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REVIEW

The Diverse Spectrum of Invasive Meningococcal Disease in Pediatric and Adolescent Patients: Narrative Review of Cases and Case Series

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ABSTRACT

Introduction: Invasive meningococcal disease (IMD) is a potentially life-threatening disease caused by *Neisseria meningitidis* infection. We reviewed case reports of IMD from newborns, infants, children, and adolescents, and described the real-life clinical presentations, diagnoses, treatment paradigms, and clinical outcomes.

Methods: PubMed and Embase were searched for IMD case reports on patients aged ≤ 19 years published from January 2011 to March 2023 (search terms "*Neisseria meningitidis*" or "invasive meningococcal disease", and "infant", "children", "paediatric", pediatric", or "adolescent").

Results: We identified 97 publications reporting 184 cases of IMD, including 25 cases with a fatal outcome. Most cases were in adolescents aged 13–19 years (34.2%), followed by children aged 1–5 years (27.6%), children aged 6–12 years (17.1%), infants aged 1–12 months (17.1%), and neonates (3.9%). The most common disease-causing serogroups were W (40.2%), B (31.7%), and C (10.4%). Serogroup W was the most common serogroup in adolescents (17.2%), and serogroup B was the most common in the other age groups, including children aged 1–5 years (11.5%). The most common clinical presentations were meningitis (46.6%) and sepsis (36.8%).

Conclusions: IMD continues to pose a threat to the health of children and adolescents. While this review was limited to case reports and is not reflective of global epidemiology, adolescents represented the largest group with IMD. Additionally, nearly half of the patients who died were adolescents, emphasizing the importance of monitoring and vaccination in this age group. Different infecting serogroups were predominant in different age groups, highlighting the usefulness of multivalent vaccines to provide the broadest possible

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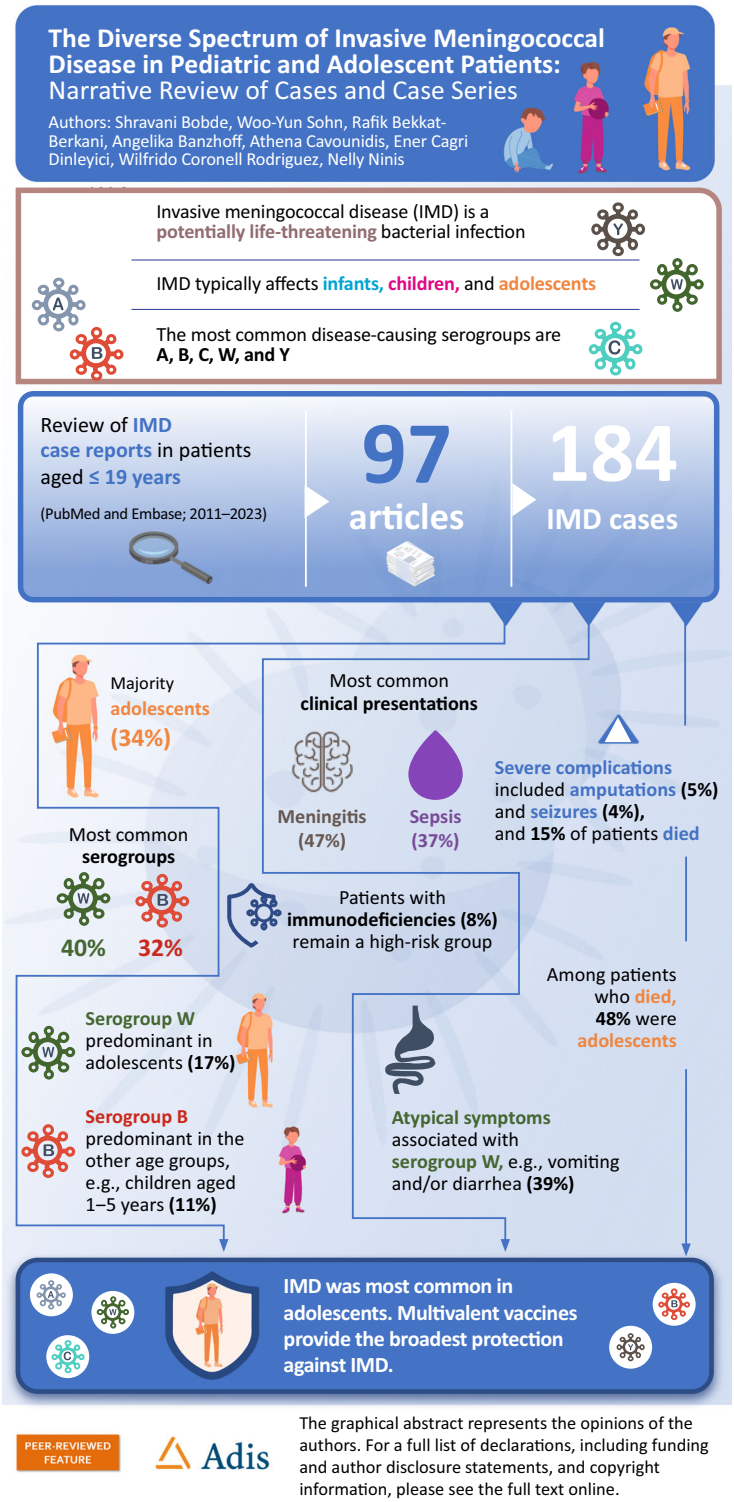
protection against IMD. Overall, this review provides useful insights into real-life clinical presentations, treatment paradigms, diagnoses, and clinical outcomes to help clinicians diagnose, treat, and, ultimately, protect patients from this devastating disease.

Graphical Abstract:



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Keywords: Adolescents; Case reports; Children; Complications; Meningococcal disease; Pediatrics

Key Summary Points

Invasive meningococcal disease (IMD) is rare but life-threatening, posing substantial challenges for clinicians because of the diverse and often non-specific spectrum of presenting clinical features.

We reviewed IMD case reports published from 2011 to 2023 to describe real-life clinical presentations of IMD in newborns, infants, children, and adolescents to help clinicians manage IMD in routine clinical practice.

Approximately one-third of the reviewed cases were in adolescents, and atypical gastrointestinal presentations were observed with serogroup W infections.

Clinicians should at least consider the possibility of IMD in any unwell newborn, infant, child, or adolescent to enable early diagnosis, prompt treatment initiation, and, ultimately, protect these patients from this devastating disease.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.24799116.

INTRODUCTION

Invasive meningococcal disease (IMD) can be devastating, with an overall case fatality rate of 8.3% (range 4.1–20.0%) [1] and long-term physical sequelae and/or neurological sequelae experienced by 10–20% of patients who do not die, including consequences as severe as amputation and hearing loss. The introduction of meningococcal vaccines in national immunization programs (NIPs) and for the immunization of high-risk individuals has enabled great progress in the control and prevention of IMD globally, encompassing protection of the unvaccinated and immunocompromised by passive immunity [2]. The increasing incidence of serogroups W and Y observed globally during the first two decades of the 21st century led to the introduction of multivalent vaccines simultaneously protecting against multiple serogroups [3–5]. Currently, the array of licensed meningococcal vaccines includes monovalent vaccines targeting serogroup C and serogroup A, quadrivalent vaccines simultaneously targeting serogroups A, C, W, and Y, and two protein-based vaccines protecting against serogroup B [5]. Inclusion in NIPs, vaccination strategies, and recommendations vary globally [5–7]. Although pediatricians' experience with IMD may vary as a result, the severity of this disease highlights the importance of early diagnosis and prompt antibiotic treatment initiation.

The spectrum of clinical presentation of IMD is diverse, varying from a mild febrile illness to meningitis and sepsis, affecting 30–60% and 20–30% of infected individuals, respectively, with 12% having features of both meningitis and sepsis [8–10]. Focalized infections, such as conjunctivitis or septic arthritis, can accompany meningitis and/or sepsis, or present alone [8]. The clinical picture changes rapidly after an incubation period of 3–4 days (range 1–10 days) [9]. The onset of IMD is sudden and the disease can be fatal within 24–48 h after developing symptoms (e.g., fever, vomiting, headache, petechial, or purpuric rash) [8, 9]. Clinical presentation varies and can differ by age, and it is not uncommon for children to be initially misdiagnosed as a result of non-specific signs (e.g., irritability and/or lethargy) [10]. The importance of prompt clinical management in infants and children was highlighted by the substantial burden associated with *Neisseria meningitidis* infections observed in a large European prospective cohort study of 2844 individuals aged 1 month to 18 years old, where

these infections were found to be the cause of 29.9% cases of meningitis, 17.1% cases of sepsis, 30.7% cases of septic shock, 33.8% cases of severe sepsis, and 22.8% of deaths [11].

