The Journal of Antibiotics (2019) 72:185–188
https://doi.org/10.1038/s41429-018-0125-0

JARA Japan Antibiotics Research Association
The Society for Actinomycetes Japan

BRIEF COMMUNICATION

Emergence and spread of resistant *N. meningitidis* implicated in invasive meningococcal diseases during the past decade (2008–2017)

Yassine Zouheir[1] · Taha Atany[2] · Najma Boudebouch[3]

Received: 19 June 2018 / Accepted: 5 November 2018 / Published online: 27 November 2018

Abstract

Neisseria meningitidis is one of the most crucial causes of bacterial meningitis worldwide. The incidence of meningitis due to *N. meningitidis* greatly changes from one geographical area to the other: 500,000–1,200,000 invasive meningococcal diseases occur each year, with 50,000–135,000 deaths. Once the diagnosis of bacterial meningitis is made, parenteral antibiotic treatment is started as soon as possible. A preventive treatment can also be proposed for those subjects at risk of exposure. Globally, resistance to antibiotics used in the treatment of prophylaxis of meningococcal disease is relatively rare. Penicillin is becoming less useful in the treatment of invasive meningococcal diseases because meningococcal isolates are increasingly less susceptible to this antibiotic. Meningococcal strains less susceptible to ceftriaxone or ciprofloxacin are rare. In addition, resistance to rifampicin is not a current concern as resistant isolates are rarely reported. In conclusion, the emergence of new meningococcal strains with decreasing susceptibility during the last decade should not be ignored, as this could be a worrying phenomenon in the future and justifies a judicious epidemiological survey on a continuous basis.

Introduction

Neisseria meningitidis (or meningococcus), a Gram-negative diplococcus, has been and proceeds to be one of the most important causes of bacterial meningitis worldwide. The pathogen has the ability to cause different forms of disease: major epidemics, case groups, and hyperendemic and endemic diseases. The highest incidence (10–100 cases per 100,000 population) is reported in a region of sub-Saharan Africa, which is known as the "meningitis belt". In Europe, North America and Australia, the incidence ranges between 0.3 and 3 cases per 100,000 inhabitants [1]. Once the diagnosis of bacterial meningitis is made, parenteral antibiotic treatment is started as soon as possible. A prophylactic vaccine is also available. It seems that meningococcus is following the same evolution as gonococcus concerning the increase of MICs to penicillin. This gradual increase in MICs among gonococcus occurred because of lack of or inadequate monitoring. The disappearance of penicillin as an effective treatment for gonococcus is due to the accumulation of several chromosomal determinants of antibiotic resistance [2]. Being closely related pathogens, gonococcal resistance scenario to penicillin (or to other antibiotics) could be repeated in *N. meningitidis*. The aim of this review is to provide an updated overview of in vitro resistance of invasive *N. meningitidis* to the antibiotics commonly used for therapy or for prophylaxis. Only data published between January 2008 and December 2017 were incorporated in this study to ensure that the results were of contemporary relevance.

✉ Yassine Zouheir
yassine.zouheir@pasteur.ma

[1] Laboratory of Molecular Bacteriology Institut Pasteur du Maroc, Casablanca, Morocco

[2] Independent Researcher, Hassan II Univeristy, Casablanca, Morocco

[3] Laboratory of Bacteriology and Parasitology, Institut Pasteur du Maroc, Casablanca, Morocco

Antimicrobial susceptibility testing methods of *N. meningitidis*

Minimal inhibitory concentration (MIC) is the lowest concentration of antibiotics that can inhibit in vitro any visible

culture of the studied strain during a period of time. MIC is expressed in mgl^{-1} or μgml^{-1}. The bacterial susceptibility to a given antibiotic is interpreted based on the MIC value as follows: susceptible (organism is inhibited by the serum concentration of the drug that is achieved using the usual dosage), intermediately susceptible (organism is inhibited only by the maximum recommended dosage) and resistant (organism is resistant to the usually achievable serum drug levels). Antibiotic susceptibility testing of *N. meningitides* is complicated by lack of consensus regarding the best techniques to use and MIC breakpoints. The Clinical and Laboratory Standards Institute (CLSI) has recommended broth and agar dilution MIC susceptibility methods for *N. meningitidis* [3]. On the other hand, both the Etest and agar dilution methods are recommended by the European Monitoring Group on Meningococci (EMGM). Microdilution, also a recommended method, is not used across Europe. Various MIC breakpoints for *N. meningitidis* were determined by different organizations around the world. In Table 1, we report MIC breakpoints established by CLSI and by European Committee on Antimicrobial susceptibility testing (EUCAST) concerning the four antibiotics discussed in this review.

