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# Pediatric Invasive Pneumococcal Disease (IPD) in Yogyakarta, Indonesia: A Case Series

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**Abstract**

Given the fact that invasive pneumococcal disease (IPD) has a high clinical burden, particularly among children in developing countries, data on its occurrence and clinical profile in Indonesia is still insufficient. We presented 3 cases of IPD in children who were admitted to Dr. Sardjito General Hospital, Yogyakarta, Indonesia between 2016 and 2019. While our first 2 patients had milder course of disease, our third patient who presented with meningoencephalitis had poor outcome. Risk factors shown in our cases were young age and malignancy history. Multiple antibiotic resistance was observed in our isolates. The fact that none of our patients have received pneumococcal vaccination marks the necessity of this vaccine especially for at-risk children.

**Keywords**

*Streptococcus pneumoniae*, invasive pneumococcal disease, pediatric, case series, developing countries

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## Introduction

*Streptococcus pneumoniae* infection is one of the most leading etiologies of morbidity and mortality worldwide, particularly among children. Pneumococcal infections were responsible for 294 000 of the estimated 3.26 million deaths among children under the age of 5 worldwide in 2015.[1] While *S. pneumoniae* may normally colonize the upper respiratory tract, it has the potential to spread to other organs, causing serious illness. The term invasive pneumococcal disease (IPD) is defined as the finding of *Streptococcus pneumoniae* in a symptomatic patient through culture from normally sterile sites (blood, cerebrospinal fluid, pleural fluid, and joint fluid).[2] The clinical presentations of the disease vary depending on the primary locus; the major clinical manifestations of IPD are pneumonia, bacteremia, and meningitis. In developing countries, the disease burden is high, and mortality rates are higher than in high-income countries.[3]

There is no routine surveillance of IPD in Indonesia,[4] therefore data on its occurrence and clinical profile are limited. Here, we reported 3 cases of pediatric IPD patients hospitalized in Dr. Sardjito General Hospital, Yogyakarta, Indonesia; which were collected retrospectively during 2016 to 2019.

## Presentation of Cases

### *Case 1*

A 6-year-old boy patient came to the outpatient clinic with fever and cough for 1 week before admission. He had no shortness of breath. The patient was diagnosed with acute lymphoblastic leukemia a year prior and had been undergoing maintenance chemotherapy

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according to the protocol. Vital signs showed an elevated body temperature, with normal results on his remaining vital signs. Physical findings were within normal limits. Blood tests showed anemia (Hb 9.7 g/dL), leukopenia (1200/μL), a neutrophil count of 77.5%, thrombocytopenia (53 000/μL), and an increase in procalcitonin of 5.60 ng/mL. Chest X-rays revealed no signs of infection or pulmonary metastasis. Blood culture was then collected and moderate number of gram-positive diplococci were identified, pertinent with *Streptococcus pneumoniae*. The isolate was susceptible to the following 6 antibiotics: erythromycin, clindamycin, levofloxacin, linezolid, vancomycin, and ceftriaxone; and resistant to tetracycline. The patient was treated for febrile neutropenia with 1 g of ceftriaxone every 12 hours intravenously and 960 mg of trimethoprim/sulfamethoxazole every 8 hours orally. The patient was discharged from the hospital 4 days after admission.

### *Case 2*

A 13-year-old boy came to the outpatient clinic with a chief complaint of fever and experienced no other symptoms. He had a history of acute lymphoblastic leukemia. The physical examination showed normal findings. Complete blood count revealed mild anemia with Hb of 10.9 g/dL; and procalcitonin was within normal range. Blood culture examination showed numerous gram-positive cocci in chains, positive for *S. pneumoniae*. The bacteria were susceptible to the following 6 antibiotics: erythromycin, clindamycin, levofloxacin, linezolid, vancomycin, and ceftriaxone; and resistant to tetracycline. The patient was treated with 750 mg of ceftriaxone every 12 hours intravenously for 3 days. He was discharged after 5 days of hospitalization.