Known risk factors for IMD include immunocompromised status (e.g., due to genetic complement deficiencies, asplenia, uncontrolled HIV infection, or treatment with eculizumab) [7, 12–14], and environmental risk factors, such as household crowding (e.g., college students living in on-campus residences and military recruits in barracks [7]) and routine exposure to *N. meningitidis* isolates (e.g., laboratory workers) [7, 15]. Carriage is high in adolescents and young adults, mostly as a result of their lifestyle [5]. Nonetheless, most cases of IMD occur in previously healthy individuals, without warning signs [16].

Given the rarity of the disease and the rapid but potentially fatal progression, it is paramount that clinicians maintain awareness of the diverse clinical spectrum of IMD in routine practice [1, 17]. While case reports and case series are limited by their descriptive nature and selection bias, they can be a particularly useful design for rare diseases [18]. Specifically, case reports can be used to highlight learnings from patients with IMD in the real-life clinical setting, including unusual observations, misdiagnoses, and treatment paradigms, with the potential to help clinicians promptly recognize IMD and improve outcomes for these patients [17]. The aim of this narrative review was to collate global case reports describing the diagnosis, clinical presentation, management, and outcomes of IMD cases reported in neonates, infants, children, and adolescents.

METHODS

Search Strategy and Selection Criteria

Literature searches were conducted in PubMed and Embase using combinations of terms describing IMD ("*Neisseria meningitidis*", "invasive meningococcal disease") and terms describing pediatric and/or adolescent patients ("infant", "children", "paediatric", "pediatric", or "adolescent") and study design ("case report" and "case series") published between January 1, 2011, and March 9, 2023. The searches included both subject headings and free-text terms. The review included papers published in English, available as full-text electronic articles, and within the scope of this narrative review, that is, related to IMD, describing patients aged $\leq$ 19 years, and published as case reports or case series. Data were manually extracted (wherever available) on method of sample isolation, isolated serogroup, clinical presentation (defined as meningitis, sepsis, septic arthritis, shock, purpura fulminans, and/or pneumonia), presenting symptoms (e.g., fever, skin rash, lethargy), and clinical complications and outcomes (e.g., death, amputations, seizures); data extraction was documented on a spreadsheet. A study flowchart illustrating the criteria used to identify the reviewed cases is shown in Fig. 1.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

In total, 184 individual pediatric and adolescent patient cases were described in 97 case reports (Fig. 1), including 42.3% reports from Europe, 27.8% from Asia, 13.4% from North America, 10.3% from Oceania, and 3.1% each from South America and Africa (Supplementary Fig. S1).

Sex and Age

Overall, 54.9% of patients were male, 40.2% were female; sex was not clearly reported for 4.9% of patients. Among the 82.6% of patients with known age, 34.2% were adolescents aged 13–19 years (Supplementary Fig. S2A), 27.6% were children aged 1–5 years, 17.1% were children aged 6–12 years, 17.1% were infants aged 1–12 months, and 3.9% were newborns aged 0–28 days. Age was reported as a range for 24 patients in one case series (3 months to 14 years) [19], and eight patients in another series (5 to 46 months) [20].

Sample Isolation and Identification

The predominant sample sites for isolation of *N. meningitidis* were blood (60.3%) and cerebrospinal fluid (26.6%) (Supplementary Table S1). *N. meningitidis* was also isolated from synovial fluid (5.4%), aqueous or vitreous humor (1.6%), a conjunctival swab (1.6%), punch biopsy from a purpuric lesion of the skin (0.5%), and cerebral tissue (0.5%). A total of 5.4% reports did not document the clinical samples from which *N. meningitidis* was isolated.

Serogroup Distribution

Overall, serogroup was reported for 89.1% of patients, with the most common serogroups identified as being W (40.2%), B (31.7%), and C (10.4%) (Supplementary Fig. S2B). Where both age and serogroup were reported (66.3%), serogroup B was the most common among neonates (1.6%), infants (9.0%), children aged 1–5 years (11.5%), and children aged 6–12 years (4.9%); serogroup W was the most reported serogroup among adolescents (17.2%) (Supplementary Fig. S2C).

Clinical Presentation

One or more clinical presentations of IMD (i.e., meningitis, sepsis, septic arthritis, shock, purpura fulminans, pneumonia) were reported for 72.3% of patients. The most common clinical presentation was meningitis (46.6%), followed by sepsis (36.8%), septic arthritis (17.3%), shock (14.3%), and purpura fulminans (12.0%) (Fig. 2; citations provided in Supplementary Table S2). Among the 25 reported cases of septic arthritis, 60.9% were infected with serogroup W [19, 21–25]. Additionally, three patients (13.0%) had septic arthritis due to serogroup Y [26, 27].

Overall, the most reported symptoms were fever (78.1%), vomiting (36.5%), rash (30.7%), and headache (24.1%), with other symptoms including lethargy, neck stiffness, diarrhea, decreased appetite, hypotension, tachycardia, and tachypnea; patients with *N. meningitidis* joint infections presented with joint swelling, joint pain, and/or a painful limp (citations provided in Table 1). Symptom data stratified by age are presented in Supplementary Table S3.

Atypical clinical presentations with gastrointestinal symptoms were reported in a case series of 15 previously healthy 15–19-year-olds with serogroup W infection identified in England between 2015 and 2016, with seven individuals presenting with a short history of nausea, vomiting, and/or diarrhea [23]. For example, one patient was initially sent home by the general practitioner with a gastroenteritis diagnosis, suddenly deteriorated the following day with rapid progression and death in the accident and emergency department (A&E), following presentation with diarrhea, vomiting, stomach cramps, lethargy, and no skin rash [23]. Another patient was initially sent home with a gastroenteritis diagnosis after presenting to A&E with vomiting, diarrhea, sore limbs, and no skin rash, and died in A&E later the same day [23]. In a larger case series that included 24 patients, 11 individuals had vomiting and/or diarrhea, although only two were thought to have gastroenteritis at their initial presentation [19]. Overall, vomiting and/or diarrhea were reported in 39.3% cases with serogroup W.

Among patients with IMD, 7.6% had immune dysfunction (Table 2). Of these, 78.6% had congenital complement deficiencies and 21.4% had acquired immune deficiencies (14.3% associated with eculizumab treatment; 7.1% had an uncontrolled HIV infection).

A total of 4.3% of patients had breakthrough infections, that is, they were infected with a serogroup against which they had previously been immunized (serogroup B, 50.0%; serogroup C, 37.5%; serogroup W, 12.5%) (Table 3). For example, a 16-month-old infant in Spain with serogroup B meningococcal infection had been vaccinated with three doses of the four-component meningococcal serogroup B vaccine (4CMenB), with the last dose 7 months before presentation [28]; a 12-year-old child in Spain with serogroup B meningococcal infection had been fully vaccinated against this serogroup, including two doses of 4CMenB at age 12 years and the second one 5 months before the meningitis episode [28]; an 18-year-old adolescent in the UK with serogroup W meningococcal infection had previously

