นิพนธ์ต้นฉบับ

การพบเชื้อ *Neisseria meningitidis* serogroup W135 ที่ดื้อต่อยา Ciprofloxacin ทางภาคใต้ของประเทศไทย

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Received: *August 14, 2020* **Revised:** *September 16, 2020* **Accepted:** *November 30, 2020*

บทคัดย่อ

ที่มาของปัญหา: โรคไข้กาฬหลังแอ่นเกิดจากการติดเชื้อ *Neisseria meningitidis* ซึ่งยังพบการระบาดอยู่ในกลุ่มประเทศพัฒนาและกำลังพัฒนารวมถึงประเทศไทย ผู้สัมผัสใกล้ชิดจำเป็นต้องได้ยาป้องกันการติดเชื้อโดยเร็ว เนื่องจากมีโอกาสติดเชื้อและป่วยเป็นโรคไข้กาฬหลังแอ่นได้สูง ยาที่แนะนำในปัจจุบันคือยา Rifampicin หรือ Ciprofloxacin ซึ่งยา Ciprofloxacin ได้รับความนิยมมากกว่า เนื่องจากการบริหารยาเป็นแบบเม็ดเดียว ครั้งเดียว ในขณะที่ Rifampicin ต้องกินวันละ 2 ครั้ง เป็นเวลา 2 วัน อย่างไรก็ตาม ในต่างประเทศเริ่มมีรายงานเชื้อ *Neisseria meningitidis* ที่ดื้อต่อยา Ciprofloxacin แต่ยังไม่มีรายงานในประเทศไทย

วัตถุประสงค์: เพื่อหาความไวของเชื้อ *Neisseria meningitidis* ต่อยา Ciprofloxacin ตั้งแต่เดือนกันยายน พ.ศ. 2552 ถึงเดือนกันยายน พ.ศ. 2561

วิธีการศึกษา: เป็นการศึกษาย้อนหลังโดยการทบทวนเวชระเบียนผู้ป่วยของโรงพยาบาลสงขลาที่มีผลเพาะเชื้อยืนยันว่ามีการติดเชื้อ *Neisseria meningitidis* โดยเก็บข้อมูลทั่วไป อาการ อาการแสดง ผลความไวต่อยา Ciprofloxacin และ Serogroup ของเชื้อ

ผลการศึกษา: พบว่า มีผู้ป่วยจำนวน 11 รายที่มีผลการเพาะเชื้อยืนยัน โดยเป็นเด็ก 4 รายและผู้ใหญ่ 7 ราย ไม่พบผู้เสียชีวิต เชื้อ *Neisseria meningitidis* ที่พบในช่วงปี พ.ศ. 2552-2560 เป็น Serogroup B และไวต่อยา Ciprofloxacin คิดเป็นร้อยละ 100 แต่หลังจากปี พ.ศ. 2560 พบว่า เป็น Serogroup W135 และดื้อต่อยา Ciprofloxacin คิดเป็นร้อยละ 100 แต่ก็ยังคงไวต่อยา Ceftriaxone

สรุป: การค้นพบเชื้อ *Neisseria meningitidis* serogroup W135 ซึ่งดื้อต่อยา Ciprofloxacin ทางภาคใต้ของประเทศไทย ทำให้ต้องมีการทบทวนการใช้ยา Ciprofloxacin ในการป้องกันการติดเชื้อสำหรับผู้สัมผัสใกล้ชิด

คำสำคัญ: ไข้กาฬหลังแอ่น, ยา ciprofloxacin, การดื้อยา, ยาป้องกันการติดเชื้อ

ORIGINAL ARTICLE

Emerging ciprofloxacin–resistant *Neisseria meningitidis* serogroup W135 in Southern Thailand

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ABSTRACT

BACKGROUND: *Neisseria meningitidis* is a cause of endemic and epidemic disease in developed and developing countries including Thailand. Close contacts of case patients are at increased risk for disease, and chemoprophylaxis is an urgent intervention for prevention of disease. Rifampicin and Ciprofloxacin are acceptable antimicrobial agents. Ciprofloxacin is more commonly used than Rifampicin because of convenience. However, the emergence of ciprofloxacin-resistant *N. meningitidis* has been reported in many countries but has never been previously reported in Thailand.

OBJECTIVE: To evaluate ciprofloxacin susceptibility of *N. meningitidis* from September 2009 to September 2018

METHODS: A retrospective descriptive study was done in Songkhla Hospital. All available medical records of all clinical specimens with culture-confirmed *N. meningitidis* were reviewed to explore the clinical manifestation and susceptibility pattern.

