

## Invasive pneumococcal infection despite 7-valent conjugated vaccine

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### Abstract

Despite good cover with 7-valent vaccination, invasive pneumococcal infections may still be misdiagnosed and may lead to life-threatening situations or death in young children. New serotypes are emerging and, therefore, clinicians must keep a high level of suspicion in young children regardless of their vaccination status. We report three cases of invasive pneumococcal infection due to new serotypes not covered by the 7-valent conjugated vaccine, two of which led children to death.

### Introduction

Considerable progress has been achieved in both prevention and management of invasive pneumococcal infections (IPI). Yet high fatality rates ranging from 2.6% to 6% have been reported in industrialized countries.<sup>1</sup> In Switzerland, Gessler *et al.* have reported an age specific incidence of IPI of: 33.1% in children below 1<sup>st</sup> year of age, 28.8% under 2 years, 13.4% between 2 and 4 years and 3.1% between 5 and 6 years, highlighting hence the higher vulnerability in toddlers.<sup>2</sup> In 1983, the first vaccine against 23 serotypes of *Streptococcus Pneumoniae* was unfortunately not effective in children under the age of 2. The implementation of a 7-valent conjugated vaccine (7-VCV) in 2000 reduced IPI by 87% in children below 1 year, 58% under 2 and 62% under 5.<sup>3</sup> However, in 2010, the Mortality and Morbidity Weekly Report despite confirming the decrease in resistance and carriage of pneumococcal serotypes contained in the 7-VCV, noted a sharp rise in other serotypes causing new invasive pneumococcal diseases.<sup>4</sup> That is why clinicians must keep, regardless of vaccination status in children with fever, a high level of suspicion of IPI. We report three cases of severe IPI in vaccinated children.

### Case Reports

#### Case #1

An 11-months-old girl with unremarkable medical history, who had received two doses of 7-VCV, presented with chief complaint of 10 min partial seizure involving left hemi-face. Three days prior to presentation she had developed high fever (40°C) that was associated with diarrhea and vomiting. Seizure activity had ceased upon arrival on emergency ward and was soon after followed by another generalized seizure lasting 45 min and requiring 5 mg intra-rectal diazepam and 0.2 mg intravenous clonazepam to resolve. On admission, a post ictal left facial paralysis was noted, which spontaneously resolved 3 h later. Clinical examination revealed bilateral acute otitis media. Initial work-up showed mildly raised C-reactive protein (CRP 54 mg/L), white blood cell (WBC) count 25.3 G/L with 13.5% immature granulocytes. As the child was recovering normal clinical status, the diagnosis retained was an atypical febrile seizure, and the child was admitted for observation for 24 h. During the night she presented tonico-clonic seizures associated with loss of consciousness, bilateral mydriasis and right-sided hemi syndrome that was managed with two injections of benzodiazepine. The child's neurological status remained seriously impaired with Glasgow Coma Scale (GCS) of 9, and left-sided hemiparesis. The second laboratory work-up showed a CRP of 260 mg/L, WBC 12.0G/L and 42% immature forms. Cerebral computed tomography (CT)-scan showed severe right-sided brain edema with significant deviation of midline structures to the left. A dose of 100 mg/kg of Ceftriaxone was administered and the child transferred to Pediatric Intensive Care Unit (PICU) where her condition worsened with hemodynamic instability and GCS of 4, needing mechanical ventilatory support and vasopressive therapy. Decompression craniotomy showed mildly raised intracranial pressure (18 mm Hg), signs of purulent meningitis as well as multiple brain abscesses. Microbiologic cultures were positive for *Streptococcus pneumoniae* serotype 1 [blood, urines, cerebrospinal fluid (CSF) and nasopharyngeal secretions]. Despite very active management, she developed diabetes insipidus; the brain magnetic resonance imaging (MRI) performed on day 5 showed widespread bilateral cytotoxic edema and necrosis and electroencephalogram (EEG) major cortical depression. The child died on day 6.

#### Case #2

A 2-year-old child was admitted to the emergency ward with a three days history of fever (40.7°C) associated with lethargy, headache and five episodes of vomiting. His past medical

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history was unremarkable; he had received 3 doses of 7-VCV. Physical examination revealed tachycardia (124/), tachypnea (40/), pallor, mild signs of dehydration and right acute otitis media. Although he was drowsy, he responded normally to verbal stimuli. Neurological examination revealed minimal nuchal stiffness, a dubious Kernig and Brudzinski with no focal neurological signs. A fluid bolus with normal saline was administered along with 100 mg/kg ceftriaxone. The clinical response was rapid, his general condition improved and he was able to take few steps. He was admitted to the ward for observation.

Suddenly, his condition worsened with the occurrence of generalized tonico-clonic seizures with left lateralization that stopped after intravenous administration of 0.5 mg/kg diazepam. Physical examination at this point revealed areactive bilateral mydriasis and altered consciousness with GCS of 8. The child also developed rapidly Cushing's triad (systolic blood pressure 160 mmHg, bradycardia 80/ and irregular respiratory pattern). He was rapidly intubated and transferred to the PICU for subsequent management. Cerebral CT-scan showed extensive cerebral oedema with lateral ventricles collapse, and right-sided acute mastoiditis. Despite maximal neurological support, hypertonic fluid administration (mannitol and 3% NaCl) and corticosteroid treatment, his state worsened: bilateral non-reactive mydriasis persisted along with a loss of brainstem reflexes. Intracranial hypertension was com-

plicated by diabetes insipidus requiring desmopressin therapy. Hemodynamic instability developed, requiring a vasoactive treatment with norepinephrine and dopamine. The laboratory work-up showed raised CRP 305 mg/L and WBC of 90 G/L. Microbiologic cultures were positive for *Streptococcus Pneumoniae* serotype 7. Viral tests in CSF (herpes, varicella, Epstein-Barr virus, *Parvovirus*, cytomegalovirus, adenovirus) remained negative. A second cerebral CT-scan performed six hours after admission to PICU to evaluate the indication for decompression craniotomy showed an extensive cerebral edema with absent cerebral perfusion. EEG was non-reactive and the cerebral MRI confirmed the diffuse cerebral edema without cerebral perfusion. The child died on day 2. The autopsy confirmed pneumococcal meningitis.