Penicillin

African meningitis belt

Recent studies in sub-Saharan countries have identified the predominance of strains with intermediate susceptibility to penicillin. In Cameroon, the resistance rate of *N. meningitidis* is alarming. About 80% of cultured strains (only 20/40 strains were cultured) were highly resistant (MIC ≥0.25 mg l^{-1}, Table 2) [4].

Table 1 MIC breakpoints

Antibiotics	Organizations	R≥	S≤
Penicillin	CLSI [a]	0.5	0.06
	EUCAST [b]	0.25	0.06
Ceftriaxone	CLSI	0.12	0.12
	EUCAST	0.125	0.125
Ciprofloxacin	CLSI	0.12	0.03
	EUCAST	0.03	0.03
Rifampicin	CLSI	2	0.5
	EUCAST	0.25	0.25

R resistant, *S* susceptible

[a]Ref. [22]

[b]Ref. [23]

Table 2 Reported resistance of *N. meningitidis* to four antibiotics

	Countries (MIC values in mgl^{-1})	Total number of strains tested	References
Penicillin	Cameroon (≥0.25)	20	[3]
	India (0.5)	1	[4]
	Singapore (0.38–0.47)	75	[5]
	Belgium (≥0.5)	1933	[6]
	Romania (≥ 1)	31	[7]
	Australia (≥ 1)	149[a]—189[b]	[8, 9]
Ceftriaxone	Ethiopia (MIC not specified but noted to be resistant)	49	[10]
Ciprofloxacin	China (≥0.12)	487	[11]
	India (0.5)	1	[4]
	Singapore (0.25)	75	[5]
	Croatian (0.25)	50	[12]
	Canada (0.19–0.38)	346	[13]
	U.S (0.06–0.25)	3	[14]
	Argentina (0.12)	133	[15]
Rifampicin	Hungary (>32)	1	[16]
	Brazil (>256)	1096	[18]
	Uruguay (≥32)	2	[19]
	Australia (1)	174	[20]

[a]2008 report

[b]2016 report

Asia

In Asia, access to information on antibiotics resistance is limited, probably due to the absence of national surveillance systems in several Asian countries. In India, a case report showed that a strain was found to be resistant to penicillin (MIC: 0.5 mg l^{-1}) [5]. In Singapore, last published data indicated a low rate of intermediate susceptibility (17%) to penicillin, while resistant strains (MICs: 0.38–0.47 mg l^{-1}) were rare (3%) [6].

Europe

In Europe, resistant strains to penicillin have been observed at a lower rate compared to those found in sub-Saharan Africa. In Belgium, the rate of isolates with intermediate susceptiblity to penicillin (MICs: 0.125–0.25 mg l^{-1}) increased significantly over the years: this rate increased from 36.3% in 2008 to 40.9% in 2010; resistance rate recorded in 2010 was 7.8% (MIC: ≥0.5 mg l^{-1}) [7]. In addition, 38.7% of strains isolated in Romania had intermediate susceptibility to penicillin (MICs: 0.06–1 mg l^{-1}), while 3.3% were resistant (MIC: >1 mg l^{-1}) [8].

Australia

Over the past decade, invasive *N. meningitides* isolates have become less susceptible to penicillin in Australia. Between 2008 and 2016, the Australian National *Neisseria* Network confirmed an ongoing increasing rate of intermediate susceptibility to penicillin (2008: 72%, 2016: 90% (MICs: 0.06–0.5 mg l^{-1})). Fortunately, resistance to penicillin remains rare in 2016 (6%; MIC: ≥1 mg l^{-1}), but it is crucial to continue national surveillance for antimicrobial resistance in *N. meningitidis* [9, 10].

Ceftriaxone

Generally, meningococcal resistance to ceftriaxone is rare worldwide. Importantly, in Ethiopia, isolates (non-invasive) from healthy children and adolescents showed resistance to ceftriaxone (69.4%; MIC not specified Table 2) [11].