RESULTS: Eleven patients were confirmed as meningococcal diseases and one case of nasopharyngeal colonization. Four patients were children under one year of age and all presented with acute meningitis, while one patient developed meningococcal septicemia. Seven adult patients presented with meningococcemia and only one patient had meningococcal meningitis. There were no case fatalities. Before 2017 only serogroup B was identified and all were susceptible to Ciprofloxacin. In 2018, three patients were identified as serogroup W135 and 100% were resistant to Ciprofloxacin. All isolates had 100% susceptible to Ceftriaxone.

CONCLUSIONS: Emerging ciprofloxacin-resistant *N. meningitidis* serogroup W135 in southern Thailand is raising public concern about the spread of colonization, infection, and outbreak in the community. Drug recommendation for post-exposure chemoprophylaxis is another concern. Rifampicin or Ceftriaxone may be appropriate drugs for chemoprophylaxis at this time.

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

Note: This abstract was presented as a paper-poster presentation **"Should ciprofloxacin be recommended as post-exposure chemoprophylaxis in meningococcal disease in Thailand?"** at European Congress of Clinical Microbiology and Infectious Diseases 2019, Amsterdam, Netherlands.

INTRODUCTION

Infections with *Neisseria meningitidis* (*N. meningitidis*) may occur as outbreaks or epidemics in developed and developing countries. The high-incidence countries (> 10 cases/100,000 population) are found in the African meningitis belt. The moderate-incidence countries (2–10 cases/100,000 population per year) are found in the African regions, Europe, and Australia. The low-incidence group countries (<2 cases/100,000 population per year) are found in Europe, the Americas, and the South-East Asia Region which reported most of the cases in Thailand and Korea.[1, 2] Even though there are 12 serogroups of *N. meningitidis*, the most invasive meningococcal infections are caused by serogroups A, B, C, X, Y, or W135.[3] Invasive meningococcal disease (IMD) can present as nonspecific symptoms and may progress to septic shock or multiple organ dysfunction with an average case-fatality rate of 10.0%.[4] Chemoprophylaxis is an urgent intervention to prevent risk for IMD in patients who have had close contact with case-patients. Rifampin, ciprofloxacin, or ceftriaxone. are currently recommended.[5] Ciprofloxacin is the preferred antibiotic for chemoprophylaxis in persons without contraindications due to ease of oral administration as a single dose. Global surveillance studies demonstrated an increasing rate of fluoroquinolone resistance in almost all bacterial species.[6] Emergence of ciprofloxacin-resistant *N. meningitidis* has been reported in many countries around the world such as China in 2015[7] the United States of America in 2015,[8] Korea in 2016,[9] and Brazil in 2018[10] which raises concerns about the currently recommended chemoprophylactic antibiotics for meningococcal disease.

The aim of this study was to report the ciprofloxacin susceptibility pattern of *N. meningitidis* from September 2009 to September 2018.

METHODS

A retrospective descriptive study was conducted in Songkhla Hospital which is a secondary care hospital with 508 beds located in the Muang District of Songkhla Province in southern Thailand. All hospitalized patients with isolates of N. meningitidis from blood culture or cerebrospinal fluid culture from September 2009 to September 2018 were included. All isolates were confirmed N. meningitidis by polymerase chain reaction from the Department of Medical Science, Ministry of Public Health, Thailand. Patient characteristics and previous medical illnesses were reviewed using medical records. The collected data included age, sex, clinical presentation, laboratory investigation, antibiotic treatment, clinical outcome, and antimicrobial susceptibility pattern.

Antimicrobial susceptibility test methods were done by disk diffusion and interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guideline.

RESULTS

During the 9-year study period, 11 patients were confirmed meningococcal disease and one case of nasopharyngeal colonization. Four patients were children under one year of age and all of them presented with acute meningitis, while only one patient had complications of meningococcal septicemia. Among seven adult patients who presented with meningococcemia, only one patient had meningococcal meningitis. The medical records of only eight patients were available for review while three medical records that included susceptibility tests between 2009 and 2012 were unavailable. There were no case fatalities and no secondary case from close contact but complications were found in three

of eight cases including septic shock, acute renal failure, acute respiratory failure, and disseminated intravascular coagulation. One pediatric patient was referred to a tertiary hospital without a referral outcome. The clinical characteristics of the patients are shown in Table 1.

The antimicrobial susceptibility tests among nine isolates of *N. meningitidis* showed 100.0% susceptible to ampicillin, ceftriaxone, and cefotaxime, while 56.0% were susceptible to ciprofloxacin and 100.0% were resistance to trimethoprim-sulfamethoxazole. Three isolates from 2018 were serogroup W135 and all of them were resistant to ciprofloxacin as well as one case of nasopharyngeal colonization that was found in an adult with serogroup W135 and was also resistant to ciprofloxacin (Table 2).

