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Editorial

The importance of (at least) a clinical typification of non-typeable *Haemophilus influenzae* infection

Importancia de una tipificación al menos clínica de la infección por *Haemophilus influenzae* no-tipable

The Gram-negative coccobacillus *Haemophilus influenzae* (HI) is a common respiratory, and sometimes invasive pathogen, that mostly affects children, elderly people, or subjects with impaired immunity. There are 6 HI serotypes (designated as a to f) according to the characteristics of the bacterial polysaccharide capsule; non-capsulated strains are thereby designated as non-typeable HI (NTHi). For years HI serotype b (Hib) has been related with invasive infections, particularly in children below 5 years old; this association has remarkably changed with the introduction of conjugated Hib vaccination in pediatric immunization programs. As has occurred with other capsulated bacteria for which there are conjugated vaccines (i.e. *Streptococcus pneumoniae* or *Neisseria meningitidis*) the seroprevalence of infecting HI isolates has shifted toward serotypes different to Hib, either capsulated or non-capsulated, namely NTHi for the latter.[1–3]

Although the overall incidence of invasive disease caused by NTHi and HI non-B serotypes remains low, there has been an increase of respiratory tract infections and also of systemic infections caused by NTHi since 2000. Both adults and children can be affected by NTHi, which causes today the majority of invasive HI infections in all age groups.[4] In adults NTHi is the main cause of exacerbation in chronic obstructive pulmonary disease[5]; in children, the clinical manifestations are more diverse as they include sinusitis, conjunctivitis, and pneumonia, but NTHi is best known for being the predominant pathogen of chronic and recurrent otitis media.[6–9]

Resistance to antibiotics is today another challenge for the management of severe HI infections. Two main mechanism have been described, B-lactamase production or mutations in the protein-binding domain, which may be found in around a third of clinical HI samples.[10]

Two studies in this issue shed light upon the epidemiology and resistance patterns of HI infections, what is very welcome information for this emerging pathogen. The paper by León et al.[11] is a cross-sectional retrospective observational study of all HI isolates from cerebrospinal fluid, and respiratory, otic and ocular secretions received in the National Reference Laboratory in Paraguay between 1999 and 2017. Most infected cases were younger than 5 years-old up to 2013; from this year on most isolates were found in older than 5 years-old individuals, period when NTHi isolates showed a remarkable increase in frequency. Among 523 samples analyzed, more than 90% of patients had invasive infection (this means infection beyond the respiratory tract, namely pneumonia, meningitis, or sepsis in this study). Nearly half of invasive and 84% of non-invasive infections were caused by NTHi; conversely, 46% and 14% of invasive and non-invasive infections were respectively caused by Hib. The rate of ampicillin resistance among HI isolates was 13%, with marked tendency to increase after 2011. It may be concluded that the introduction of Hib immunization as part of children vaccination campaigns has reduced the frequency of these infections, particularly in ages below 5 years and, as a consequence, there has been a relative surge in NTHi infections, particularly in ages above 5 years.[12–14]

The study by Ibar-Bariain et al.,[15] analyses the susceptibility patterns of HI to mostly used antibiotics (namely, amoxicillin, amoxicillin/clavulanate, ampicillin, cefotaxime, ceftriaxone, imipenem and ciprofloxacin). The efficacy of intravenous antimicrobial therapy was estimated with the cumulative fraction of response (CFR), a composite score defined as the probability of attaining effective drug levels for each given drug dose and bacterial population. Although information about HI serotypes is lacking in this Spanish study, non-Hib isolates are mostly expected given that Hib conjugated vaccine was introduced in the country in 1997 and the isolates used for this study were collected between 2004 and 2009. Of note, B-lactamase production, affecting amoxicillin and ampicillin, was the only driver of expected lack of antibiotic efficacy. Of note, regardless of MIC values the CFR score seemed to ensure treatment efficacy for all other antibiotics tested (namely, third generation cephalosporins, carbapenems and quinolones).

The development a vaccine to prevent HiNT infection has become a challenging objective, that under the light of the data presented in this issue owes renewed efforts.[16,17] Different vaccine antigens for NTHi have been evaluated in preclinical studies, but none of them has been fully satisfactory yet.[18] Combining multiple antigens is the strategy expected to increase strain coverage and limit the ability of NTHi to adapt to immune system pressure

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by presenting antigenic heterogeneity.[19] While effective prevention of NTHi disease is awaiting it is good news to learn that most treatment options for severe infections are spared for antibiotic resistance, what it seems mostly affects the family of B-lactams.

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