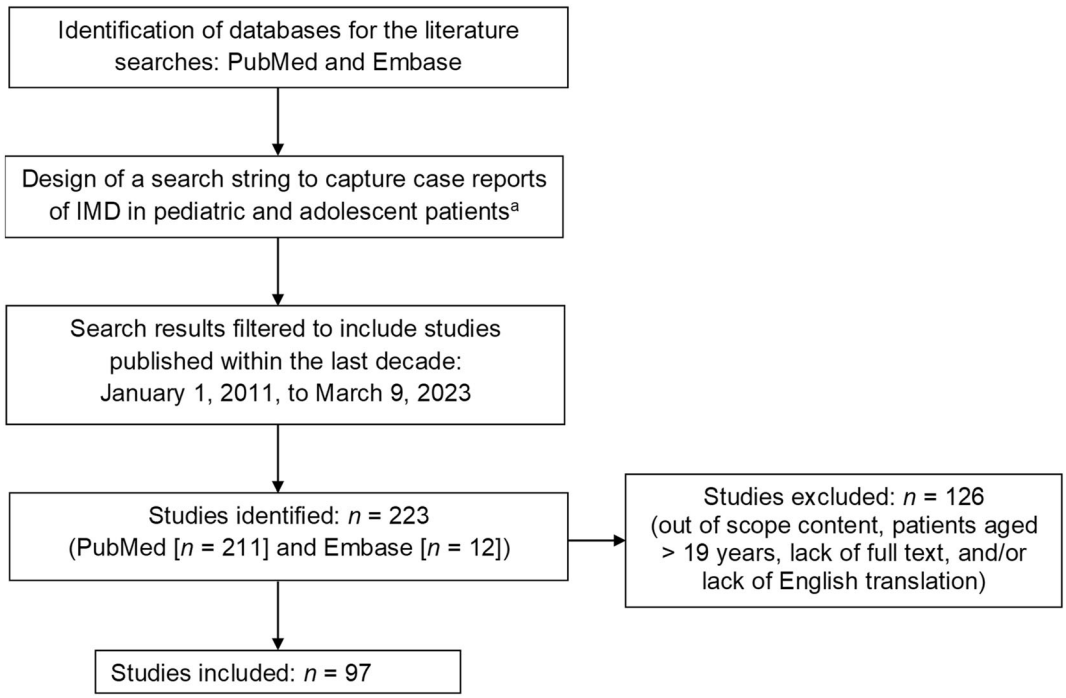

Fig. 1 Study flowchart. [a]Search terms ("*Neisseria meningitidis*", "invasive meningococcal disease") and ("infant", "children", "paediatric", "pediatric", or "adolescent") and ("case report" and "case series"). *IMD* invasive meningococcal disease

completed the full course of MenACWY vaccination [22].

Among the 16 patients who had previously received a meningococcal vaccine, 37.5% had risk factors for meningococcal infection, including complement deficiency (6.3%), splenectomy (6.3%), treatment with eculizumab (12.5%), poorly controlled HIV infection (6.3%), and a history of recurrent meningococcal septicemia (6.3%).

Clinical Complications and Outcomes

Complications and outcomes of IMD were reported for 92.9% of patients (Table 4). Among these patients, 14.6% died, 5.3% underwent amputations, 3.5% had seizures, 1.2% underwent enucleation for fulminant endophthalmitis, 0.6% had severe neurological deficits, and 0.6% had residual motor weakness. Among the 25 patients who died, 12 (48.0%) were adolescents; serogroup W was identified in 75.0% of the adolescents who died. Two 15–19-year-olds, cases from the UK case series in 2015–2016 are

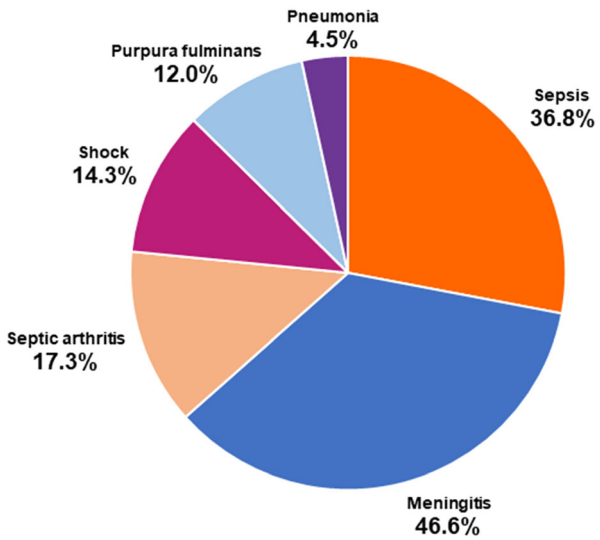

Fig. 2 Clinical presentations in 133 IMD cases. Multiple clinical presentations may be reported for each patient. The data represent the total number of occurrences of each clinical presentation, with each patient potentially included in multiple sections of the pie chart. *IMD* invasive meningococcal disease

Table 1 Clinical symptoms in 137 IMD cases

Symptom	*n* (%)
Fever	107 (78.1)
Vomiting	50 (36.5)
Rash	42 (30.7)
Headache	33 (24.1)
Petechiae	20 (14.6)
Joint stiffness or pain	20 (14.6)
Neck stiffness or pain	18 (13.1)
Lethargy or fatigue	18 (13.1)
Diarrhea	14 (10.2)
Tachycardia	13 (9.5)
Myalgia	12 (8.8)
Irritability	8 (5.8)
Refusal to eat/drink or reduced appetite	7 (5.1)
Sore throat	7 (5.1)
Hypotension	6 (4.4)
Nausea	6 (4.4)
Respiratory difficulties	6 (4.4)
Bulging fontanel	6 (4.4)
Chills	5 (3.6)
Purpuric lesions	5 (3.6)
Cough	4 (2.9)
Photophobia	4 (2.9)
Malaise	4 (2.9)
Abdominal pain	4 (2.9)
Dyspnea	3 (2.2)
Hypoglycemia	3 (2.2)
Altered consciousness, bradycardia, dehydration, erythema, leukocytosis, pallor, prostration, skin mottling, tachypnea	2 (1.5)
Adenopathy, anorexia, anuria, bilateral lower limb compartment syndrome, blurred vision, cervical lymphadenopathy, chest pain, conjunctival hyperemia, cool extremities, coryza, coughing blood, decreased urine output, diaphoresis, discharge both eyes, dizziness, dysphagia, dysphonia, ear pain, elbow swelling, elevated jugular venous pressure, epigastric pain, eye swelling, high inflammatory syndrome, Howell-Jolly bodies, hypertension, hypocalcemia, hypotonia, icterus, labial cyanosis, leukopenia, limb swelling, lymphadenopathy, macular exanthema, nasal congestion, ocular pain, ocular pressure, odynophagia, phonophobia, polypnea, poor perfusion, pyrexia, redness of eye, refusal to bear weight, rhinorrhea, splenomegaly, spontaneous rectal bleeding, stomach cramps, tachypnea, upper respiratory tract symptoms	1 (0.7)

Multiple symptoms may be reported for each patient. Symptoms were reported as defined in the original publications, although some overlap is likely in clinical practice (e.g., fever and pyrexia; respiratory difficulties, dyspnea, and polypnea). References: [20–33, 38, 43, 50–122]
IMD invasive meningococcal disease

described in more detail in the previous section (Clinical Presentation) [23]. Two adolescents (14 and 17 years old, respectively) who died following a serogroup W infection were identified in China in 2012–2013 and had no history of MenACWY vaccination [29]. Overall, IMD-associated complications in patients who died included acute petrified myocardium, disseminated intravascular coagulation, multiorgan failure, pneumonia, and Waterhouse–Friderichsen syndrome. The outcomes of patients with immune dysfunction are reported in Table 2.

Treatment

Antibiotic treatment was reported for 75.0% of patients (Supplementary Table S4). Among these patients, the most prescribed antibiotic

Table 2 IMD cases with immune dysfunction

Patient, age, sex, region	Cause of immune dysfunction	Infecting serogroup	Clinical presentation/complications	Outcome
17-mo, female, Spain [123]	Complement C5 deficiency	E	Meningococcal sepsis	Not reported
17-mo, female, Italy [124]	Complement C8 deficiency	B	Sepsis	Recovery
23-mo, female, USA [125]	Complement deficiency	Non-groupable	Septic shock	Recovery
34-mo, male, Spain [123]	Complement C5 deficiency	Y	IMD	Recovery
4-yo, female, Italy [124]	Complement C8 deficiency	Not reported	Sepsis	Recovery
5-yo, female, Australia [38]	Complement C7 deficiency	E	Meningitis	Not reported
6-yo, female, Portugal [87]	Complement C5 deficiency	B	Septic shock	Recovery
6-yo, female,[a] Netherlands [114]	Complement C8 deficiency	Z, C, then non-typable	Recurrent meningococcemia (3 episodes)	Recovery
7-yo, female, Spain [123]	Complement C5 deficiency	Non-groupable	Recurrent IMD (2 episodes)	Not reported
9-yo, female,[b] Spain [28]	Eculizumab treatment	B	IMD, meningitis	Recovery
12-yo, female, France [76]	Complement C6 deficiency	W	Purpura fulminans	Recovery
15-yo, male, Italy [124]	Complement C8 deficiency	Non-groupable	Sepsis	Recovery
16-yo, female, USA [92]	Eculizumab treatment	Non-groupable	Waterhouse–Friderichsen syndrome	Death
18-yo, male, Belgium [121]	Complement C6 deficiency	Y	Recurrent meningitis (2 episodes), shock, purpura fulminans	Limb amputation
19-yo, male, Brazil [64]	HIV, detectable viral load	C	Chronic meningococcemia, sepsis	Recovery