Close contact cases of patients with serotype W135 initially received chemoprophylaxis with a single dose of ciprofloxacin (500 mg) and repeated with a single dose of azithromycin (500 mg) after susceptibility was reported and no secondary case was found. All three patients with serotype W135 did not have an area of association between patients.

DISCUSSION

The study findings showed that ciprofloxacin resistant *N. meningitidis* was found in Thailand to the same extent as in other countries. Mutations in the quinolone resistance-determining regions of the gyrA and parC genes have led to development of fluoroquinolone resistant *N. meningitidis*.[11] The rate of ciprofloxacin resistant *N. meningitidis* has increased from 0.0% in the years of 1965–1985 to 84.0% in the years of 2005–2013 in some area.[7]

The cause of change in the meningococcal serogroup in southern Thailand may be associated with *N. meningitidis* carriage among Umrah and Hajj pilgrims. The rate of *N. meningitidis* carriage varies from 1.3% in returning Singaporean Hajj pilgrims 14 to 18.3% in Turkey.[15] Serogroup W135 has become the predominant *N. meningitidis* carriage among pilgrims since the 2000 outbreak.[16] More than 5,000 people from southern Thailand (unpublished data) attend the Hajj and Umrah religious mass gatherings hosted by the Kingdom of Saudi Arabia. It is possible that carriage of this organism may occur and spread to close contact people.

Ciprofloxacin-resistant *N. meningitidis* serotype W135 in southern Thailand is a rising public concern about the spread of colonization, infection, and outbreak in the community.

Before 2018, a single dose of ciprofloxacin (500 mg) was used widely for post-exposure chemoprophylaxis in cases of close contact for *N. meningitidis.* The emergence of ciprofloxacin-resistant *N. meningitidis* serotype W135 is a rising concern for inappropriate post-exposure chemoprophylaxis. A drug recommendation for post-exposure chemoprophylaxis is an important action to prevent the spread of disease. Widespread use of quinolones and azithromycin in the community for bacterial infection should be a concern due to the change in susceptibility of N. meningitides.

The limitation of this study is a retrospective descriptive study in a single-center and a small study population which might not represent a true trend of susceptibility. Rifampicin susceptibility was unavailable to evaluate due to the rifampicin disk diffusion test is not routinely used. Thus, the importance of continuing surveillance to monitor susceptibility pattern and trends of *N. meningitidis* susceptibility profiles is necessary.

Conflict of Interest: None

Financial Support: None

Table 1 Characteristics and outcome of treatment of culture-confirmed *Neisseria meningitidis* from September 2009 to September 2018

Cases	Year	Age (Month/Year)	Gender	Presented Symptoms	Site of positive culture	Co- morbidity	Complication	Antibiotic treatment	Outcome	Serogroup
1	2013*	1 M	male	NA	CSF	N/A	N/A	N/A	N/A	B
2	2014	60 Y	female	Acute fever with abdominal pain	blood	DM	None	Ceftriaxone plus metronidazole	Improved	B
3	2015	19 Y	male	Septic shock	Blood CSF: NG	No	DIC, acute renal failure, acute respiratory failure	Ceftriaxone	Improved (LOS: 50 days)	B
4	2015	31 Y	male	Acute meningitis	Blood, CSF	DM, ESRD	None	Ceftriaxone	Improved	B
5	2017	4 M	male	Fever with rash	Blood CSF: NG	No	DIC, acute renal failure, septic shock	Cefotaxime	Referred	B
6	2018	37 Y	male	Acute meningitis	Blood CSF: NG	Pulmonary tuberculosis	Acute respiratory failure, septic shock	Ceftriaxone	Improved	W135
7	2018	64 Y**	female	Cellulitis	Blood LP: not done	DM, HT	None	Ceftriaxone	Improved	W135
8	2018	47 Y	male	Acute febrile illness	Blood CSF: NG	HT	None	Ceftriaxone	Improved	W135

*Three medical records were unavailable, **Nasopharyngeal swab of close contact positive culture for *N. meningitidis* serogroup W135

Abbreviations: N/A, not available; CSF, cerebrospinal fluid; DM, diabetic mellitus; NG, no growth;; DIC, disseminated intravascular coagulation; LOS, length of stay; ESRD, end-stage renal disease; LP, lumbar puncture; HT, hypertension; M, month; Y, year.

Table 2 Antimicrobial susceptibility of *Neisseria meningitidis* from September 2009 to September 2018

Antimicrobial agent	Serogroup B (N=5) % susceptible	Serogroup W135 (N=4) % susceptible
Ampicillin	100	100
Trimethoprim- sulfamethoxazole	0	0
Ceftriaxone	100	100
Cefotaxime	100	100
Ciprofloxacin	100	0

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