole possible preventive measure is vigilance and perhaps chemoprophylaxis in household contacts of affected patients, whereas in the case of IMD, meningococcal vaccines offer effective prevention.

Although the incidence of invasive GAS diseases (arthritis, pneumonia, necrotising fasciitis, sepsis and STSS) in developed countries is low, of between 2 and 4 cases per 100 000 inhabitants, there seems to have been an increase in recent years, as the study published in this issue of *Anales de Pediatría* also suggests.

Another hospital located in Barcelona has also recently analysed its experience with invasive GAS disease.[3] Similarly to other industrialised countries, the mortality found in the 2 studies in Spain was low, as only 1 out of the total 107 of patients included in these 2 studies died. Mortality is lower in children compared to adults (10%–20% in the latter), which is associated with a lower proportion of severe forms of disease like necrotising fasciitis (NF) and STSS, and the absence of comorbidities. In both studies, the use of clindamycin and polyclonal intravenous immunoglobulin (IVIG) therapy was infrequent, even though both of these interventions are recommended by many authors for treatment of NF and STSS, in addition to surgical debridement and β-lactam antibiotics.

The rationale for the use of clindamycin is that it has a longer post-antibiotic effect compared to β-lactam agents and its ability to inhibit the synthesis of GAS virulence factors. It has been shown to improve outcomes of NF lesions in murine models and human patients, even if the involved GAS strain is resistant to clindamycin. The beneficial effect of IVIG may be due to its ability to neutralise toxins that act as

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* Corresponding author.
E-mail addresses: jesus.ruiz@salud.madrid.org, jesuruiz@ucm.es

superantigens in addition to increasing bacterial clearance. Several studies have demonstrated that both strategies are associated with a decreasing trend in the fatality rate of NF and STSS, but since none were able to obtain a large enough sample of patients, it has not been possible to draw definitive conclusions.[4] This lack of evidence may have contributed to the underutilization of these interventions.

However, a recent meta-analysis has shown that the addition of IVIG therapy to the management of patients with STSS (adult and paediatric) already receiving clindamycin decreases mortality by 54%, from 33.7% to 15.7%, that it can prevent 1 death for every 6 patients treated.[5] In my opinion, these results justify the inclusion of both of these measures in the treatment of STSS, a disease with a high mortality in children,[4] and possibly in the treatment of NF, too. The optimal dose of IVIG, however, is yet to be established. It is likely that the doses used in different studies are not optimal for obtaining the desired degree of immunomodulation, and perhaps a dose of 2 g/kg of body weight, like the dose used for Kawasaki disease, would be more appropriate.[4]

Another aspect that remains unresolved in invasive GAS disease is the approach to the management of household contacts, whose risk of acquiring the disease is between 200 and 2000 times greater compared to the general population, even if the absolute risk is low. Taking into account the higher rates of transmission,[6] it has been estimated that antibiotic prophylaxis needs to be given to 271 (194–454) household contacts (number needed to treat [NNT]) to prevent 1 case of transmission,[6] a figure similar to the number estimated for household contacts of patients with IMD. The benefit is greater in high-risk groups, such as the mother-newborn dyad when one of them has the infection, and individuals aged more than 75 years, populations in which the NNT would be 50 and 82, respectively.[6] The risk of transmission is highest in the first 10 days, and especially in the first 2, which means that prophylaxis should be given early.

If to all of this we add that the use of chemoprophylaxis under these circumstances is not supported by evidence, the current lack of clear recommendations is only to be expected. In general, chemoprophylaxis is only recommended in household contacts of patients with the most severe forms of disease (NF, STSS, myositis and pneumonia), which are associated with a higher risk of transmission, and possibly those aged more than 65 years.[7] There is also no clear recommendation as to which antibiotic should be used, but the use of oral penicillin V or of azithromycin in case of penicillin allergy have been proposed. If a mother has invasive GAS disease in the peripartum period, the newborn infant should receive a 10-day course of intravenous penicillin. In any case, all household contacts should be advised to seek medical care should they develop any compatible symptoms.

As is the case of invasive GAS disease, IMD is infrequent, with a current incidence of 0.74 cases per 100 000 individuals. However, it has a high case fatality rate (12.7% in Spain in the last epidemic season) and can cause serious sequelae. It frequently manifests with a fulminant course that becomes life-threatening within hours from onset. Unfortunately, given the nonspecificity of the initial signs and symptoms, in 50% cases the diagnosis is not made in the first medical visit,[8] which illustrates the difficulty of early diagnosis. To further complicate matters, serogroup W, whose incidence is increasing sharply, has an atypical presentation (pneumonia, septic arthritis, epiglottitis, gastrointestinal symptoms) in up to 25% of patients[9] and a high fatality rate, which in Spain ranges between 20% and 30%. In adolescents, the mortality is very high when infection manifests with acute gastrointestinal symptoms (nausea, vomiting and abdominal pain, followed by diarrhoea), reaching up to 50%.[10]

Given all of the above, the most effective—and possibly the only—way to prevent fatalities and sequelae due to IMD is immunization with meningococcal vaccines, either through individual choice or, ideally, by the inclusion of these vaccines in state-funded routine immunization schedules.

As has occurred in other European countries and continents, the most relevant epidemiological shift in Spain in recent years has been the increased incidence of group W IMD due to the spread of the hypervirulent clonal complex 11 (CC11).[9,11] The European strain is the same already detected in Latin America in 2004, which amounted to 50% of meningococcal isolates in some countries, such as Argentina and Chile.

In Spain, the incidence of infection by serogroup W has increased tenfold since the 2014/2015 season. As in the rest of Europe, the highest absolute frequency and percentage of IMD due to group W is found in individuals aged more than 45 years and especially those aged more than 65 years.[9,11] In contrast, in other countries such as Argentina and Chile, up to 50% of cases occur in infants.[9]

In Spain, the most frequent serogroup (52% of cases) is group B, followed by W (18%), C (15%) and Y (14%). By age group, the highest incidence of IMD is found in infants aged less than 1 year (8.65 cases/100 000), mostly on account of infection by group B (5.85 cases/100 000).

There is no question that given the burden of disease, vaccination of infants against group B meningococcus should be considered, especially considering that there is evidence suggesting that this vaccine induces bactericidal activity against other serogroups in vaccinated individuals, which could increase its effectiveness.

The response of Spain and other European countries to the increase in the incidence of group W infection, given its high fatality rate, has been to vaccinate adolescents with the meningococcal ACWY vaccine, seeking the indirect protection of other subpopulations. However, since it appears that vaccination of adolescents has little impact on IMD caused by serogroup W in other age groups, new vaccination strategies may be required if this increase ends up significantly affecting infants, as seems to be happening in the United Kingdom and the Netherlands. In this situation, the pertinent question that ought to be settled ahead of time is what incidence or number of cases has to be reached before making the appropriate changes.

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