### *Case 3*

A 6-month-old boy complained of fever and no other symptoms. Four days later, the fever persisted, then the patient had 1 episode of watery stool and 1 episode of generalized tonic-clonic seizure which lasted for 10 minutes. The patient was awake after the seizure ceased, and he was admitted to a district hospital later. On the first day of hospitalization, the patient experienced seizures 6 times and decreased level of consciousness with a pediatric coma scale (PCS) of 5. Physical examination revealed that the patient had fever of 38.5°C, stiff neck, and anisocoria; he was transferred to the Pediatric Intensive Care Unit (PICU) of the same hospital subsequently. Head computed tomography (CT) scan demonstrated signs of meningoencephalitis. Patient was eventually referred to the PICU of our hospital because of status epilepticus.

Upon arrival to the PICU, the patient was still in a coma with PCS of 5; the physical findings were persistent fever, anisocoria, sluggish pupillary light reflex, positive Babinski reflex, positive clonus, and positive Brudzinski sign. The initial hemogram was: Hb 11.1 g/dL; leukocyte count 8620/μL (69.8% neutrophils; 27.0% lymphocytes; 3.1% monocytes); platelet count 125 000/$mm^3$. There was an increase in C-reactive protein (CRP) of 139 mg/L. A cerebrospinal fluid (CSF) analysis revealed: red and turbid in appearance, proteins 1.59 g/dL; glucose 1 mg/dL (serum glucose 117 mg/dL); blood cells 1120/μL (64% polymorphonuclear and 36% mononuclear); erythrocytes 7300/μL; lactate dehydrogenase (LDH) 2659 U/L; positive Nonne and Pandy tests; which was typical for bacterial meningitis. The patient was administered 100 mg/kgBW/day of ceftriaxone, paracetamol, mannitol, dexamethasone, and maintenance dose of phenytoin.

On the fifth day of hospitalization, the patient experienced Cushing triad. An evaluation head CT scan demonstrated signs of obstructive hydrocephalus and diffuse cerebral edema, a neurosurgery consult was made and ventricular tapping were performed. Interferon gamma release assay (IGRA) blood test of CSF was performed for any Tuberculosis suspicious, and result test was intermediate. Considering the clinical deterioration and the indeterminate IGRA test result, the tuberculous meningoencephalitis regimen protocol was then initiated.

CSF culture showed moderate number of gram-positive cocci in chains, consistent with *S. pneumoniae*. The isolate was susceptible to the following 10 antibiotics: ampicillin, penicillin G, clindamycin, ampicillin-sulbactam, ciprofloxacin, ertapenem, imipenem, meropenem, vancomycin, moxifloxacin; ceftriaxone was not tested due to lack of reagent. The bacteria were resistant to: azithromycin, oxacillin, amikacin, cefoxitin, doxycycline, tetracycline, trimethoprim/sulfamethoxazole, chloramphenicol. After 7 days of ceftriaxone administration, the antibiotic regimen was switched into 400 mg ampicillin/kgBW/day IV devided q6h of ampicillin-sulbactam according to the antibiogram. Three days following the administration of ampicillin-sulbactam, the fever significantly increased, then antibiotic was escalating to 40 mg/kgBW IV q8h. The patient experienced recurrent seizures and decerebration. Unfortunately, the patient died due to cardiorespiratory failure on day 17th of hospitalization (Table 1).

## Discussion

We presented 3 cases of IPD in children who were admitted to Dr. Sardjito General Hospital, Yogyakarta,

**Table 1.** Clinical Features of Pediatric IPD Patients Admitted to Dr. Sardjito General Hospital, Yogyakarta, Indonesia From 2016 to 2019.

| Characteristic | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| Age | 6 years | 13 years | 6 months |
| Sex | Male | Male | Male |
| Sample collection | Ward | Ward | PICU |
| Prior antibiotic use before sample collection | No | No | Yes |
| Clinical presentation | Bacteremia | Bacteremia | Meningoencephalitis |
| Immunization | | | |
| Primary | Unknown | Yes | No |
| PCV | No | No | No |
| Sign(s) and symptom(s) | Fever, cough | Fever | Fever, seizure, coma |
| Antibiotic regimen | Ceftriaxone, trimethoprim/sulfamethoxazole | Ceftriaxone | Ceftriaxone, ampicillin-sulbactam, meropenem |
| Outcome | Survived | Survived | Died |
| Length-of-stay (day) | 4 | 5 | 17 |

Indonesia between 2016 and 2019. Pneumococcal bacteremia was present in the first and second cases, while pneumococcal meningoencephalitis was found in the third patient.