Ciprofloxacin

Asia

Researchers in China noted the expanding prevalence of ciprofloxacin-resistant isolates in China since 2005 (MIC: ≥0.12 mg l^{-1}). These isolates are mostly related to the spread of lineages CC4821 and CC5 known for their hypervirulence [12]. Another case of resistance was declared in Asia in India, where a case report for a one-year-old patient infected with *N. meningitidis* had an isolate that was resistant to ciprofloxacin (MIC: 0.5 mg l^{-1}) [5]. Furthermore, 3% of isolates were resistant to ciprofloxacin in Singapore (MIC: 0.25 mg l^{-1} Table 2) [6].

Europe

In Africa, as well as in the European continent, resistance to ciprofloxacin is rare. A Croatian study showed that 2% of isolates collected from June 2009 to January 2014 was ciprofloxacin-resistant (MIC: 0.25 mg l^{-1}) [13].

North America

In Canada, resistance to ciprofloxacin was detected in two isolates of *N. meningitidis* (serogroup C, MIC: 0.38 mg l^{-1}). Both of them were typed as sequence-type ST4821. This clone is unique in China, which led to suggest that both isolates might be imported cases to Canada [14]. In addition, three isolates (serogroup A, ST 4789) were resistant to ciprofloxacin in the same Canadian study (MIC: 0.19–0.25 mg l^{-1}). In the US, one study revealed that three strains were ciprofloxacin resistant (MICs: 0.06–0.25 mg l^{-1}) [15].

South America

In Argentina, a large study of 133 isolates revealed two strains with ciprofloxacin resistance (MIC: 0.12 mg l^{-1}) [16]. For the other countries, we noted a paucity of data regarding the susceptibility of meningococcus to ciprofloxacin.

Rifampicin

(Table 2) In Hungary, the first case of rifampicin resistance was reported in 2017 (MIC: >32 mg l^{-1} Table 2), and the researchers suggested that this resistance might be a result of prophylactic treatment of contacts with this antibiotic [17]. A French study described cluster of two meningococcal isolates with rifampicin resistance (MIC not specified) [18].

In Brazil, a study reported that 0.2% of meningococcal strains showed high resistance to rifampicin (MIC: > 256 mg l^{-1}) and 0.5% of them displayed intermediate susceptibility (MICs: 0.25–2 mg l^{-1}) [19]. Rifampicin-resistant isolates were also rare in Uruguay; just two resistant strains were reported in 2010 (MICs: ≥32 mg l^{-1}) [20].

Finaly, one isolate was reported as resistant to rifampicin in Australia in 2016 (MIC: 1 mg l^{-1}) [21].

Conclusion

Similar to *Neisseria gonorrheae*, the strains of *N. meningitidis* become increasingly less susceptible to penicillin and other antibiotics. Fortunately, resistance to therapeutic or prophylactic antibiotics remains rare in the world. However, microbiologists should not ignore the emergence of new meningococcal-resistant strains during the last decade, which could be a worrying phenomenon in the future. In order to limit the spread of meningococcal-resistant strains, it is interesting to take advantage of worldwide experience in gonococcal infections management by the implementation of an expanded plan for phenotypic and genotypic surveillance of *N. meningitidis*.

