ELMER PRESS

Case Report

J Med Cases. 2022;13(8):396-401

Fatal Meningitis and Sepsis Caused by Nontypeable *Haemophilus influenzae*

Olga M. Klibanov[a, b, f], Heather Kehr[c], Zanesha Jeter[b, d], Tabugbo Ekwonu[e]

Abstract

The rates of nontypeable *Haemophilus influenzae* (NTHi) invasive disease have been increasing since the introduction of the *Haemophilus influenzae* type b (Hib) vaccine, but its significance in adults is unclear. A 33-year-old man with human immunodeficiency virus (HIV) was admitted for fever and acute confusion. The day prior to admission he presented to another emergency department for nausea, vomiting and diarrhea where he was thought to have food poisoning and was sent home. Ten days prior to admission, his primary physician thought his nasopharyngitis symptoms were due to the common cold. The patient's HIV had been controlled on antiretroviral therapy for the past 3 years; 1 month prior to admission his viral load was undetectable. Laboratory evaluation on admission was significant for elevated lactic acid and $CD4^+$ cell count of less than 200. A head computed tomography (CT) was unremarkable, but a lumbar puncture was consistent with bacterial meningitis. *Neisseria meningitidis* was suspected and the patient was placed on empiric antibiotics. Shortly after admission the patient was intubated and suffered a cardiac arrest. The patient was placed on vasopressor support after circulation returned; a repeat head CT showed increased swelling of his brain. An electroencephalogram (EEG) indicated complete suppression of activity and the patient expired on day 2 of hospitalization. After the patient's death, cerebrospinal fluid (CSF) cultures reported as positive for *Haemophilus influenzae* (*H. influenzae*) and sent to the state lab where it was further classified as NTHi, biotype I. NTHi strains can cause invasive disease in adults and should be considered as a potential pathogen for meningitis and bacteremia.

Keywords: *Haemophilus influenzae*; Meningitis; Bacteremia; HIV disease

Manuscript submitted June 12, 2022, accepted July 25, 2022
Published online August 19, 2022

[a]IQVIA, Medical and Patient Communications, Pasippany, NJ, USA
[b]Wingate University, Wingate, NC, USA
[c]School of Pharmacy, Wingate University, Wingate, NC, USA
[d]Harris Teeter, Pharmacy, Cornelius, NC, USA
[e]Eastowne Family Physicians, Charlotte, NC, USA
[f]Corresponding Author: Olga M. Klibanov, IQVIA, Medical and Patient Communications, Parsippany, NJ, USA. Email: oklibanov@gmail.com

doi: https://doi.org/10.14740/jmc3974

Introduction

Haemophilus spp are small fastidious gram-negative coccobacilli that typically colonize the upper respiratory tract. Polysaccharide encapsulated forms of *Haemophilus influenzae* (*H. influenzae*) can be categorized as serotypes a-f. Unencapsulated variations of this pathogen are referred to as nontypeable *Haemophilus influenzae* (NTHi) strains [1]. NTHi is a recognizable cause of many noninvasive infections, such as otitis media, sinusitis, conjunctivitis, chronic obstructive pulmonary disease (COPD) exacerbations, and non-bacteremic pneumonia [1]. Historically, this organism has not had the same prominent profile as encapsulated *H. influenzae* type b (Hib) or *Streptococcus pneumoniae* in causing serious infections. However, as the rates of invasive disease caused by Hib have dramatically declined since the introduction of the Hib vaccine in the 1980s, the incidence of invasive infection due to NTHi has been increasing [2-7]. There are no reports of invasive NTHi disease in persons living with human immunodeficiency virus (HIV) (PLWH) in the literature. We present a case of a 33-year-old male with HIV who presented with altered mental status and was subsequently found to have fatal NTHi meningitis with bacteremia. The literature describing invasive NTHi disease in adults is also reviewed.

Case Report

Investigations

A 33-year-old male presented to the emergency department (ED) via ambulance after experiencing fever and altered mental status at home. The day prior to admission, the patient visited a different emergency room (ER) with complaints of nausea, vomiting, and diarrhea thought to be caused by food poisoning. At that initial ER visit, computed tomography (CT) of the head, abdomen and pelvis were unremarkable, so the patient was discharged to home. By the following day, the patient developed a fever of 39.4 °C, became acutely confused with nonsensical speech, leading to emergency medical services (EMS) being called by his family. During EMS transport to the ER, the patient had a tonic clinic seizure that lasted for approximately 1 min and a temperature of 39.1 °C. No medications were administered *en route* to the hospital.

