An Infant Infected with Macrolide-Resistant *Bordetella pertussis*

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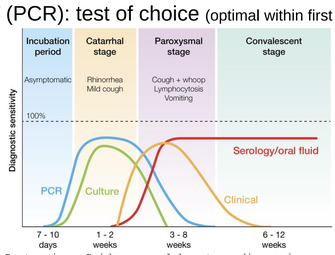
Abstract

A 52-day-old male infant infected with *Bordetella pertussis* was transferred to pediatric intensive care unit (PICU). At the previous hospital, the patient received five days of azithromycin. For history, the patient was born at 35^{+1} weeks of gestation, with a weight of 2.2 kg, appropriate for gestational age. His immunization was up to date (BCG and two doses of hepatitis B vaccine). For family history, the patient's father had a two-week history of cough prior to the patient's illness, and had not received Tdap vaccine, while the mother received Tdap vaccine during pregnancy. At the time of transfer, he had lip cyanosis on 2 liters per minute of nasal cannula oxygen (O_2), and diffuse wheezing in both lungs without retraction. Laboratory results were WBC 14,830/mL (ANC 7,710/mL (52%), ALC 5,640/mL (38%)), C-Reactive protein 0.06 mg/dL, and venous blood gas analysis of pH 7.38, pCO_2 43mmHg, pO_2 37 mmHg, and O_2 saturation 65%. Under conservative management, O_2 supply was gradually weaned to room air, and the patient was transferred to the general ward on hospital day nine. On hospital day 11, the patient had increasing cough frequency followed by cyanotic apnea and was transferred back to PICU. Laboratory evaluation showed no abnormalities, with only persistent positive PCR results for *B. pertussis*.
A multi-locus antigen sequence typing (MAST) identified pertactin allele 150 (*prn150*) and pertussis toxin subunit A allele 3 (*prxA3*). Taking macrolide-resistance into consideration, an additional 23S rRNA gene sequencing analysis was performed and revealed substitution of Adenine to Guanine at position 2047, confirming the mutation associated with macrolide resistance *B. pertussis* (MRBP). On hospital day 23, the patient was discharged without complications. *B. pertussis* is a highly contagious bacterium with humans being the only host, and the emergence of MRBP is a growing concern. We hereby report the first genetically confirmed case of MRBP infection in Korea.

Background

- *Bordetella pertussis (B. pertussis)* is a fastidious gram-negative coccobacillus with humans being the only host
- Incubation: 7-10 days (range, 5-21days)
- Highly contagious with up to 80% infection rate
- NAAT (PCR): test of choice (optimal within first 3 weeks of cough)



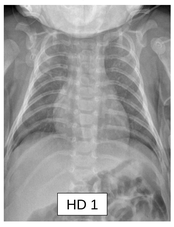
Pertussis – Guidance on laboratory diagnosis. Stockholm: ECDC; 2018.

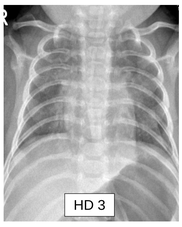
- Macrolide resistant *B. pertussis*
  - First reported in 1994 (CDC MMWR) and 1995 (JAMA 1995)
  - Confirmed mechanism

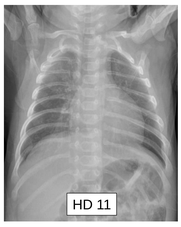
A2047G SNP in the 23S rRNA gene within the domain V	Acquisition of the ERY-resistant methylase (erm) gene	MexAB-OprM efflux pump
• Most common mechanism • Alters the macrolide binding site in the 23S rRNA of the 50S ribosomal subunit, preventing inhibition of peptide elongation	• Leads to methylation of 23S rRNA and blocks erythromycin binding • This mechanism has not been identified in *B. pertussis*	• Excretes macrolides out of the bacterial cell • This operon is not functional in *B. pertussis* (d/t gene deletions)

Present illness and history

- A 52-day-old male infant with *Bordetella pertussis* in pediatric intensive care unit (PICU)
- Patient did not receive 1st dose of DTaP yet.
- Family hx: Tdap vaccine in mother (+) and father (-), Father had history of prolonged cough.
- Repetitive episodes of apnea and cyanosis, along with paroxysmal cough spells, were observed during 28 hospital days.