HIV human immunodeficiency virus, *IMD* invasive meningococcal disease, *mo* month-old, *yo* year-old

[a]The patient had complement C8 deficiency and experienced three episodes of meningococcemia over ≥ 2.5 years. She had discontinued amoxicillin prophylaxis 6 months before the third episode

[b]The patient was receiving eculizumab, prednisone, and mycophenolate mofetil for hemolytic uremic syndrome

Table 3 IMD cases who had previously received a vaccine against *Neisseria meningitidis*

Patient, age, sex, region	Previous vaccine received	Risk factor	Infecting serogroup	Complications	Outcome
15-mo, male, UK [119]	MenC	–	B	Sepsis, meningitis, endophthalmitis	Recovery
16-mo, male,[a] Spain* [28]	4CMenB	–	B	IMD, meningitis	Recovery
21-mo, male, Australia [99]	MenC	–	W	IMD, splenic cyst	Recovery
2-yo, male, China [117]	MenA polysaccharide	–	Y	Fulminant meningococcemia	Recovery
4-yo, female,[b] Germany* [43]	MenC	–	C	Fulminant endophthalmitis	Recovery, enucleation
4-yo, male,[c,d] Spain* [28]	4CMenB	–	B	IMD, meningitis	Recovery
6-yo, female,[e] Netherlands* [114]	MenC, MenACYW, 4CMenB	Complement C8 deficiency	Z, C, then non-typable	Recurrent meningococcemia	Recovery
6-yo, female, Netherlands [25]	MenC		W	Sepsis, arthritis	Recovery
9-yo, female,[f] Spain* [28]	4CMenB	Eculizumab	B	IMD, meningitis	Recovery
10-yo, female, Turkey [98]	MenACWY-TT, MenB-4C	Splenectomy	Non-groupable	Meningococcemia	Recovery
12-yo, female,[d,g] Spain* [28]	4CMenB	Recurrent *N. meningitidis* infection	B	IMD, meningitis	Recovery
16-yo, female,[h] USA [92]	MenACWY-D, 4CMenB	Eculizumab	Non-groupable	Waterhouse–Friderichsen syndrome	Death
17-yo, male, China [30]	Bivalent A and C vaccine	–	Y	Meningitis	Recovery
18-yo, female, UK* [22]	MenACWY	–	W	Arthritis	Recovery
19-yo, male,[I] Brazil* [64]	MenC	HIV, detectable viral load	C	Chronic meningococcemia, sepsis	Recovery

Table 3 continued

Patient, age, sex, region	Previous vaccine received	Risk factor	Infecting serogroup	Complications	Outcome
19-yo, male, USA [58]	Meningococcal conjugate vaccine (1 dose); MenB (1 dose)	–	C	Meningococcemia, shock, multiorgan failure	Recovery, amputations

HIV human immunodeficiency virus, *IMD* invasive meningococcal disease, *mo* month-old, *yo* year-old
*Breakthrough infection
[a]The patient had received three doses of 4CMenB at ages 3, 6, and 9 months, with the last dose 7 months before the episode described in the case report
[b]The patient had received MenC vaccine (Meningitec) 26 months before the episode described in the case report. Serum samples obtained on two occasions during the episode described in the case report showed highly protective titers (> 1:1024) of bactericidal antibodies against *N. meningitidis* serogroup C
[c]The patient had received two doses of 4CMenB at ages 35 and 37 months and a booster dose at age 4 years, 6 months before the episode described in the case report
[d]Antibodies induced by 4CMenB likely were not effective against the isolated strains
[e]The patient had complement C8 deficiency and experienced three episodes of meningococcemia over ≥ 2.5 years. She had received MenC vaccine 5 years before the first two episodes, and MenACYW and 4CMenB before the third episode described in the case report. She also discontinued amoxicillin prophylaxis 6 months before the third episode
[f]The patient was receiving eculizumab, prednisone, and mycophenolate mofetil for hemolytic uremic syndrome. She had received two doses of 4CMenB doses at age 8 years, the second dose 8 months before the episode described in the case report
[g]The patient's medical history included two previous episodes of bacterial meningitis without septicemia at age 5 years (serotype 14 pneumococcal meningitis) and at age 6 years (MenB meningitis). She had received two doses of 4CMenB at age 12 years, the second dose 5 months before the episode described in the case report
[h]Meningococcal vaccines were administered 4 months prior to initiating eculizumab for paroxysmal nocturnal hemoglobinuria
[i]The patient had received two doses of MenC conjugate vaccine 15 and 3 years before the episode described in the case report

for suspected or confirmed *N. meningitidis* infection was a third-generation cephalosporin (ceftriaxone, 63.8%; cefotaxime, 19.6%; not specified, 0.7%). Other antibiotic regimens were described in 3.8% of patients, including piperacillin/tazobactam, meropenem, and penicillin (1.4% each), and amikacin (0.7%). The antibiotic administered was not identified for 10.9% of patients, and a further 2.9% of patients suddenly died before antibiotic therapy could be initiated (all because of sudden death before routine diagnosis procedures could be carried out). Regarding the 25 recorded deaths, eight patients died after receiving antibiotics, four did not receive antibiotics, and treatment was not recorded for the remaining 13 patients.

The results of antibiotic sensitivity testing were provided for 38 cases (22.2%). Reduced susceptibility to penicillin antibiotics (penicillin, amoxicillin, amoxicillin/clavulanate, and ampicillin) was reported for 33 isolates (serogroup W, 75.8%; serogroup Y, 9.1%; serogroup B, 9.1%; serogroup X, 3.0%; non-groupable, 3.0%). Reduced sensitivity to quinolone (nalidixic acid [30]) or fluoroquinolone (ciprofloxacin [31, 32]) antibiotics was reported for 7.9% isolates (serogroups B, C, and Y). A total of 10.3% of isolates were reported to be resistant to more than one antibiotic class, including 5.3% of isolates (serogroups B and X) resistant to both penicillin and ciprofloxacin and 2.6% of non-groupable isolates resistant to

Table 4 Clinical complications and outcomes in 171 IMD cases

Complications/outcomes	*n* (%)	References
Death	25 (14.6)	[23, 29, 51, 66, 75, 79, 83, 91, 92, 103, 104, 107, 122, 126]
Multiorgan failure	11 (6.4)	[23, 29, 58, 66, 94, 122]
Disseminated intravascular coagulation/coagulopathy	9 (5.3)	[29, 65, 93, 94, 107, 117, 121, 127]
Amputation	9 (5.3)	[50, 58, 65, 72, 82, 121, 124, 126, 127]
Seizures	6 (3.5)	[31, 52, 62, 95, 101, 122, 125]
Chronic meningococcemia	5 (2.9)	[60, 64, 71, 89, 116]
Adrenal hemorrhage (Waterhouse–Friderichsen syndrome)	4 (2.3)	[33, 51, 75, 92]
Myocarditis	3 (1.8)	[33, 61, 77]
Conjunctivitis	3 (1.8)	[19, 43, 105]
Encephalitis	3 (1.8)	[73, 95, 108]
Gangrene of extremities	3 (1.8)	[50, 58, 117]
Acute renal failure	2 (1.2)	[62, 64]
Endophthalmitis (enucleation)	2 (1.2)	[43, 119]
Cerebral abscess	2 (1.2)	[31, 93]
Subdural empyema	2 (1.2)	[55, 101]
Rhabdomyolysis	1 (0.6)	[121]
Pachymeningitis	1 (0.6)	[113]
Ventriculitis	1 (0.6)	[115]
Skeletal dysplasia[a]	1 (0.6)	[82]
Splenic cyst	1 (0.6)	[99]
Secondary asplenia	1 (0.6)	[65]
Petrified myocardium	1 (0.6)	[103]
Epiglottitis	1 (0.6)	[57]
Kawasaki disease complicated by macrophage activation syndrome	1 (0.6)	[70]
Residual motor weakness	1 (0.6)	[125]
Cortical atrophy, right-sided hemiparesis	1 (0.6)	[65]
Acute respiratory distress syndrome	1 (0.6)	[64]
Peritonitis, mesenteric lymphadenitis	1 (0.6)	[68]

IMD invasive meningococcal disease

Multiple complications may be reported for each patient (37 patients had one complication, 10 patients had two complications, six patients had three complications, and one patient had five complications)

[a]Skeletal dysplasia was a misdiagnosis in a child aged 12 years and 8 months with short stature and limb discrepancy due to meningococcemia

cotrimoxazole, nalidixic acid, and ciprofloxacin.

