การพบเชื้อ *Neisseria meningitidis* serogroup B ที่ดื้อต่อยา ciprofloxacin ในการระบาดของโรคในเรือนจำจังหวัดน่าน: รายงานกลุ่มผู้ป่วย

ธัญญารักษ์ วงค์คำหล้า, พ.บ.*

บทนำ

โรคไข้กาฬหลังแอ่นเกิดจากการติดเชื้อแบคทีเรียแกรมลบ *Neisseria meningitidis* ซึ่งอาศัยอยู่ที่เยื่อบุผิวบริเวณลำคอของคนได้โดยไม่ก่อโรค โดยเชื้อจะสามารถเข้าผ่านเข้าเยื่อบุของร่างกาย เข้าสู่กระแสเลือดทำให้ติดเชื้อลุกลามได้ ผู้ที่สัมผัสใกล้ชิดกับผู้ที่มีเชื้ออยู่ในร่างกายจัดเป็นผู้มีความเสี่ยงสูงที่จะติดเชื้อ การให้ยาฆ่าเชื้อหลังสัมผัสเพื่อป้องกันการติดเชื้อจึงเป็นสิ่งจำเป็น และควรทำอย่างเร่งด่วน ยาที่สามารถป้องกันการติดเชื้อได้ คือ ciprofloxacin และยา rifampicin โดยยา ciprofloxacin เป็นยาที่นิยมใช้มากกว่า เนื่องจากเป็นยาที่หาง่าย รับประทานง่ายเพียงครั้งละ 1 เม็ด และมีอาการข้างเคียงจากการใช้ยาต่ำ อย่างไรก็ตามมีรายงานการเกิดเชื้อ *Neisseria meningitidis* ที่ดื้อต่อยา ciprofloxacin มากขึ้นทั้งในประเทศและต่างประเทศ รายงานกลุ่มผู้ป่วยฉบับนี้จัดทำขึ้นเพื่อแสดงข้อมูลด้านอาการ อาการแสดง ผลเพาะเชื้อทางห้องปฏิบัติการ และความไวต่อยาของผู้ป่วยที่ติดเชื้อ *Neisseria meningitidis* ที่ดื้อต่อยา ciprofloxacin จากสถานการณ์การระบาดในเรือนจำจังหวัดน่าน

คำสำคัญ : ไข้กาฬหลังแอ่น ยา ciprofloxacin การดื้อยา ยาป้องกัน การระบาดในเรือนจำ

*กลุ่มงานอายุรกรรม โรงพยาบาลน่าน

Corresponding Author: Thanyarak Wongkamhla E-mail: jcfanclub_2@hotmail.com
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EMERGING CIPROFLOXACIN RESISTANT *NEISSERIA MENINGITIDIS* SEROGROUP B AMONG PRISON OUTBREAK IN NAN PROVINCE; CASE SERIES

Thanyarak Wongkamhla, M.D.*

ABSTRACT

The Gram-negative bacterium, *Neisseria meningitidis,* is a human pathogen that colonizes the nasopharyngeal mucosa. It can cause invasive meningococcal disease (IMD) by passing into the bloodstream via the mucosal membrane. Close contacts of case patients are at increased risk for disease, and chemoprophylaxis is an urgent intervention for the prevention of the disease. Ciprofloxacin and rifampicin are acceptable antimicrobial agents. Ciprofloxacin is more commonly used than rifampicin because of its convenience. However, the emergence of ciprofloxacin-resistant *N. meningitidis* has been reported in many countries as well as in Thailand. This case series from the outbreak within the Nan provincial prison aims to describe the clinical manifestations, laboratory culture results, and drug resistance profile of the *N. meningitidis* resistance to ciprofloxacin..