### Case #3

A one-year old girl, with unremarkable past history and two doses 7-VCV developed high fever (up to 39.5°C). On the same night, the child's conditions deteriorated, and she was admitted on the following morning to Pediatric Emergency Room with tachycardia (210/), hypotension (70/50 mmHg), mottled skin with cold extremities, tachypnea (60/). Upon clinical examination, a purpuric rash and neck stiffness were noted. Meningococcal septic shock was suspected and fluid resuscitation immediately started, along with IV antibiotics and corticosteroid therapy (ceftriaxone 100 mg/kg, hydrocortisone 2 mg/kg). Laboratory investigations revealed metabolic acidosis (pH 7.13, bicarbonates 13 mmol/L and BE 12.5 mmol/L), hypoglycemia (1.4 mmol/L), raised CRP 386 mg/L, procalcitonin 122 mcg/L, hyperleukocytosis 15 G/L with 20% immature bands) and stigmata of intravascular disseminated coagulation (thrombocytes 75 G/L, TP 19, PTT 121, fibrinogen 0.7 g/L).

As hemodynamic instability persisted, vasoactive amines were started and the child transferred to PICU where she required subsequent fluid resuscitation, fresh frozen plasma to correct the coagulation parameters along with the introduction of noradrenalin to stabilize blood pressure. As she presented only mild respiratory distress, non invasive ventilation with bilevel positive airway pressure (8 mmHg) was initiated. Lumbar puncture revealed hyperproteinemia and hypoglycemia but microbiology was negative. Blood cultures, however, turned positive for *Streptococcus Pneumoniae* (Serotypes 15B and 15C). Her status rapidly improved allowing hemodynamic support to be withdrawn after 48 h. Corticosteroids were stopped after 5 days and antibiotics after 2 weeks. The child was discharged from hospital at the end of antibiotic therapy.

One month later, she presented a second episode of septic shock, identical to the first that was managed with IV fluids and corticosteroids in the Pediatric Emergency Ward, before transfer to PICU. Blood cultures showed again *Streptococcus Pneumoniae* (serotype 15B and 15C) sensitive to ceftriaxone. Her clinical course was identical to the first: she received IV antibiotics, fluid resuscitation, hemodynamic and ventilator support but no intubation. Further investigations showed asplenia and multiple osteomyelitis foci (right humerus, right tibia and left radius). Ceftriaxone was consequently pursued for 4 weeks, followed by oral amoxicillin (80 mg/kg/j) during a week. A prophylactic antibiotic regimen with oral penicillin was then prescribed to prevent recurrence of severe septic episodes.

### Discussion

These three situations illustrate that IPI occur frequently despite the presumed protection conferred by the 7-VCV. New serotypes are emerging, equally virulent, and cause invasive infections which may lead to death or life-threatening situations.

Most studies observe a decline in the incidence of IPI after the introduction of the 7-VCV. In the UK, the number of cases of IPI in children under the age of five decreased by 41% after vaccine introduction.<sup>5</sup> In the United States, pneumococcal meningitis incidence decreased by 64% among children younger than 2 years.<sup>6</sup> Studies conducted in other European countries and in Australia have also concluded to overall reduction of IPI.<sup>7,8</sup> However, as vaccination successfully diminishes colonization of vaccinated serotypes, it also leaves a niche which is colonized by other pneumococcal serotypes, eventually leading to replacement diseases.<sup>9</sup> This phenomenon has been described in many countries after the introduction of 7-VCV. In the United-States, for instance, disease rates of non-vaccinated serotypes increased by 60.5% and pneumococcal meningitis caused by non-vaccinated serotypes among children under two years increased by 275%.<sup>6</sup>

Both serotypes 1 and 7, which were isolated from our cases, significantly increased after the introduction of the 7-VCV.<sup>7</sup> In Scotland the 7F serotype was reported to be the most common serotype of IPI in 2009. Before vaccination it had not been isolated from any IPI.<sup>5</sup> However, serotype 1 increased in the UK before vaccine implementation, which illustrates the fact that other factors apart from vaccine pressure play a role in pneumococcal epidemiology.<sup>5</sup>

Serotypes 1 and 7 are included in both vac-

inations which were developed after the 7-VCV (Prevenar 13® (Pfizer AG, Zürich, Switzerland) and Synflorix® (Glaxo-SmithKline SA, Belgium)].). These new vaccines may therefore have prevented invasive pneumococcal infection in our 2 patients. Indeed, the 13-valent pneumococcal vaccine could have theoretically covered 50% of IPI in the United States in 2004-2005, 6, 60% of pneumococcal meningitis in France in 2007-2008<sup>10</sup> and 73% of IPI in 2009 in Switzerland.<sup>11</sup>

One of these vaccines, Prevenar 13® (Pfizer AG), is recommended in Switzerland only since January 2011. The question remaining is: will the introduction of these new vaccines bring up other serotypes not yet known? Continuous monitoring of the serotypes involved in IPI is mandatory to adapt pneumococcal vaccines consequently.

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