The patient's past medical history was significant for HIV diagnosed 6 years prior to admission; $CD4^+$ cell count

was 1,782 cells/mm^3 (54%) and HIV-1 RNA level < 20 copies/mL 1 month prior to admission. The patient had no history of HIV-related complications and had been on stable antiretroviral therapy with dolutegravir/lamivudine/abacavir (DTG/3TC/ABC) for 3 years prior to admission. The patient was up-to-date on his vaccinations against Hib, *Streptococcus pneumoniae* (*S. pneumoniae*), and *Neisseria meningitidis* (*N. meningitidis*). The patient's history was negative for a splenectomy. The patient had a history of two episodes of secondary syphilis over the last 6 years. Additionally, patient presented with nasopharyngitis symptoms to his primary care physician 10 days prior to hospital admission. Group A Streptococcus test was negative; the symptoms were thought to be consistent with the common cold and patient was prescribed supportive care.

Diagnosis

Vital signs on admission were as follows: temperature 39.1 °C, heart rate 114 beats/min, respiratory rate 32 breaths/min, blood pressure 163/94 mm Hg, oxygen saturation (SpO_2) 100% on room air; weight 83 kg, body mass index (BMI) 24.8. Physical exam was notable for a Glasgow Coma Scale score of 11 (E4V2M5), nuchal rigidity, and agitation; the patient was opening his eyes and looking around but was noncompliant to simple commands. Pupils were equal and equally reactive to light. Head/ears/eyes/nose/throat (HEENT) exam noted several dental caries, without any oral patches, redness, or swelling. Pulmonary exam was clear to auscultation, without rhonchi or wheezing; no lesions were seen on skin exam.

A laboratory evaluation on admission was significant for lactic acid level of 14.79 mmol/L, sodium 143 mmol/L, potassium 3.1 mmol/L, chloride 109 mmol/L, CO_2 12 mmol/L, blood urea nitrogen (BUN) 14 mg/dL, creatinine 1.1 mg/dL, glucose 74 mg/dL, calcium 7.9, anion gap 26 mmol/L, white blood cell (WBC) 3.5 × 10^3/µL (89% neutrophils, 10% lymphocytes, 1% monocytes), hemoglobin (Hb) 12.7 g/dL, platelet (Plt) 95 × 10^3/µL, international normalized ratio (INR) 1.6, prothrombin time (PT) 18.9 s. Liver function tests were normal except for the alkaline phosphatase of 226 IU/L. Toxicology screen was positive for marijuana; ethanol level was < 10 mg/dL. CD4$^+$ cell count drawn on admission was reported as 182 cells/mm^3 (55.2%); HIV-1 RNA was not drawn.

A CT of the head was unremarkable. Blood cultures were obtained and a lumbar puncture that was performed on arrival showed yellow/turbid cerebrospinal fluid (CSF) fluid, glucose < 10 mg/dL, protein 1,185 mg/dL, WBC 2,663/µL (90% segs, 2% monocytes, 8% lymphocytes), negative cryptococcal antigen, nonreactive Venereal Disease Research Laboratory (VDRL) test. The Gram smear of the CSF fluid was reported to be growing gram-negative diplococci and *Neisseria meningitidis* was suspected

Treatment

The patient was transferred to the intensive care unit (ICU) and empiric vancomycin 15 mg/kg intravenous (IV) every 12 h (q12h), ceftriaxone 2 g IV q12h, ampicillin 2 g IV q4h, acyclovir 10 mg/kg IV q8h, and dexamethasone 10 mg IV q6h were initiated. The patient was intubated shortly after ICU admission due to increased difficulty breathing.

Follow-up and outcomes

On the morning after admission, the patient had a sudden drop in blood pressure, followed by a pulseless electrical activity (PEA) arrest with a return of spontaneous circulation after two rounds of cardiopulmonary resuscitation (CPR). He required vasopressors after return of circulation. After this event, patient's pupils were dilated and non-reactive. A repeat CT of the head showed increased edema bilaterally, increased effacement of basil cisterns, and mild increase in temporal horns. The patient was unresponsive on physical examination. The EEG indicated the complete suppression of activity and the patient expired on day 2 of hospitalization.