KEYWORDS: *Neisseria meningitidis* , ciprofloxacin, drug resistance, chemoprophylaxis, prison outbreak

*Department of internal medicine, Nan Hospital

Corresponding Author: Thanyarak Wongkamhla E-mail: jcfanclub_2@hotmail.com
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INTRODUCTION

Invasive meningococcal disease (IMD) incidence is fairly similar across the Asia–Pacific region, ranging from 0.02 to 0.2 cases per 100,000 persons per year in the Philippines and Singapore, respectively.[1]

However, higher reported incidences have occurred in certain countries or within specific sub-populations. In New Zealand, for instance, the average incidence of IMD was 2.3 cases per 100,000 persons in 2019, with cases ranging from 0.0 to 4.5 cases per 100,000 persons, depending on the district health board.[2] IMD can present with nonspecific symptoms and may progress to septic shock or multiple organ dysfunction with an average case-fatality rate of 10.0%.[3] In Thailand, the incidence was 0.01- 0.04 cases per 100,000 persons between 2012-2021.[4] Incidences are generally higher in young infants (0–4 years).[5] Serogroup B was the most common among the reported cases (1994–1999: 56.3%).[5] Case fatality rate (CFR) peaked at 37.5% in 2012 for meningococcal meningitis.[5] In 2021, There were 7 outbreaks occurred, a total of 7 patients, and the death of 2 patients.[5] There are not many cases in Nan province, and no previous outbreaks have occurred before.

Risk factors for the prison outbreak were close contact with infected patients, the overcrowded environment, and direct and indirect contact with the pathogen, such as coughing and sharing drinking glasses, plates, and spoons. At that time, Nan prison had 1,202 prisoners. All of them used shared dining halls and bathrooms, and some prisoners shared the same bedroom.

Chemoprophylaxis is an urgent intervention to prevent the risk for IMD in patients who have had close contact with case patients. Rifampin, ciprofloxacin, or ceftriaxone is currently recommended.[6] Ciprofloxacin is the preferred antibiotic for chemoprophylaxis in persons without contraindications due to the ease of oral administration as a single dose. Global surveillance studies demonstrated an increasing rate of fluoroquinolone resistance in almost all bacterial species.[7] Emergence of ciprofloxacin-resistant *N. meningitidis* has been reported in many countries around the world such as China in 2015,[8] the United States of America in 2015,[9] Korea in 2016,[10] and Brazil in 2018[11] which raises concerns about the currently recommended chemoprophylactic antibiotics for meningococcal disease. The emergence of ciprofloxacin-resistant *N. meningitidis* has been reported in southern Thailand in 2021.[12] The patients were identified as serogroup W135 and 100% resistant to ciprofloxacin.[12] Before 2017, only serogroup B was identified, and all were susceptible to ciprofloxacin.[12]

These case series from the prison outbreak aim to show the clinical syndrome, clinical outcome, and proper antibiotics for treatment and chemoprophylaxis.

Case presentation

In this outbreak, seven cases were confirmed as an invasive meningococcal disease and one case was suspected due to clinical syndrome from 15th October 2023 to 28th October 2023. The outbreak investigation team was alerted by the cluster of 4 patients in the same prison at the same time. They were all previously healthy man and had clinical sepsis. Some of them had meningitis. While the hemoculture results are pending, they were given antibiotics and supportive treatment. All cases are shown in Table 1.

Case I: A 47-year-old man was admitted due to sepsis with acute respiratory failure. First, his hemoculture was positive for Gram-negative diplococci and was misidentified as *Moraxella* spp. After re-identification of the hemoculture, the result was confirmed as *Neisseria meningitidis.* The patient was given Ceftriaxone (2 g OD), and his clinical condition improved in 5 days, the endotracheal tube was removed. He was discharged after 7 days of admission.

Case II: A 27-year-old man was admitted due to sepsis with an alteration of consciousness. He was intubated for respiratory failure. His cerebrospinal fluid (CSF) showed a bacterial meningitis profile, but the CSF culture showed no growth. He was given ceftriaxone 2 g. intravenously every 12 hours. The clinical condition was improved and then discharged after 14 days of admission. This case was suspected of IMD due to clinical syndrome.

Case III: A 22-year-old man was admitted due to sepsis and alteration of consciousness. He was intubated for acute respiratory failure. His CSF showed a bacterial meningitis profile as in case II. Hemoculture was first misidentified as *Moraxella* spp. After re-identification, this case was confirmed to be *Neisseria meningitidis*. After treatment with Ampicillin 2 g intravenously every 4 hours, he was discharged after 14 days of admission.