While our first 2 patients had milder course of disease, our third patient who presented with meningoencephalitis had much more severe illness and poor outcome. This result was in line with a Taiwanese hospital-based study, which found that meningitis was the most serious form of IPD admitted to the PICU and was linked to a poor prognosis.[5] This unfavorable outcome also consistent with high rates of pneumococcal meningitis mortality in other nations.[6-10] One of the main risk factors for IPD which also present in this patient was being under the age of 2.[11]

Two of our patients had a comorbidity of malignancy. In a case-control study in Brazil, severe neutropenia was found to be a significant risk factor for IPD in pediatric oncology patients. From 51 episodes of IPD recorded there, majority of them (52.9%) presented with occult bacteremia.[12] These findings were consistent with our cases, with our first patient presented with febrile neutropenia, and our second patient had occult bacteremia.

All of pneumococci isolated in this study were resistant to tetracycline. Tetracycline resistance was found in up to 74% of cases in China[13] and 52% in Malaysia.[14] Furthermore, our isolate from the third patient was also resistant to trimethoprim/sulfamethoxazole, oxacillin, and azithromycin. High co-trimoxazole resistance was observed in several countries[6,7,9,14,15] and a systematic review reported that the co-trimoxazole resistance in South Asian countries is growing over time.[16] There was also a high prevalence of resistance to macrolides[6,7,13,17,18] and penicillin[18] reported in other nations.

To the best of our knowledge, there are only a few studies of pediatric IPD occurrence and clinical presentation available in Indonesia. In a small study carried out in 2 hospitals in Jakarta, Indonesia reported that *S. pneumoniae* was identified as the causative agent in only 1 child out of 205 subjects who were admitted with IPD over a 18-month period.[19] Meanwhile, an active hospital-based surveillance of IPD and pneumonia among children in Bali, Indonesia showed that no pneumococcus was identified from 736 subjects recruited during a period of 1 year.[20] These findings may indicate that the rate of blood culture positivity for pneumococcus is poor, despite the fact that microbiological confirmation is needed for IPD diagnosis. Some possible causes of this issue are prior antibiotic use, fastidious characteristic of the bacteria (particularly toward carbon dioxide), pneumococcal autolysis during the stationary phase, or technical errors during sample collection and handling.[21-24] As a result, IPD cases may be underdiagnosed, and the disease burden may also be underestimated. Such non-culture-based approaches, as well as improved health workers competencies, may be necessary.

The main limitation of our study is the absence of serotype data on our isolates since the test was not performed due to resource unavailability. As some serotypes are more likely to cause invasive disease than the others,[25] serotype determination would have been useful in understanding its association with the clinical presentation and developing vaccination policies to reduce the disease burden.[4] Even though, the pneumococcal conjugate vaccine (PCV) is currently not part of the national immunization program in Indonesia, the vaccine is commercially available and regional introduction has begun in late 2017. Indonesian Pediatric Association endorses

PCV as important additional vaccine. The fact that none of our patients have received this vaccine marks the necessity of pneumococcal vaccination especially for at-risk children.

## Conclusion

Our cases further corroborate the clinical burden of pediatric IPD in Indonesia. This initial study may illustrate the varying clinical presentations of pediatric IPD and the significance of establishing a national pneumococcal disease surveillance system.

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### Author Contributions

EA and CRW: conceptualized the study, data collected, drafted the initial manuscript, and revised the manuscript. RI, ISL, and NI: gave final approval, critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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### Statement of Ethics

This report is part of the retrospective study that has been approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada Ref. No.: KE/FK/1459/EC/2019. The individual informed consent was not required by this study.

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