The details of additional non-antibiotic therapy were generally not provided, although one report described the first case of successful use of hemadsorption for cytokine removal therapy in a 10-year-old child with meningococcal septic shock and Waterhouse–Friderichsen syndrome [33]. In this patient, hemadsorption therapy was administered within 48 h of them presenting with septic shock, which resulted in a stabilization of hemodynamics and well-controlled hyperinflammation [33]. Other treatments described in reports included administration of vasopressors and/or inotropes (21.2%), mechanical ventilation (19.7%), corticosteroids (19.7%), fresh frozen plasma infusion (15.2%), platelet transfusion (10.6%), antiepileptics (2.1%), and immunoglobulins (2.1%) (Supplementary Table S4).

A total of 11.4% of patients required surgery. Various surgical procedures were described, including craniotomy (19.0%), joint drainage (19.0%), limb amputation (42.9%), insertion of a ventricular drain and decompression of the foramen magnum (4.8%), placement of a ventriculo-peritoneal shunt for hydrocephalus (4.8%), plastic surgery for cutaneous sequelae (4.8%), and ocular enucleation (5.3%).

DISCUSSION

This review of IMD case reports published over the past decade highlights that, despite being rare, IMD continues to pose a threat to the health of children and adolescents. Although no epidemiological inferences can be drawn from the selected case reports, this review provides useful insights into real-life clinical presentations, treatment paradigms, diagnoses, and clinical outcomes, emphasizing the importance of remaining vigilant to the diverse clinical spectrum of IMD, including any atypical presentations.

The case reports reviewed here reflect the diverse clinical features of IMD observed throughout childhood and adolescence, ranging from mild febrile illness with rapid progression to severe systemic disease and potentially life-threatening complications. Across the reviewed case reports, 14.6% of patients died as a result of IMD; however, estimations of fatality rates based on case studies should be interpreted with caution because of limited sample sizes and publication and reporting bias. Previous studies have estimated case fatality ratios ranging from 4% to 20% [1], with mortality reaching up to 50% in patients who do not receive timely treatment [34]. This highlights the severity of IMD and the importance of initiating treatment promptly.

Although no epidemiological inferences can be drawn from the selected case reports, adolescents represented over one-third of the reviewed cases, followed by children aged 6–12 and 1–5 years, with the caveat that there may be some bias due to the age cutoffs. High infection rates have been previously reported in adolescents and infants, with adolescents often being asymptomatic carriers [35, 36]. Risk factors for carriage and transmission include living in college dormitories, having active social habits/participating in nightlife, smoking, and having intimate/sexual contact, emphasizing the importance of prevention by vaccination [37]. The findings that adolescents represented the largest group with IMD in this review, and that 48.0% of the patients who died were adolescents, emphasize the importance of performing large-scale epidemiological studies focusing on this age group to better understand the impact of IMD in adolescents and to inform vaccination policies.

The most reported serogroups in the reviewed cases with available data were serogroup W in adolescents and serogroup B in all other age groups, with serogroups A, C, E, X, and Y also reported. Serogroup E is rare and generally associated with infection in immunocompromised patients [38]. Accordingly, three of the four cases of serogroup E identified here were in patients with known immunocompromised status. Pentavalent vaccines are currently in development, which could offer broad protection against serogroups A, B, C, W, and Y, and serogroups A, C, W, Y, and X [39–41].

Clinicians should maintain awareness of the atypical extrameningeal presentations

associated with serogroup W (e.g., gastrointestinal symptoms and focal infections), as failure to identify these signs could delay diagnosis and treatment initiation [42]. In a study of 65 cases of unusual meningococcal disease in France, serogroup W was significantly associated with arthritis and with meningococcal pneumonia in 54.5% of patients (particularly those aged > 70 years). Importantly, blood culture was central to identifying the underlying cause of disease [42]. In this review, we identified patients presenting with atypical gastrointestinal symptoms and joint infections; however, it is unclear whether these reports were the result of increased awareness of this association. Other atypical conditions included epiglottitis, Kawasaki disease complicated by macrophage activation syndrome, skeletal dysplasia, and conjunctivitis.

Reports of patients who previously received meningococcal vaccination and subsequently developed IMD were identified. One of the cases included in this review suggested that vaccination prevented severe disease in a patient who had previously received the MenC conjugate vaccine [43]. This 4.5-year-old child developed fulminant ophthalmitis attributed to serogroup C (detected by 16S ribosomal DNA analysis in aqueous humor) despite having bactericidal serum titers. The authors hypothesized that these antibodies prevented the development of meningococcemia and meningitis (microbiological cultures were negative), but did not prevent intraocular infection; however, they prevented severe or fatal consequences associated with IMD [43].

Eight patients (4.3%) who developed IMD were infected with a serogroup for which they had previously been immunized. These included a patient with a complement deficiency, a patient with HIV, a patient with recurrent IMD, and a patient treated with eculizumab. Patients with known immunodeficiencies (e.g., asplenia) remain a high-risk patient population, which should be considered in national vaccination programs and promptly managed by clinicians. Immunosuppressed cases were reported in multiple countries with different NIPs and vaccine recommendations. For example, in one case from Australia, a 5-year-old with complement C7 deficiency was infected with serogroup E [38]. In South Australia, the introduction of a 4CMenB vaccination program demonstrated coverage rates of 91.4% for two doses and 79.4% for three doses in infants, with a two-dose vaccine effectiveness against serogroup B IMD of 94.2% (95% confidence interval [CI] 36.6–99.5) or 94.7% (95% CI 40.3–99.5) in children (depending on the estimation method) [44]. Two-dose coverage rates among those aged approximately 16 years was 69.0%, with no IMD cases reported in adolescents and young adults after implementation of the program [44]. The first real-world evidence of 4CMenB was from the UK, with 87.9% coverage resulting in a 75% reduction in meningitis B in eligible age groups after 3 years in England [45, 46]. No IMD cases with serogroup B infection in immunocompromised patients were identified in the UK in this review.

Where details on antibiotic treatment were provided, patients generally received antibiotic therapy with a third-generation cephalosporin (ceftriaxone or cefotaxime), which is the recommended treatment for IMD [47]. These antibiotics were administered either empirically or following identification of *N. meningitidis* in clinical specimens. No evidence of resistance to third-generation cephalosporins was reported in the reviewed cases. However, reduced susceptibility to penicillin, ciprofloxacin, cotrimoxazole, nalidixic acid, and ciprofloxacin was observed. Antibiotic resistance has been reported in other studies; for example, in a UK study, out of 4122 IMD isolates, 113 were shown to be penicillin-resistant, five were ciprofloxacin-resistant, two were rifampicin-resistant, and one was cefotaxime-resistant [48]. A recent evaluation of IMD cases submitted to the US Centers for Disease Control and Prevention for whole-genome sequencing identified an emerging strain of ciprofloxacin-resistant β-lactamase-producing *N. meningitidis* in 33 of 2097 isolates [49]. Although outside the scope of this review, increased monitoring of resistant strains will be key to tailoring treatment.

Case series and case reviews involve a description of the characteristics and outcomes among a group of individuals with a disease over a period of time, without a control group or any randomization. By definition, the

objective is to describe the population of interest, without statistically comparing risk across groups, making the case series design neither exhaustive nor comprehensive. Additionally, selection bias typically favors cases of clinical interest, such as those with an unusual underlying condition, unexpected disease course, or severe complications. Nonetheless, case reviews are particularly useful for rare diseases, as demonstrated by the case review highlighting the atypical gastrointestinal presentations in adolescents with serogroup W infections following anecdotal reports in the UK [23]. Limitations specific to this review are its non-systematic nature and the inclusion only of publications where the full text was available in English. The information available in each report was generally limited and, overall, a substantial amount of information regarding the treatment and the clinical course of IMD was missing. Publication bias is also evident in the paucity of cases from South America and Africa and the potential overrepresentation of Oceania.

This review of case reports provides insights into the diverse clinical spectrum of IMD in cases identified in routine practice. It highlights the need for increased surveillance in adolescents and for vaccination programs providing the broadest possible protection against the main disease-causing serogroups. Our findings also reinforce the need for the establishment of a multicenter/national registry system collating data for all IMD cases.