Case IV: A 46-year-old man was admitted due to sepsis. Hemoculture was misidentified as Moraxella spp., as in cases I and III. After re-identification of hemoculture, this case was confirmed as IMD. After treatment with Ceftriaxone 2 g intravenously OD, he was discharged after 7 days of admission.

Case V: A 33-year-old man was admitted due to sepsis and alteration of consciousness. His CSF showed a bacterial meningitis profile, however, his CSF culture and hemoculture showed no growth, like in case II. Because of the suspected IMD case, his CSF was sent for identification of the organism by RT-PCR and the result was confirmed of *N. meningitidis*. He was given Ceftriaxone 2 g intravenously every 12 hours for 7 days and was discharged.

Case VI: A 43-year-old man was admitted due to sepsis and headache. He presented with skin purpura on his left hand. His CSF showed a bacterial meningitis profile. However, his hemoculture and CSF culture showed no growth. His CSF was sent for pathogen identification by RT-PCR, and the result was confirmed to *N. meningitidis*. He was given Ampicillin 2 g intravenously every 4 hours for 14 days and was discharged.

Case VII: A 51-year-old man was admitted due to clinical sepsis. He presented with skin purpura on his both hands. His hemoculture showed growth for *N. meningitidis*. He was discharged after 7 days of antibiotic treatment (Ceftriaxone 2 g intravenously OD).

Case VIII: A 53-year-old man was alerted by the prison team because of an alteration of consciousness and generalized purpura on the face and trunk. He was found unconscious; the Emergency Medical Services (EMS) team was sent to the scene. After that, he had a cardiac arrest, and CPR was activated, but the patient did not Return to Spontaneous Circulation (ROSC). His hemoculture showed growth of *N. meningitidis*, so IMD was the cause of his death.

All 8 patients had sepsis and rapid clinical worsening after illness. 4 out of 8 cases had meningitis and the CSF profiles showed very high protein (400.8-737.7 mg/dL), very low sugar (0-3 mg/dL), and only 1 case (case II) had normal sugar. The antimicrobial susceptibility test among 5 isolates of *N. meningitidis* showed 100% susceptibility to ceftriaxone and meropenem while 100% resistance to ciprofloxacin and trimethoprim-sulfamethoxazole (Table. 2). All 7 patients were given proper antibiotics and supportive treatment. The last case of IMD died in prison because of cardiac arrest before receiving proper antibiotics treatment.

The samples of *N. meningitidis* from cases III, IV, and VII were sent for serotyping at the Department of Medical Sciences, the results were serogroup B.

Mass chemoprophylaxis was given to all prisoners and guards after *N. meningitidis* infection was confirmed. Contact tracing was done for the healthcare professional of Nan Hospital and the chemoprophylaxis was prescribed. Ciprofloxacin was chosen as the first choice because of its convenience and drug availability at that time. Before this outbreak, there were no reported cases of ciprofloxacin-resistant *N. meningitidis* infection. After an antimicrobial sensitivity test of *N. meningitidis* was done and showed ciprofloxacin resistance, rifampicin was selected as the next choice. However, the limitation of this intervention was due to the shortage of rifampicin for mass chemoprophylaxis (totaling 8000 tablets of rifampicin 300 mg), the chemoprophylaxis was delayed for a few days.

Discussion

Neisseria meningitidis, is a human pathogen that colonizes the nasopharyngeal mucosa. These organisms are fastidious bacteria and are sometimes difficult to cultivate and identify. *N. meningitidis* may be misidentified by automated machines as Moraxella species as both are gram-negative diplococci, oxidase test positive, and catalase positive. The differences among 2 species are the morphology of colonies on blood agar. *N. meningitidis* colonies are smooth, round large grey/brown colonies, but Moraxella spp. colonies are white or buff, convex colonies. *N. meningitidis* produces acid from glucose and maltose, but Moraxella spp. cannot produce sugar. The biochemistry tests for the identification of species that have glucose and maltose production are unavailable in the Nan hospital microbiology laboratory, so the microbiologists must rely on gram stain and blood agar morphology for early identification of the pathogen is the key success for the treatment of IMD. Delays in diagnosis can lead to increased mortality rates.