After the patient's death, blood and CSF cultures were reported as positive for *H. influenzae* and were sent to the state laboratory, where the organism was further classified as NTHi, biotype I. Susceptibility analysis was not performed; however, according to the institution's antibiotic susceptibility surveillance report, 66% of *H. influenzae* isolates were susceptible to ampicillin, with recommendations for a second/third generation cephalosporin for resistant isolates. The final autopsy report identified the patient's cause of death as complications of sepsis and meningitis caused by NTHi. Challenges in our case included patient's late presentation, fast decline, and lack of susceptibility report of the NTHi strain.

Discussion

Prior to implementation of routine Hib vaccination, < 20% of invasive *H. influenzae* infections were due to NTHi. Recent national surveillance reports in the USA and Europe, however, indicate that NTHi is responsible for up to 90% of invasive *H. influenzae* infections [2-7]. Although the highest incidence of invasive NTHi disease is in infants and older (> 65 years) individuals, immunocompromised persons and those with chronic respiratory conditions are also at risk. Overall, pneumonia is the most common clinical presentation of invasive NTHi, increasing with age and occurring primarily in older adults with underlying respiratory conditions. Sepsis is the most common clinical presentation of invasive NTHi in neonates, and meningitis is common in older infants and children.

Although pediatric NTHi-induced meningitis is thoroughly elucidated in the literature [8-14], cases in adults are not as well described. Cases of non-fatal NTHi meningitis were initially described in 1982 in six adult patients with trauma (five of six) and diabetes (one of six) as underlying conditions [15]. In 1992, a case of non-fatal NTHi meningitis and bacteremia was described in a 54-year-old female with a history of chronic sinusitis and cerebrospinal rhinorrhea [16]. A surveillance program of *H. influenzae* in the USA (1989 - 2008) identified 144

CSF isolates in persons ≥ 18 years of age, but details regarding their clinical course were not reported [12]. Additionally, epidemiology studies conducted in Canada and Australia reported two and four cases of CNS infection with NTHi, respectively, but the age of the patients and their clinical course were not reported [5, 6].

This is the first report of fatal, invasive NTHi disease in a PLWH. Although our patient was infected with HIV, his $CD4^+$ cell count prior to admission was 1,782 cells/mm^3 (54%) with an undetectable and HIV-1 RNA level; therefore, he was not considered to be immunosuppressed. On admission, the patient's $CD4^+$ cell count was dramatically lower at 182 cells/mm^3, likely a reflection of the low WBC count of 3.5×10^3/µL. His CD4%, however, was stable at 55.2%, and given that CD4% is the best prognostic measure with least variability on repeated measures in HIV infection [17-19], we do not think that our patient was immunocompromised.

The pathogenesis of meningitis caused by NTHi is different in children compared to adults. Whereas in children the seeding of the meninges results from hematogenous spread of the organism, contiguous dissemination is thought to be the most common mechanism of *H. influenzae* meningitis in adults, with most common predisposing factors in adults being sinusitis, otitis media, or a CSF leak [20]. Our patient was 33 years old at the time of presentation, which is not a typical age for meningitis due to NTHi. He did, however, present with symptoms of nasopharyngitis to his primary care physician 10 days prior to admission, which may have been a predisposing factor for meningitis.

H. influenzae strains are differentiated by biotyping, a method that identifies the presence of three biochemical features: ornithine decarboxylation, indole production, and urea hydrolysis. Whereas most Hib strains are either biotype I or II, NTHi strains are mainly distributed among biotypes II through VI [20]. Clear clinical correlations between biotypes and most infections caused by NTHi are lacking. Some earlier data suggest that NTHi biotype IV correlates to many genital isolates from women and blood isolates from neonates and women with postpartum sepsis; whereas, NTHi biotype I isolates frequently cause pneumonia [21-23]. A Canadian surveillance study of invasive *H. influenzae* isolates reported that 66% of cases were caused by NTHi and biotype II was the most common biotype among the nontypeable strains [5]. Our patient's NTHi strain was identified as biotype I, which may reflect the circulating strain of NTHi in our community.