Acknowledgements We thank all the participants in this review.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Dwilow R, Fanella S. Invasive meningococcal disease in the 21st century-an update for the clinician. Curr Neurol Neurosci Rep. 2015;15:015–0524.
2. Unemo M, Shafer WM. Antimicrobial resistance in *Neisseria gonorrhoeae* in the 21st Century: past, evolution, and future. Clin Microbiol Rev. 2014;27:587–613. https://doi.org/10.1128/CMR.00010-14.
3. CLSI. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard. 9th edn. CLSI document M07-A9. Wayne: Clinical and Laboratory Standards Institute; 2012.
4. Bouba G, Nelly Michèle G, Lombart JP. *Neisseria meningitidis* susceptibility in North-Cameroon. Méd Mal Infect. 2014;44:443–4.
5. Aggarwal M, Manchanda V, Talukdar B. Meningitis due to *Neisseria meningitidis* serogroup B in India. Indian Pediatr. 2013;50:601–3.
6. Donaldson AD, Tang WY, Tan AL, Barkham T. *Neisseria meningitidis* with reduced susceptibility to quinolones in Singapore. J Antimicrob Chemother. 2010;65:362–4.
7. Bertrand S, Carion F, Wintjens R, Mathys V, Vanhoof R. Evolutionary changes in antimicrobial resistance of invasive *Neisseria meningitidis* isolates in Belgium from 2000 to 2010: increasing prevalence of penicillin nonsusceptibility. Antimicrob Agents Chemother. 2012;56:2268–72.
8. Pana M, Ghita M, Levenet I, Nica M, Botea S, Osz T. The in vitro susceptibility to 7 antibiotics of *Neisseria meningitidis* strains isolated last years in Romania. Roum Arch Microbiol Immunol. 2009;68:38–43.
9. Tapsall J. Annual report of the Australian Meningococcal Surveillance Programme, 2008. Commun Dis Intell Q Rep. 2009;33:259–67.
10. Lahra MM, Enriquez R. Australian Meningococcal Surveillance Programme annual report, 2016. Commun Dis Intell Q Rep. 2017;41:E369–E82.
11. Alemayehu T, Mekasha A, Abebe T. Nasal carriage rate and antibiotic susceptibility pattern of *Neisseria meningitidis* in healthy Ethiopian children and adolescents: a cross-sectional study. PLoS ONE. 2017;12:e0187207.
12. Zhu B, Fan Y, Xu Z, Xu L, Du P, Gao Y, et al. Genetic diversity and clonal characteristics of ciprofloxacin-resistant meningococcal strains in China. J Med Microbiol. 2014;63(Pt 11):1411–8.
13. Bukovski S, Vacca P, Anselmo A, Knezovic I, Fazio C, Neri A, et al. Molecular characterization of a collection of *Neisseria meningitidis* isolates from Croatia, June 2009 to January 2014. J Med Microbiol. 2016;65:1013–9.
14. Tsang RS, Law DK, Deng S, Hoang L. Ciprofloxacin-resistant *Neisseria meningitidis* in Canada: likely imported strains. Can J Microbiol. 2017;63:265–8.
15. Wu HM, Harcourt BH, Hatcher CP, Wei SC, Novak RT, Wang X, et al. Emergence of ciprofloxacin-resistant Neisseria meningitidis in North America. N Engl J Med. 2009;360:886–92.
16. Sorhouet-Pereira C, Efron A, Gagetti P, Faccone D, Regueira M, Corso A, et al. Phenotypic and genotypic characteristics of *Neisseria meningitidis* disease-causing strains in Argentina, 2010. PLoS ONE. 2013;8:4.
17. Toth A, Berta B, Tirczka T, Jekkel C, Abraham A, Prohaszka Z, et al. First description of a rifampicin-resistant *Neisseria meningitidis* serogroup Y strain causing recurrent invasive meningococcal disease in Hungary. Acta Microbiol Immunol Hung. 2017;64:1–7.
18. Mounchetrou Njoya I, Deghmane A, Taha M, Isnard H, Parent, du Chatelet I. A cluster of meningococcal disease caused by rifampicin-resistant C meningococci in France, April 2012. Eur Surveill. 2012;17:34.
19. Gorla MC, de Paiva MV, Salgueiro VC, Lemos AP, Brandao AP, Vazquez JA, et al. Antimicrobial susceptibility of *Neisseria meningitidis* strains isolated from meningitis cases in Brazil from 2006 to 2008. Enferm Infecc Microbiol Clin. 2011;29:85–9.
20. Perez Giffoni G, Garcia Gabarrot G, Alfonso A, Pujadas M, Camou T. Detection of rifampicin-resistant strains of *Neisseria meningitidis* in Uruguay. Rev Panam Salud Publica. 2011;30:540–4.
21. Lahra MM, Enriquez RP. Australian Meningococcal Surveillance Programme annual report, 2015. Commun Dis Intell Q Rep. 2016;40:E503–E11.
22. CLSI. *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fifth Informational Supplement*. CLSI document M100-S25. Wayne, PA: Clinical and Laboratory Standards Institute; 2015.
23. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 8.1, 2018. http://www.eucast.org.