CONCLUSIONS

While IMD has become uncommon where vaccination programs have been introduced, infants, children, and adolescents still die from this disease every year. Many of the symptoms are non-specific and onset is rapid, making it advisable to at least consider the possibility of IMD in any unwell newborn, infant, child, or adolescent [17]. High-risk patients should be promptly identified, and treatment initiated immediately [17]. Clinicians should be particularly alert to any atypical extrameningeal presentations (e.g., gastrointestinal symptoms) potentially associated with serogroup W. Although this review highlighted the importance of monitoring the real-life clinical management of IMD, including reports of atypical presentations, large-scale epidemiological studies are required to inform vaccination policies and programs, at a time when meningococcal vaccines against the five most common disease-causing serogroups are available, and combination vaccines are in development.

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Declarations

Conflicts of Interest. Shravani Bobde, Woo-Yun Sohn, Rafik Bekkat-Berkani, and Athena Cavounidis are employees of GSK and

may hold stock or stock options. Shravani Bobde holds patents on antimicrobial peptides and related methods issued prior to employment at GSK and before this work began. Angelika Banzhoff was an employee of GSK, holding stock or stock options when this study was undertaken. Ener Cagri Dinleyici performs contract work for the Eskisehir Osmangazi University funded by GSK, Pfizer, and Sanofi Pasteur. Wilfrido Coronell Rodriguez has received honoraria from Merck Sharp & Dohme and Sanofi Pasteur, and has participated on advisory boards at GSK, Pfizer, and Sanofi Pasteur. Nelly Ninis has received payment and/or honoraria from GSK.

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REFERENCES

1. Wang B, Santoreneos R, Giles L, Haji Ali Afzali H, Marshall H. Case fatality rates of invasive meningococcal disease by serogroup and age: a systematic review and meta-analysis. Vaccine. 2019;37:2768–82. https://doi.org/10.1016/j.vaccine.2019.04.020.

2. Mallory ML, Lindesmith LC, Baric RS. Vaccination-induced herd immunity: successes and challenges. J Allergy Clin Immunol. 2018;142:64–6. https://doi.org/10.1016/j.jaci.2018.05.007.

3. Taha S, Taha MK, Deghmane AE. Impact of mandatory vaccination against serogroup C meningococci in targeted and non-targeted populations in France. NPJ Vaccines. 2022;7:73. https://doi.org/10.1038/s41541-022-00488-8.

4. Carr JP, MacLennan JM, Plested E, et al. Impact of meningococcal ACWY conjugate vaccines on pharyngeal carriage in adolescents: evidence for herd protection from the UK MenACWY programme. Clin Microbiol Infect. 2022;28:1649.e1–e8. https://doi.org/10.1016/j.cmi.2022.07.004.

5. Pizza M, Bekkat-Berkani R, Rappuoli R. Vaccines against meningococcal diseases. Microorganisms. 2020;8:1521. https://doi.org/10.3390/microorganisms8101521.

6. Martinón-Torres F, Taha MK, Knuf M, et al. Evolving strategies for meningococcal vaccination in Europe: overview and key determinants for current and future considerations. Pathog Glob Health. 2022;116:85–98. https://doi.org/10.1080/20477724.2021.1972663.

7. Mbaeyi SA, Bozio CH, Duffy J, et al. Meningococcal vaccination: recommendations of the Advisory Committee on Immunization Practices, United States, 2020. MMWR Recomm Rep. 2020;69:1–41. https://doi.org/10.15585/mmwr.rr6909a1.

8. Pace D, Pollard AJ. Meningococcal disease: clinical presentation and sequelae. Vaccine. 2012;30:B3–9. https://doi.org/10.1016/j.vaccine.2011.12.062.

9. Centers for Disease Control and Prevention. Chapter 14: Meningococcal Disease. In: Hall E, Wodi AP, Hamborsky J, et al, editors. The Pink Book: Epidemiology and Prevention of Vaccine-Preventable Diseases. Washington D.C.: Public Health Foundation; 2021.

10. Bosis S, Mayer A, Esposito S. Meningococcal disease in childhood: epidemiology, clinical features and prevention. J Prev Med Hyg. 2015;56:E121–4.

11. Martinón-Torres F, Salas A, Rivero-Calle I, et al. Life-threatening infections in children in Europe (the EUCLIDS Project): a prospective cohort study. Lancet Child Adolesc Health. 2018;2:404–14. https://doi.org/10.1016/s2352-4642(18)30113-5.

12. Miller L, Arakaki L, Ramautar A, et al. Elevated risk for invasive meningococcal disease among persons

with HIV. Ann Intern Med. 2014;160:30–7. https://doi.org/10.7326/0003-4819-160-1-201401070-00731.

13. Cohn AC, MacNeil JR, Clark TA, et al. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2013;62:1–28.

14. Applegate AO, Fong VC, Tardivel K, Lippold SA, Zarate S. Notes from the field: meningococcal disease in an international traveler on eculizumab therapy — United States, 2015. MMWR Morb Mortal Wkly Rep. 2016;65:696–7. https://doi.org/10.15585/mmwr.mm6527a3.

15. Sejvar JJ, Johnson D, Popovic T, et al. Assessing the risk of laboratory-acquired meningococcal disease. J Clin Microbiol. 2005;43:4811–4. https://doi.org/10.1128/jcm.43.9.4811-4814.2005.

16. Martinelli D, Fortunato F, Prato R. Estimates of the burden of meningococcal disease in Italy: implications for prevention and control. J Prev Med Hyg. 2015;56:E112–5.

17. Corr M, Waterfield T, Shields M. Fifteen-minute consultation: symptoms and signs of meningococcal disease. Arch Dis Child Educ Pract Ed. 2020;105:200–3. https://doi.org/10.1136/archdischild-2019-317722.

18. Torres-Duque CA, Patino CM, Ferreira JC. Case series: an essential study design to build knowledge and pose hypotheses for rare and new diseases. J Bras Pneumol. 2020;46:e20200389. https://doi.org/10.36416/1806-3756/e20200389.

19. Sudbury EL, O'Sullivan S, Lister D, Varghese D, Satharasinghe K. Case manifestations and public health response for outbreak of meningococcal W disease, Central Australia, 2017. Emerg Infect Dis. 2020;26:1355–63. https://doi.org/10.3201/eid2607.181941.

20. O'Connor L, Ward M, Bennett D, et al. A prolonged outbreak of invasive meningococcal disease in an extended Irish Traveller family across three Health Service Executive (HSE) areas in Ireland, 2010 to 2013. Euro Surveill. 2015;20:21139. https://doi.org/10.2807/1560-7917.es2015.20.21.21139.

21. Anderson AJ, Bowen AC, Hazelton B, O'Brien M, Blyth CC, Campbell AJ. Meningococcal serotype W septic arthritis: case series in children. J Paediatr Child Health. 2021;57:1990–4. https://doi.org/10.1111/jpc.15385.

22. Boyle C, Howard T, Griffith D, Cowie J. Primary meningococcal septic arthritis with multiple native joint involvement. BMJ Case Rep. 2018;2018:bcr2017223197. https://doi.org/10.1136/bcr-2017-223197.

23. Campbell H, Parikh SR, Borrow R, Kaczmarski E, Ramsay ME, Ladhani SN. Presentation with gastrointestinal symptoms and high case fatality associated with group W meningococcal disease (MenW) in teenagers, England, July 2015 to January 2016. Euro Surveill. 2016;21:pii=30175. https://doi.org/10.2807/1560-7917.Es.2016.21.12.30175.

24. Dapueto G, Barrios P, Zabala C, Peluffo G, Giachetto G. Primary meningococcal arthritis of the hip due to serogroup W in a pediatric patient. Bol Med Hosp Infant Mex. 2021;78:631–5. https://doi.org/10.24875/bmhim.20000375.

25. Fidder AR, de Hartog B, Faber T. Child with serogroup W135 primary meningococcal septic arthritis. BMJ Case Rep. 2019;12:e229510. https://doi.org/10.1136/bcr-2019-229510.

26. Ricci S, Montemaggi A, Nieddu F, et al. Is primary meningococcal arthritis in children more frequent than we expect? Two pediatric case reports revealed by molecular test. BMC Infect Dis. 2018;18:703. https://doi.org/10.1186/s12879-018-3602-y.

27. O'Rourke C, Garden M, Joyce P, Pagliaro T, Gray H, Wilks K. Serogroup Y primary meningococcal arthritis in a child. J Paediatr Child Health. 2018;54:689–91. https://doi.org/10.1111/jpc.13844.

28. Soler-Garcia A, Fernández de Sevilla M, Abad R, et al. Meningococcal serogroup B disease in vaccinated children. J Pediatr Infect Dis Soc. 2020;9:454–9. https://doi.org/10.1093/jpids/piz071.