The most common mechanism of β-lactam resistance in NTHi is via β-lactamase production, with varying global prevalence of 10-25% in most regions (South Africa, Europe, USA, Canada, Central America, South America) [24-29] and up to 55% in some Asian countries (Taiwan, Vietnam, Japan, South Korea) [30-34]. Although TEM-type extended-spectrum β-lactamases (ESBLs) have not yet been detected in *H. influenzae*, the possibility of broader spectrum β-lactamases emerging in *H. influenzae* cannot be excluded. Another, more worrisome resistant *H. influenzae* strains, are the β-lactamase-negative ampicillin resistant (BLNAR) isolates that are resistant to ampicillin. Although in the USA and many European countries there have been few or no reports of BLNAR strains, some regions such as Taiwan, Vietnam, South Korea, Spain, Poland, France, Portugal, and Sweden have reported increased prevalence of BLNAR strains, with reported prevalence ranging from 12.8% (Poland) to 56% (Spain) and increasing minimum inhibitory concentrations (MICs) for cefuroxime (up to 16 µg/mL) and cefotaxime (up to 4 µg/mL) [30, 32, 33, 35-41]. Because regular surveillance of NTHi is absent in most regions and microbiological workup of NTHi is often absent or restricted to a nitrocefin test for β-lactamase production, the prevalence of BLNAR strains is likely underestimated or unknown [1]. Our patient was initially thought to have *N. meningitidis* meningitis after the laboratory preliminary identified gram-negative diplococci in the CSF Gram stain. He was initiated on an antimicrobial regimen that included ceftriaxone as well as ampicillin. After the patient's death, NTHi was isolated from the blood and CSF but susceptibility testing was not reported by the institution. It is unlikely that this was a case of a BLNAR NTHi and if this was a case of a β-lactamase-producing NTHi strain, ceftriaxone should have been effective therapy for the patient.

Unfortunately, our patient expired within 24 h of hospitalization after suffering a PEA and subsequent complete suppression by EEG. The overall case fatality ratio (CFR) for invasive NTHi disease has been estimated to be 12-22% [42-47]. Invasive NTHi disease has been associated with a higher risk of death compared to Hib, with an age-adjusted odds ratio for death of 2.4 (95% confidence interval (CI): 1.9 - 3.1; $P < 0.0001$) overall, 3.3 (95% CI: 1.5 - 7.5; $P = 0.004$) for pneumonia, 3.3 (95% CI: 1.5 - 7.5; $P = 0.004$) for bacteremia, and no significant difference reported for meningitis [1].

Learning points

Our case of a 33-year-old man with HIV infection, albeit seemingly non-immunocompromised, highlights the importance of NTHi strains causing significant and potentially fatal invasive disease in adults. This organism should be taken into consideration as a potential pathogen that can cause meningitis and bacteremia, even in previously healthy individuals. In the post-Hib vaccine era, continuous monitoring of NTHi strains is important to detect changes in the epidemiology and resistance patterns of this pathogen.

Acknowledgments

None to declare.

Financial Disclosure

This report received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors report no conflict of interest.

Informed Consent

Due to patient's demise, informed consent could not be obtained for the publication of this report; however, clearance/permission for publication was obtained from the research review board at Wingate University.

Author Contributions

Olga M. Klibanov contributed to conception of manuscript, data acquisition, drafting of the manuscript, final approval of the version to be published. Heather Kehr contributed to data acquisition, interpretation of data, drafting of the manuscript, final approval of the version to be published. Zanesha Jeter contributed to data acquisition, interpretation of data, drafting of the manuscript. Tabugbo Ekwonu contributed to data acquisition, interpretation of data, drafting of the manuscript.

Data Availability

The data supporting the findings of this report are available from the corresponding author upon reasonable request.