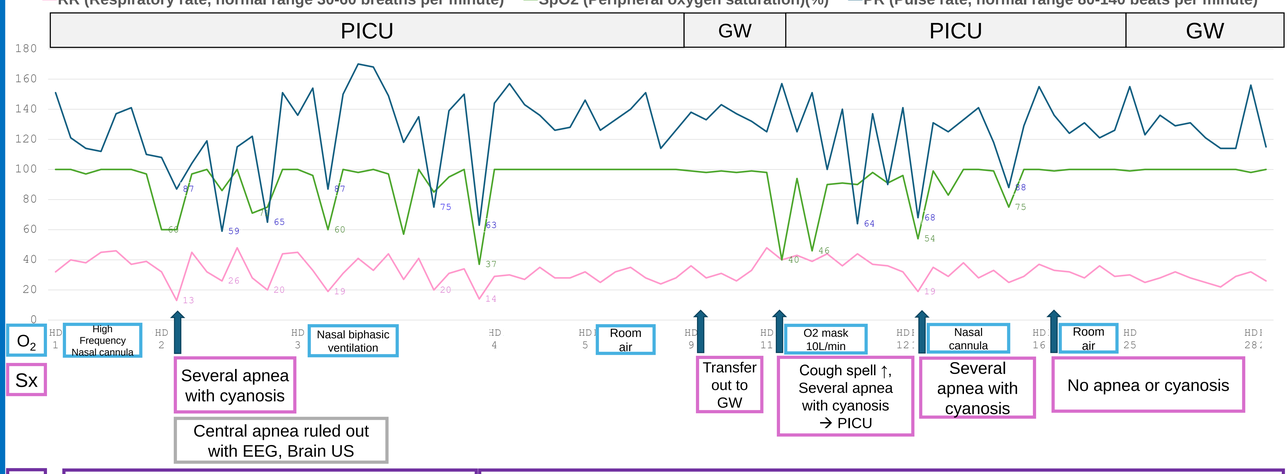


Laboratory findings

Laboratory Tests	HD 1	HD 12	Unit
WBC Count, Blood	▲14.83	▲10.71	x10³/μL
Hemoglobin, Blood	▼9.5	▼8.9	g/dL
Hematocrit, Blood	▼28.7	▼28.0	%
Platelet Count, Blood	▲694	▲574	x10³/μL
Segmented neutrophil	52	48	%
Lymphocyte	38	41	%
ANC (Absolute Neutrophil Count)	7.71	5.14	x10³/μL
ALC (Absolute Lymphocyte Count)	▲5.64	4.39	x10³/μL
Reticulocyte	▲4.96		%
CRP (C-Reactive Protein)	0.06	0.06	㎎/㎗
pH, venous	7.38	7.39	pH
pCO2, venous	43	41	mmHg
pO2, venous	37	38	mmHg
HCO3, venous	▼21.1	24.8	mmol/ℓ
Base Excess, venous	▼-5.6	-0.2	mmol/ℓ
O2 Saturation, venous	65	69.8	%

Bordetella pertussis DNA PCR (Nasopharyngeal swab) : Positive

Hospital Course



O_2: High Frequency Nasal cannula → Nasal biphasic ventilation → Room air → O2 mask 10L/min → Nasal cannula → Room air

Sx: Several apnea with cyanosis; Central apnea ruled out with EEG, Brain US → Transfer out to GW → Cough spell ↑, Several apnea with cyanosis → PICU → Several apnea with cyanosis → No apnea or cyanosis

Tx: Roxithromycin (Previously used 5 days of Azithromycin & 3 days of Roxithromycin (before admission)) → Conservative care

Macrolide resistance test

- A multi-locus antigen sequence typing (MAST)
  - Pertactin allele 150 (*prn150*) & pertussis toxin subunit A allele 3 (*prxA3*)
- 23S rRNA gene sequencing analysis for macrolide resistance
  - **Adenine → Guanine substitution** at position 2047
  - → **Confirmation of the mutation associated with macrolide resistance *B. pertussis***

Summary and Conclusion

- This is the first genetically confirmed case of MRBP infection in Korea
- Macrolide resistance is still geographically uneven but poses an increasing global treatment challenge

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