29. Hu S, Zhang W, Li F, et al. *Neisseria meningitidis* serogroup W135 sequence type 11, Anhui Province, China, 2011–2013. Emerg Infect Dis. 2014;20:1236–8. https://doi.org/10.3201/eid2007.131138.

30. Li B, Zhang L, Liu M, et al. The molecular characteristics of *Neisseria meningitidis* serogroup Y clonal complex 23 first emerge in China. J Infect. 2019;79:612–25. https://doi.org/10.1016/j.jinf.2019.07.001.

31. Basani L, Aepala R. *Neisseria meningitidis* causing multiple cerebral abscesses in early neonatal period: case report and review of literature. J Clin Diagn Res. 2017;11:SD01–3. https://doi.org/10.7860/jcdr/2017/25284.10151.

32. Kawasaki Y, Matsubara K, Takahashi H, et al. Invasive meningococcal disease due to ciprofloxacin-resistant *Neisseria meningitidis* sequence type 4821: the first case in Japan. J Infect Chemother. 2018;24:305–8. https://doi.org/10.1016/j.jiac.2017.11.001.

33. Akcay N, Kihtir HS, Ozcelik G, Barlas UK, Petmezci MT, Sevketoglu E. Immunoadsorption therapy for a

meningococcemia patient with myocarditis, adrenal hemorrhage, and purpura fulminans: a case report. Braz J Anesthesiol. 2022;72:819–22. https://doi.org/10.1016/j.bjane.2021.06.021.

34. Nguyen N, Ashong D. *Neisseria Meningitidis*. Treasure Island: StatPearls; 2022.

35. Burman C, Serra L, Nuttens C, Presa J, Balmer P, York L. Meningococcal disease in adolescents and young adults: a review of the rationale for prevention through vaccination. Hum Vaccine Immunother. 2019;15:459–69. https://doi.org/10.1080/21645515.2018.1528831.

36. Di Pietro GM, Biffi G, Castellazzi ML, et al. Meningococcal disease in pediatric age: a focus on epidemiology and prevention. Int J Environ Res Public Health. 2022;19:4035. https://doi.org/10.3390/ijerph19074035.

37. Tully J, Viner RM, Coen PG, et al. Risk and protective factors for meningococcal disease in adolescents: matched cohort study. BMJ. 2006;332:445–50. https://doi.org/10.1136/bmj.38725.728472.BE.

38. Thangarajah D, Guglielmino CJD, Lambert SB, et al. Genomic characterization of recent and historic meningococcal serogroup E invasive disease in Australia: a case series. Clin Infect Dis. 2020;70:1761–3. https://doi.org/10.1093/cid/ciz767.

39. Marshall GS, Fergie J, Presa J, Peyrani P. Rationale for the development of a pentavalent meningococcal vaccine: a US-focused review. Infect Dis Ther. 2022;11:937–51. https://doi.org/10.1007/s40121-022-00609-9.

40. Chen WH, Neuzil KM, Boyce CR, et al. Safety and immunogenicity of a pentavalent meningococcal conjugate vaccine containing serogroups A, C, Y, W, and X in healthy adults: a phase 1, single-centre, double-blind, randomised, controlled study. Lancet Infect Dis. 2018;18:1088–96. https://doi.org/10.1016/s1473-3099(18)30400-6.

41. ClinicalTrials.gov. Identifier NCT04502693. Effectiveness of GlaxoSmithKline Biologicals S.A's meningococcal group B and combined ABCWY vaccines in healthy adolescents and young adults. https://clinicaltrials.gov/ct2/show/NCT04502693?term=205416&draw=2&rank=1. Accessed 21 Mar 2023.

42. Vienne P, Ducos-Galand M, Guiyoule A, et al. The role of particular strains of *Neisseria meningitidis* in meningococcal arthritis, pericarditis, and pneumonia. Clin Infect Dis. 2003;37:1639–42. https://doi.org/10.1086/379719.

43. Kallinich T, von Bernuth H, Kuhns M, Elias J, Bertelmann E, Pleyer U. Fulminant endophthalmitis in a child caused by *Neisseria meningitidis* serogroup C detected by specific DNA. J Pediatric Infect Dis Soc. 2016;5:e13–6. https://doi.org/10.1093/jpids/piw012.

44. Wang B, Giles L, Andraweera P, et al. Effectiveness and impact of the 4CMenB vaccine against invasive serogroup B meningococcal disease and gonorrhoea in an infant, child, and adolescent programme: an observational cohort and case-control study. Lancet Infect Dis. 2022;22:1011–20. https://doi.org/10.1016/s1473-3099(21)00754-4.

45. Ladhani SN, Andrews N, Parikh SR, et al. Vaccination of infants with meningococcal group B vaccine (4CMenB) in England. N Engl J Med. 2020;382:309–17. https://doi.org/10.1056/NEJMoa1901229.

46. Sohn WY, Tahrat H, Novy P, Bekkat-Berkani R. Real-world implementation of 4-component meningococcal serogroup B vaccine (4CMenB): implications for clinical practices. Expert Rev Vaccines. 2022;21:325–35. https://doi.org/10.1080/14760584.2022.2021881.

47. van de Beek D, Cabellos C, Dzupova O, et al. ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. Clin Microbiol Infect. 2016;22:S37–62. https://doi.org/10.1016/j.cmi.2016.01.007.

48. Willerton L, Lucidarme J, Walker A, et al. Antibiotic resistance among invasive *Neisseria meningitidis* isolates in England, Wales and Northern Ireland (2010/11 to 2018/19). PLoS ONE. 2021;16:e0260677. https://doi.org/10.1371/journal.pone.0260677.

49. McNamara LA, Potts C, Blain AE, et al. Detection of ciprofloxacin-resistant, β-lactamase-producing *Neisseria meningitidis* serogroup Y isolates—United States, 2019–2020. MMWR Morb Mortal Wkly Rep. 2020;69:735–9. https://doi.org/10.15585/mmwr.mm6924a2.

50. Abbas A, Mujeeb AA. Purpura fulminans caused by meningococcemia in an infant. BMJ Case Rep. 2013;2013:bcr2013200265. https://doi.org/10.1136/bcr-2013-200265.

51. Abouzahir H, Nya S, Benyaich H. Illustrated forensic pathology: fatal Waterhouse-Friderichsen syndrome. Am J Forensic Med Pathol. 2020;41:e58–60. https://doi.org/10.1097/paf.0000000000000581.

52. Aggarwal M, Manchanda V, Talukdar B. Meningitis due to *Neisseria meningitidis* serogroup B in India. Indian Pediatr. 2013;50:601–3.

53. Ali J, Walsh H, Sanapala S, Syed N. Concurrent meningococcal and herpes simplex infection in a

non-immunocompromised child. BMJ Case Rep. 2014;2014:bcr2013203395. https://doi.org/10.1136/bcr-2013-203395.

54. Ankam JV, Torres S, Halse TA, et al. Rapid diagnosis of meningococcal meningitis in a patient with familial Mediterranean fever by the FilmArray Meningitis/Encephalitis Panel: a case report. Neurohospitalist. 2020;10:297–300. https://doi.org/10.1177/1941874420908421.

55. Arora PK, Alsford L. A 2-month-old girl with bifrontal/bitemporal meningococcal subdural empyema: complete radiological and clinical recovery after treatment. BMJ Case Rep. 2011;2011:bcr0720103183. https://doi.org/10.1136/bcr.07.2010.3183.

56. Beau C, Vlassova N, Sarlangue J, Brissaud O, Léauté-Labrèze C, Boralevi F. Diagnostic value of polymerase chain reaction analysis of skin biopsies in purpura fulminans. Pediatr Dermatol. 2013;30:e276–7. https://doi.org/10.1111/pde.12181.

57. Beltrami D, Guilcher P, Longchamp D, Crisinel PA. Meningococcal serogroup W135 epiglottitis in an adolescent patient. BMJ Case Rep. 2018;2018:bcr2017223038. https://doi.org/10.1136/bcr-2017-223038.

58. Bendapudi PK, Whalen MJ, Lahoud-Rahme M, Villalba JA. Case 7–2021: a 19-year-old man with shock, multiple organ failure, and rash. N Engl J Med. 2021;384:953–63. https://doi.org/10.1056/NEJMcpc2027093.

59. Berbescu S, Matt M, Dinh A, et al. Successful treatment of meningococcal bacteremia using oral doxycycline: a case report. Int J Infect Dis. 2020;92:78–80. https://doi.org/10.1016/j.ijid.2019.12.032.