References

1. Van Eldere J, Slack MP, Ladhani S, Cripps AW. Non-typeable Haemophilus influenzae, an under-recognised pathogen. Lancet Infect Dis. 2014;14(12):1281-1292.
2. European Centre for Disease Prevention and Control (ECDC). Surveillance of invasive bacterial diseases in Europe (2008/09). Available at: https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/1107_SUR_IBD_2008-09.pdf. Accessed June 7, 2022.
3. Kastrin T, Paragi M, Kolman J, Cizman M, Kraigher A, Gubina M, Slovenian Meningitidis Study Group. Characterisation of invasive Haemophilus influenzae isolates in Slovenia, 1993-2008. Eur J Clin Microbiol Infect Dis. 2010;29(6):661-668.
4. Resman F, Ristovski M, Ahl J, Forsgren A, Gilsdorf JR, Jasir A, Kaijser B, et al. Invasive disease caused by Haemophilus influenzae in Sweden 1997-2009; evidence of increasing incidence and clinical burden of non-type b strains. Clin Microbiol Infect. 2011;17(11):1638-1645.
5. Shuel M, Hoang L, Law DK, Tsang R. Invasive Haemophilus influenzae in British Columbia: non-Hib and non-typeable strains causing disease in children and adults. Int J Infect Dis. 2011;15(3):e167-173.
6. Wan Sai Cheong J, Smith H, Heney C, Robson J, Schlebusch S, Fu J, Nourse C. Trends in the epidemiology of invasive Haemophilus influenzae disease in Queensland, Australia from 2000 to 2013: what is the impact of an increase in invasive non-typable H. influenzae (NTHi)? Epidemiol Infect. 2015;143(14):2993-3000.
7. Giufre M, Fabiani M, Cardines R, Riccardo F, Caporali MG, D'Ancona F, Pezzotti P, et al. Increasing trend in invasive non-typeable Haemophilus influenzae disease and molecular characterization of the isolates, Italy, 2012-2016. Vaccine. 2018;36(45):6615-6622.
8. Cardines R, Giufre M, Mastrantonio P, Ciofi degli Atti ML, Cerquetti M. Nontypeable Haemophilus influenzae meningitis in children: phenotypic and genotypic characterization of isolates. Pediatr Infect Dis J. 2007;26(7):577-582.
9. Cuthill SL, Farley MM, Donowitz LG. Nontypable Haemophilus influenzae meningitis. Pediatr Infect Dis J. 1999;18(7):660-662.
10. Faden H. Meningitis caused by nontypable Haemophilus influenzae in a four-month-old infant. Pediatr Infect Dis J. 1991;10(3):254-255.
11. Falla TJ, Dobson SR, Crook DW, Kraak WA, Nichols WW, Anderson EC, Jordens JZ, et al. Population-based study of non-typable Haemophilus influenzae invasive disease in children and neonates. Lancet. 1993;341(8849):851-854.
12. MacNeil JR, Cohn AC, Farley M, Mair R, Baumbach J, Bennett N, Gershman K, et al. Current epidemiology and trends in invasive Haemophilus influenzae disease—United States, 1989-2008. Clin Infect Dis. 2011;53(12):1230-1236.
13. Martinello RA, Teitelbaum J, Young E, Hostetter MK. Nontypable haemophilus influenzae meningitis in an eleven-year-old. Pediatr Infect Dis J. 2004;23(3):281.
14. Nizet V, Colina KF, Almquist JR, Rubens CE, Smith AL. A virulent nonencapsulated Haemophilus influenzae. J Infect Dis. 1996;173(1):180-186.
15. Spagnuolo PJ, Ellner JJ, Lerner PI, McHenry MC, Flatauer F, Rosenberg P, Rosenthal MS. Haemophilus influenzae meningitis: the spectrum of disease in adults. Medicine (Baltimore). 1982;61(2):74-85.
16. Morris JT, Longfield RN. Meningitis and bacteremia due to nontypeable Haemophilus influenzae in adults. Clin Infect Dis. 1992;14(3):782-783.
17. Burcham J, Marmor M, Dubin N, Tindall B, Cooper DA, Berry G, Penny R. CD4% is the best predictor of development of AIDS in a cohort of HIV-infected homosexual men. AIDS. 1991;5(4):365-372.
18. Malone JL, Simms TE, Gray GC, Wagner KF, Burge JR, Burke DS. Sources of variability in repeated T-helper lymphocyte counts from human immunodeficiency virus type 1-infected patients: total lymphocyte count fluctuations and diurnal cycle are important. J Acquir Immune Defic Syndr (1988). 1990;3(2):144-151.
19. Taylor JM, Fahey JL, Detels R, Giorgi JV. CD4 percentage, CD4 number, and CD4:CD8 ratio in HIV infection: which to choose and how to use. J Acquir Immune Defic Syndr (1988). 1989;2(2):114-124.
20. Murphy TF, Apicella MA. Nontypable Haemophilus influenzae: a review of clinical aspects, surface antigens, and the human immune response to infection. Rev Infect Dis. 1987;9(1):1-15.
21. Musher DM. Haemophilus influenzae infections. Hosp Pract (Off Ed). 1983;18(8):158-170.
22. Wallace RJ, Jr., Baker CJ, Quinones FJ, Hollis DG,