Table 1

	Case I	Case II	Case III	Case IV	Case V	Case VI	Case VII	Case VIII
Age	47	27	22	46	33	43	51	53
Comorbidity	no	no	no	no	no	no	no	no
Admission date	15/10/2023	15/10/2023	16/10/2023	16/10/2023	19/10/2023	19/10/2023	20/10/2023	28/10/2023
Symptom at presentation	- Sepsis	- Sepsis - Alteration of consciousness	- Sepsis - Alteration of consciousness	- Sepsis	- Sepsis - Alteration of consciousness	- Sepsis - Headache	- Sepsis	- Sepsis - Cardiac arrest
Respiratory failure	✓	✓	✓	✗	✗	✗	✗	✓
Skin purpura	Not seen	Not seen	Not seen	Not seen	Not seen	localized	localized	generalized
CBC: WBC	31,420	24,800	26,930	21,620	19,810	22,160	9,880	
H/C	Growth	No growth	Growth	Growth	No growth	No growth	Growth	Growth
CSF C/S	Not done	No growth	Growth	Not done	No growth	No growth	Not done	Not done
CSF: protein (mg/dL)	Not done	519.7	607.5	Not done	400.8	737.7	Not done	Not done
CSF: sugar (mg/dL)	Not done	45	1	Not done	3	0	Not done	Not done
CSF: WBC (cells/cu.mm)	Not done	21,092	19,267	Not done	1,346	14,088	Not done	Not done
CSF: PCR	Not done	Not done	Not done	Not done	Positive	Positive	Not done	Not done
ATB	Ceftriaxone	Ceftriaxone	Ampicillin	Ceftriaxone	Ceftriaxone	Ampicillin	Ceftriaxone	-
Length of stay (days)	7	14	14	7	7	14	7	-
Outcome	Discharge	Discharge	Discharge	Discharge	Discharge	Discharge	Discharge	Death

Previously, there was no report about drug-resistant *N. meningitidis* strains in Nan Hospital. This case series showed that ciprofloxacin-resistant *N. meningitidis* can be found in Thailand to the same extent as in other countries. The widespread use of quinolones and azithromycin in the community for treatments of bacterial infections should be a concern due to the changing susceptibility of *N. meningitidis*. Mutations in the quinolone resistance-determining regions of the gyr A and par C genes have led to the development of fluoroquinolone-resistant *N. meningitidis*.[13] The rate of ciprofloxacin-resistant *N. meningitidis* has increased from 0.00% in 1965–1985 to 84.00 % in 2005–2013 in some areas.[8] The emergence of ciprofloxacin-resistant *N. meningitidis* is a rising concern for inappropriate post-exposure chemoprophylaxis.

Chemoprophylaxis is commonly used despite the lack of national recommendations in some areas. For example, the Chinese Center for Disease Control does not have strict protocols for prophylactic treatments, which has led to each province prescribing different antibiotics based on local guidance.[14] In Vietnam, all close contacts of a suspected IMD case receive either ciprofloxacin or azithromycin.[14] In the USA, the Centers for Disease Control and Prevention (CDC) recommend ciprofloxacin use only if fluoroquinolone-resistant strains of *N. meningitidis* have not been identified in the community**.** In Thailand, the National Department of Disease Control recommends rifampicin for post-exposure chemoprophylaxis.[15] The limitation of rifampicin use is rifampicin susceptibility is unavailable to evaluate due to the rifampicin disk diffusion test is not routinely used. The next choice may be ceftriaxone, that inconvenient to give because it requires intravenous or intramuscular administration. Thus, the importance of continuing surveillance to monitor the susceptibility patterns and trends of *N. meningitidis* susceptibility profiles is necessary.

Table 2

AST	*Neisseria meningitidis*
Trimethoprim/sulfamethoxazole	R
Ceftriaxone	S
Ciprofloxacin	R
Meropenem	S

Conclusion

Emerging ciprofloxacin-resistant *N. meningitidis* serogroup B in Northern Thailand raises public concern about the spread of colonization, infection, and outbreaks in the community especially in prisons. Drug recommendation for post-exposure chemoprophylaxis is another concern. Rifampicin or Ceftriaxone may be appropriate drugs for chemoprophylaxis at this time. Further evidence on the use of azithromycin for chemoprophylaxis may be studied.

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