Since the introduction of type b Haemophilus influenzae vaccination, noncapsulated H. influenzae has become responsible for most cases of invasive H. influenzae diseases. In our two cases of septic arthritis, we isolated strains with β-lactamase-positive amoxicillin-clavulanate resistance (BLPACR). Thus, the increasing prevalence of BLPACR should be taken into account when empirical therapy is chosen for septic arthritis.

**CASE REPORTS**

**Patient 1.** A 1-year-old girl was admitted to the Pediatric Hospital in Lyon, France, in November 2011 with fever and inflammatory signs in her left elbow. She was born prematurely at 31 weeks of amenorrhea and had received 3 injections of diphtheria–tetanus–whole-cell pertussis–Haemophilus influenzae type b (DTPw/Hib) vaccine during her first year of life. One week before admission, she presented with a bilateral conjunctivitis associated with a progressive cutaneous rash. The diagnosis of aviral infection was entertained, and she was treated with acetaminophen (international nonproprietary name, paracetamol). A day before admission, she had a swollen, erythematous left elbow with a limited range of motion. Oral amoxicillin treatment was initiated.

Upon admission, the patient was febrile (38.5°C) and asthenic. The left elbow was flexed, swollen, warm, slightly erythematous, and painful upon mobilization. The white blood cell count was 22.00 × 10^9/liter, with 70% neutrophils (15.42 × 10^9/liter), 20% lymphocytes, and 10% monocytes, and the C-reactive protein concentration was lower than 0.3 mg/liter. A control ultrasound scan reported a decrease of the intra-articular effusion.

Haemophilus influenzae was identified from the elbow aspirate (10^9/liter), 20% leukocytes, and 10% monocytes, and the C-reactive protein concentration was 235.3 mg/liter. An X-ray of her left elbow was normal, and an ultrasound scan showed a moderate intra-articular effusion and a superior radial metaphysis subperiosteal abscess. Aspirate from the articulation was purulent. Arthroscopy was performed promptly to drain the elbow joint, and empirical antibiotic treatment with intravenous cefamandole (150 mg/kg of body weight/day) was initiated.

The isolated strain had a penicillinase and a mutation of the penicillin-binding protein 3 (PBP3) gene, which conferred resistance to ampicillin and amoxicillin-clavulanate (MIC = 2 μg/ml). The nonenzymatic resistance to β-lactam due to a mutation of the PBP3 gene was based on the increase in MIC and confirmed by PCR amplification of the ftsI gene, encoding PBP3. According to the new antibiogram, the antibiotic treatment was modified to oral co-trimoxazole (30 mg kg⁻¹ day⁻¹ sulfamethoxazole and 6 mg kg⁻¹ day⁻¹ trimethoprim) for 2 weeks. At the end of the treatment, i.e., 2 months after admission, the patient’s elbow had improved significantly, with a range of motion back to normal. The leukocyte count had decreased to 11.5 × 10^9/liter, and the CRP concentration was lower than 0.3 mg/liter. A control ultrasound scan reported a decrease of the intra-articular effusion.

**Patient 2.** A 66-year-old woman with fever and right-hip pain sought medical attention in the emergency department of the Edouard Herriot Hospital (Lyon, France) in November 2011. The patient had a long medical history, with rheumatoid polyarthritis diagnosed at the age of 17 years, and she had been treated with corticosteroids. Her past medical history was also remarkable for corticoid-induced diabetes, dyslipidemia, hypertension, and bilateral total hip and knee replacements. The rheumatoid polyarthritis was associated with rheumatoid vasculitis, which resulted in restrictive respiratory syndrome and ulcers of the lower extremities.
ities. The ulcers were known to be infected by *Staphylococcus aureus* and had been treated with local wound care. Over the course of her treatment, multiple antibiotic-induced iatrogenic events occurred, including cytolyis, Quincke’s edema, febrile neutropenia, and tendinitis.

Upon admission, the patient presented with fever, right-hip pain, and symptoms of depression. The pelvic X ray was unremarkable. The leukocyte count was 11.6 × 10^9/liter (no differential count of leukocytes was available), and the CRP concentration was 257 mg/liter. The aspirate from the hip was purulent, containing Gram-negative cocccobacilli. The causative bacterium and the antibioticogram were identified as previously described and showed an *H. influenzae* strain resistant to ampicillin because of a penicillinase (nitrocefin test positive) and sensitive to amoxillin-clavulanate, cefotaxime, moxifloxacin, tetracycline, rifampin, co-trimoxazole, and chloramphenicol. Blood cultures were sterile. An empirical antibiotic treatment taking into account the patient’s allergy history was initiated and included intravenous imipenem (500 mg 4 times/day) associated with injections of gentamicin (15 mg/kg/day). A right-hip arthrotomy was performed 3 days later. The joint was drained and the right-hip prosthesis replaced at the same time. Blood, bones, and prosthesis material tissue cultures were all negative, but *H. influenzae* was isolated from the hip fluid. 

Antibiotic treatment was thereby completed by associating intravenous ofloxacin (200 mg 2 times/day) to the intravenous imipenem injections. Clinical and biological inflammatory markers improved within 2 weeks. The patient was discharged with her regular medication, which was associated with an antibiotic treatment comprising subcutaneous ertapenem (1 g 2 times/day) and oral ofloxacin (200 mg 2 times/day) for 3 months. A mortified tooth was considered to be the source of the *H. influenzae* infection and was extracted.