Weaver RE, Wiss K. Nontypable Haemophilus influenzae (biotype 4) as a neonatal, maternal, and genital pathogen. Rev Infect Dis. 1983;5(1):123-136.
23. Wallace RJ, Jr., Musher DM, Septimus EJ, McGowan JE, Jr., Quinones FJ, Wiss K, Vance PH, et al. Haemophilus influenzae infections in adults: characterization of strains by serotypes, biotypes, and beta-lactamase production. J Infect Dis. 1981;144(2):101-106.
24. Alpuche C, Garau J, Lim V. Global and local variations in antimicrobial susceptibilities and resistance development in the major respiratory pathogens. Int J Antimicrob Agents. 2007;30(Suppl 2):S135-138.
25. Beekmann SE, Heilmann KP, Richter SS, Garcia-de-Lomas J, Doern GV, GRASP Study Group. Antimicrobial resistance in Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis and group A beta-haemolytic streptococci in 2002-2003. Results of the multinational GRASP Surveillance Program. Int J Antimicrob Agents. 2005;25(2):148-156.
26. Heilmann KP, Rice CL, Miller AL, Miller NJ, Beekmann SE, Pfaller MA, Richter SS, et al. Decreasing prevalence of beta-lactamase production among respiratory tract isolates of Haemophilus influenzae in the United States. Antimicrob Agents Chemother. 2005;49(6):2561-2564.
27. Jansen WT, Verel A, Beitsma M, Verhoef J, Milatovic D. Surveillance study of the susceptibility of Haemophilus influenzae to various antibacterial agents in Europe and Canada. Curr Med Res Opin. 2008;24(10):2853-2861.
28. Liebowitz LD, Slabbert M, Huisamen A. National surveillance programme on susceptibility patterns of respiratory pathogens in South Africa: moxifloxacin compared with eight other antimicrobial agents. J Clin Pathol. 2003;56(5):344-347.
29. Sener B, Tunckanat F, Ulusoy S, Tunger A, Soyletir G, Mulazimoglu L, Gurler N, et al. A survey of antibiotic resistance in Streptococcus pneumoniae and Haemophilus influenzae in Turkey, 2004 2005. J Antimicrob Chemother. 2007;60(3):587-593.
30. Bae S, Lee J, Lee J, Kim E, Lee S, Yu J, Kang Y. Antimicrobial resistance in Haemophilus influenzae respiratory tract isolates in Korea: results of a nationwide acute respiratory infections surveillance. Antimicrob Agents Chemother. 2010;54(1):65-71.
31. Bae SM, Lee JH, Lee SK, Yu JY, Lee SH, Kang YH. High prevalence of nasal carriage of beta-lactamase-negative ampicillin-resistant Haemophilus influenzae in healthy children in Korea. Epidemiol Infect. 2013;141(3):481-489.
32. Gotoh K, Qin L, Watanabe K, Anh DD, Huong Ple T, Anh NT, Cat ND, et al. Prevalence of Haemophilus influenzae with resistant genes isolated from young children with acute lower respiratory tract infections in Nha Trang, Vietnam. J Infect Chemother. 2008;14(5):349-353.
33. Jean SS, Hsueh PR, Lee WS, Chang HT, Chou MY, Chen IS, Wang JH, et al. Nationwide surveillance of antimicrobial resistance among Haemophilus influenzae and Streptococcus pneumoniae in intensive care units in Taiwan. Eur J Clin Microbiol Infect Dis. 2009;28(8):1013-1017.
34. Niki Y, Hanaki H, Yagisawa M, Kohno S, Aoki N, Watanabe A, Sato J, et al. The first nationwide surveillance of bacterial respiratory pathogens conducted by the Japanese Society of Chemotherapy. Part 1: a general view of antibacterial susceptibility. J Infect Chemother. 2008;14(4):279-290.