The *H. influenzae* strain was identified by the National Reference Center of *H. influenzae* as a biotype II noncapsulated *H. influenzae* strain. It was sensitive to ceftriaxone (MIC = 0.015 µg/ml), moxifloxacin, tetracycline, and co-trimoxazole and resistant to ampicillin (because of a penicillinase) and to amoxicillin-clavulanate (MIC = 2 µg/ml) (because of a mutation of the PBP3 gene similar to that in the strain from patient 1).

Non-type b and, more specifically, noncapsulated *H. influenzae* strains are uncommon causes of invasive diseases in children and adults. However, since the introduction of *H. influenzae* type b vaccine, the relative incidence of such infections has increased (1–4). Noncapsulated *H. influenzae* has mostly been reported in association with septicemia (1–3, 5), meningitis (1, 3, 4), and pneumonia (1, 2). However, rare cases of septic arthritis have also been described (6–9).

The incidence of *H. influenzae* septic arthritis in children has decreased significantly since the introduction of vaccine-based immunization. In a retrospective study in the United Kingdom of 16 cases of *H. influenzae* septic arthritis in children, 14 cases occurred prior to immunization and 2 occurred after immunization (5). Another study reported no new cases of *H. influenzae* type b septic arthritis after the introduction of *H. influenzae* type b vaccine, whereas *H. influenzae* type b was responsible for 41% cases of septic arthritis prior to the immunization programs (10). Only 4 cases of septic arthritis due to non-type b *H. influenzae* have been reported, 2 in children with *H. influenzae* type b vaccination (on schedule for the children’s ages) and 2 in adults whose *H. influenzae* strains were sensitive to antibiotics (Table 1). In the present report, we offered two new cases of septic arthritis, one of which occurred in an immunized child, and both *H. influenzae* strains presented the same two resistance mechanisms to antibiotics.

Empirical treatment for septic arthritis is directed toward the most common causes, i.e., *Staphylococcus aureus*, *non-aureus* streptococci, and *Kingella kingae* among children. Such regimens are frequently ineffective against penicillinase-producing *H. influenzae*, as shown in the two patients reported in this article. Beta-lactamase production was determined with a nitrocefin disk by the chromogenic cephalosporin method. The modification of penicillin-binding protein type 3 (PBP3) is an emergent resistance mechanism presented by *H. influenzae*. PBP3 is one of the eight PBPs in *H. influenzae*, and it is encoded by the *fisI* gene (11). Several mutations of the *fisI* gene are responsible for amino acid substitutions within the highly conserved motifs in the transpeptidase domain (S379-S-N, K513-T-G) that alter the transpeptidase activity of PBP3 (11–13). These mutations are therefore responsible for amoxicillin-clavulenate resistance (11–13).

*H. influenzae* strains with both β-lactamase production and alteration in PBP3 are reported as β-lactamase positive and amoxicillin-clavulanic acid resistant (BLPACR) (11). While the prevalence of BLPACR strains remains low, it is probably underestimated because of the lack of a consensus-defining breakpoint and consistent technical performances (11). The incidence of BLPACR strains is highly varied among countries (Japan, 1.3% to 11%; France, 14%; United States, 0.15%) (11, 13). Dabernet and Delmas described the BLPACR prevalence among all isolates of noncapsulated *H. influenzae* in children of 5 years of age or less, and the prevalence was equal to 6.4% within the 2001–2008 period and to 2.4% among invasive isolates (14). Finally, as reported in 2011, among 141 *H. influenzae* strains with mutations in the transpeptidase domain of the *fisI* gene, 47 (58.8%) were BLPACR (15). The phenotypic description of our strains as BLPACR was not found using the ATB Haemo (08) (bioMérieux, France) method, and our current *H. influenzae* antibiogram method should therefore

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Comorbidity(ies)</th>
<th><em>H. influenzae</em> serotype</th>
<th>Resistance phenotype</th>
<th>Reference</th>
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<tr>
<td>1</td>
<td>1</td>
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<td>Noncapsulated</td>
<td>BLPACR</td>
<td>Our study</td>
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<tr>
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<td>Male</td>
<td>Rheumatoid polyarthritis, long-term corticotherapy</td>
<td>Noncapsulated</td>
<td>BLPACR</td>
<td>Our study</td>
</tr>
<tr>
<td>A</td>
<td>3</td>
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<td></td>
<td>Type a</td>
<td>β-Lactamase producer</td>
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<tr>
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<td>Type f</td>
<td>Wild type</td>
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<td>Noncapsulated</td>
<td>Wild type</td>
<td>9</td>
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be reevaluated in order to detect the modification of the PBP3 resistance mechanism.

The cases described in this report showed that a noncapsulated H. influenzae strain was capable of emerging as a pathogen causing septic arthritis in a child vaccinated with H. influenzae type b conjugate vaccine and in an immunosuppressed adult. Taking into account the resistance mechanisms occurring in the noncapsulated H. influenzae strain, empirical antibiotic therapy for septic arthritis should include coverage of the resistant strain described herein to avoid further articular and systemic deterioration.

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REFERENCES