35. Barbosa AR, Giufre M, Cerquetti M, Bajanca-Lavado MP. Polymorphism in ftsI gene and beta-lactam susceptibility in Portuguese Haemophilus influenzae strains: clonal dissemination of beta-lactamase-positive isolates with decreased susceptibility to amoxicillin/clavulanic acid. J Antimicrob Chemother. 2011;66(4):788-796.
36. Cohen R, Bingen E, Levy C, Benani M, Thollot F, Klink Z, Schlemmer C, et al. [Antibiotic resistance of pneumococci and H. influenzae isolated from the nasopharyngeal flora of children with acute otitis media between 2006 and 2010]. Arch Pediatr. 2011;18(8):926-931.
37. Dabernat H, Delmas C. Epidemiology and evolution of antibiotic resistance of Haemophilus influenzae in children 5 years of age or less in France, 2001-2008: a retrospective database analysis. Eur J Clin Microbiol Infect Dis. 2012;31(10):2745-2753.
38. Dabernat H, Seguy M, Faucon G, Delmas C. [Epidemiology of Haemophilus influenzae strains collected in 2004 in France and in vitro assessment of their susceptibility to antibiotics]. Med Mal Infect. 2007;37(6):320-324.
39. Garcia-Cobos S, Campos J, Cercenado E, Roman F, Lazaro E, Perez-Vazquez M, de Abajo F, et al. Antibiotic resistance in Haemophilus influenzae decreased, except for beta-lactamase-negative amoxicillin-resistant isolates, in parallel with community antibiotic consumption in Spain from 1997 to 2007. Antimicrob Agents Chemother. 2008;52(8):2760-2766.
40. Garcia-Cobos S, Campos J, Lazaro E, Roman F, Cercenado E, Garcia-Rey C, Perez-Vazquez M, et al. Ampicillin-resistant non-beta-lactamase-producing Haemophilus influenzae in Spain: recent emergence of clonal isolates with increased resistance to cefotaxime and cefixime. Antimicrob Agents Chemother. 2007;51(7):2564-2573.
41. Skoczynska A, Kadlubowski M, Wasko I, Fiett J, Hryniewicz W. Resistance patterns of selected respiratory tract pathogens in Poland. Clin Microbiol Infect. 2007;13(4):377-383.
42. Blain A, MacNeil J, Wang X, Bennett N, Farley MM, Harrison LH, Lexau C, et al. Invasive haemophilus influenzae disease in adults >/=65 years, United States, 2011. Open Forum Infect Dis. 2014;1(2):ofu044.
43. Campos J, Hernando M, Roman F, Perez-Vazquez M, Aracil B, Oteo J, Lazaro E, et al. Analysis of invasive Haemophilus influenzae infections after extensive vaccination against H. influenzae type b. J Clin Microbiol. 2004;42(2):524-529.
44. Dworkin MS, Park L, Borchardt SM. The changing epidemiology of invasive Haemophilus influenzae disease, especially in persons > or = 65 years old. Clin Infect Dis. 2007;44(6):810-816.
45. Ladhani SN, Ramsay M, Slack MP. The impact of Haemophilus influenzae serotype B resurgence on the epidemiology of childhood invasive Haemophilus influenzae disease in England and Wales. Pediatr Infect Dis J.

2011;30(10):893-895.
46. Perdue DG, Bulkow LR, Gellin BG, Davidson M, Petersen KM, Singleton RJ, Parkinson AJ. Invasive Haemophilus influenzae disease in Alaskan residents aged 10 years and older before and after infant vaccination programs. JAMA. 2000;283(23):3089-3094.
47. Rubach MP, Bender JM, Mottice S, Hanson K, Weng HY, Korgenski K, Daly JA, et al. Increasing incidence of invasive Haemophilus influenzae disease in adults, Utah, USA. Emerg Infect Dis. 2011;17(9):1645-1650.