60. Bonville CA, Suryadevara M, Ajagbe O, Domachowske JB. Chronic meningococcemia presenting as a recurrent painful rash without fever in a teenage girl. Pediatr Infect Dis J. 2015;34:670–2. https://doi.org/10.1097/inf.0000000000000700.

61. Bouneb R, Mellouli M, Regaieg H, Majdoub S, Chouchène I, Boussarsar M. Meningococcemia complicated by myocarditis in a 16-year-old young man: a case report. Pan Afr Med J. 2018;29:149. https://doi.org/10.11604/pamj.2018.29.149.13107.

62. Bozan G, Kilic O, Çetin N, et al. A severe course of serogroup W meningococcemia in a patient with infantile nephropathic cystinosis. Hum Vaccine Immunother. 2020;16:2787–8. https://doi.org/10.1080/21645515.2020.1742508.

63. Brostowski LE, Graf EH. Closing the brief case: meningococcemia leading to a diagnosis of complement deficiency in a 23-month-old. J Clin Microbiol. 2019;57:e01516–18. https://doi.org/10.1128/jcm.01516-18.

64. Cardona RSB, do Carmo FB, Beltrão SV, et al. Chronic meningococcemia in a vertically HIV-infected adolescent. IDCases. 2020;20:e00764. https://doi.org/10.1016/j.idcr.2020.e00764.

65. Castillo-Campos L, Bachiller-Carnicero L, Megía-Sevilla MJ, González-Tomé MI. Secondary asplenia as a complication of severe meningococcal sepsis. BMJ Case Rep. 2017;2017:bcr2016217167. https://doi.org/10.1136/bcr-2016-217167.

66. Chacón-Cruz E, Lopatynsky EZ, Machado-Contreras JR, Gatica-Herrera R, Zazueta OE. Fatal pediatric meningococcal invasive disease caused by *Neisseria meningitidis* serogroup C and co-infected with SARS-CoV-2: report of a case in Tijuana, Mexico. Cureus. 2022;14:e22100. https://doi.org/10.7759/cureus.22100.

67. David KV, Pricilla RA, Thomas B. Meningococcal meningitis C in Tamil Nadu, public health perspectives. J Fam Med Prim Care. 2014;3:438–9. https://doi.org/10.4103/2249-4863.148143.

68. Dayan N, Zonis Z, Yulevich A, Shalata A, Glikman D. Penicillin-resistant *Neisseria meningitidis* and pandemic 2009 H1N1 influenza coinfection in a child. Pediatr Infect Dis J. 2012;31:323–4. https://doi.org/10.1097/INF.0b013e318241f2c3.

69. Devi U, Mahanta J. Neonatal meningitis due to *Neisseria meningitidis* serogroup Y. Indian Pediatr. 2014;51:757.

70. Donà D, Gnoato E, Giaquinto C, Moretti C. An unexpected fever post serogroup B meningococcal sepsis. Pediatr Rep. 2016;8:6613. https://doi.org/10.4081/pr.2016.6613.

71. Ducatez N, Chancel M, Douadi Y, et al. Primary meningococcal arthritis in a COVID-19 18-year-old man: a case report and review of the literature. BMC Infect Dis. 2021;21:499. https://doi.org/10.1186/s12879-021-06211-7.

72. Eton V, Tsang RS, Ulanova M. Paediatric meningococcaemia in northwestern Ontario, Canada: a case for publicly funded meningococcal B vaccination. JMM Case Rep. 2016;3:e005017. https://doi.org/10.1099/jmmcr.0.005017.

73. Fayeye O, Pettorini BL, Smith M, Williams H, Rodrigues D, Kay A. Meningococcal encephalitis associated with cerebellar tonsillar herniation and acute cervicomedullary injury. Br J Neurosurg. 2013;27:513–5. https://doi.org/10.3109/02688697.2013.764967.

74. García-Clemente P, Menéndez-Suso JJ, Falces-Romero I, Escosa-García L, Schüffelmann C, Cendejas-Bueno E. Utility of FilmArray® ME panel for prompt *Neisseria meningitidis* detection in non-cerebrospinal fluid samples — a case report. J Infect. 2020;80:121–42. https://doi.org/10.1016/j.jinf.2019.10.016.

75. Garland J, Philcox W, Kesha K, et al. *Neisseria meningitidis* isolated in vitreous humor in a 5-month-old infant death from meningococcal sepsis. Am J Forensic Med Pathol. 2019;40:175–7. https://doi.org/10.1097/paf.0000000000000448.

76. Gaschignard J, Hassani N, El Sissy C, et al. Delayed generalized necrotic purpuric rash in a C6-deficient 12-year-old girl treated for group W meningococcal disease. Pediatr Infect Dis J. 2018;37:1014–5. https://doi.org/10.1097/inf.0000000000001966.

77. Gawalkar AA, Tale S, Chhabria BA, Bhalla A. Myocarditis and purpura fulminans in meningococcaemia. QJM. 2017;110:755–6. https://doi.org/10.1093/qjmed/hcx144.

78. Gómez BO, Feito CR, Vázquez DG, Vega MG, García Viejo MÁ. Primary meningococcal septic arthritis case report and literature review of an unusual manifestation of meningococcal disease. Bull Hosp Jt Dis. 2013;2019(77):140–5.

79. Gopinathan U, Brusletto BS, Olstad OK, et al. IL-10 immunodepletion from meningococcal sepsis plasma induces extensive changes in gene expression and cytokine release in stimulated human monocytes. Innate Immun. 2015;21:429–49. https://doi.org/10.1177/1753425914547743.

80. He B, Jia Z, Zhou H, et al. CC4821 serogroup W meningococcal disease in China. Int J Infect Dis. 2014;29:113–4. https://doi.org/10.1016/j.ijid.2014.08.022.

81. Hoehne J, Friedrich M, Brawanski A, Melter M, Schebesch KM. Decompressive craniectomy and early cranioplasty in a 15-year-old boy with *N. meningitidis* meningitis. Surg Neurol Int. 2015;6:58. https://doi.org/10.4103/2152-7806.154776.

82. Karabulut GS, Acar T, Yuksel AB, Alanay Y, Hatun Ş. Late sequel of meningococcemia: skeletal dysplasia. J Pediatr. 2016;173:264–264.e2. https://doi.org/10.1016/j.jpeds.2016.02.022.

83. Kiray Baş E, Bülbül A, Cömert S, Uslu S, Arslan S, Nuhoglu A. Neonatal infection with *Neisseria meningitidis*: analysis of a 97-year period plus case study. J Clin Microbiol. 2014;52:3478–82. https://doi.org/10.1128/jcm.01000-14.

84. Kugai T, Nakagawa H. Evolution of purpura fulminans. N Engl J Med. 2017;376:2182. https://doi.org/10.1056/NEJMicm1700231.

85. Legriel S, Merceron S, Tattevin P, et al. Favorable outcome after life-threatening meningococcal disease complicating influenza A(H1N1) infection. Infection. 2011;39:477–80. https://doi.org/10.1007/s15010-011-0134-4.

86. Manuel AR, Vieira J, Figueiredo A, Correia P. Invasive meningococcal disease: should the first episode prompt further investigation? J Paediatr Child Health. 2022;58:1091–3. https://doi.org/10.1111/jpc.15768.

87. Marujo F, Costa LC, Duarte R, et al. Invasive meningococcal disease unraveling a novel mutation in the C5 gene in a Portuguese family. Pediatr Infect Dis J. 2019;38:416–8. https://doi.org/10.1097/inf.0000000000002149.

88. Masson-Behar V, Jacquier H, Richette P, et al. Arthritis secondary to meningococcal disease: a case series of 7 patients. Medicine (Baltimore). 2017;96:e7573. https://doi.org/10.1097/md.0000000000007573.

89. Miguel-Gomez L, Bagazgoitia L, Hermosa-Gelbard A, Sanchez-Neila N, Lopez-de Pedro A, Quiñones-Coneo K. Chronic meningococcemia in an immunocompetent child. J Paediatr Child Health. 2016;52:853–4. https://doi.org/10.1111/jpc.13164.

90. Mubashar T, Turner PC, Paul SP. Early-onset neonatal sepsis caused by *Neisseria meningitidis* serogroup B: case report and literature review of a 102-year period. Turk J Pediatr. 2020;62:125–9. https://doi.org/10.24953/turkjped.2020.01.018.

91. Mularski A, Żaba C. Fatal meningococcal meningitis in a 2-year-old child: a case report. World J Clin Cases. 2019;7:636–41. https://doi.org/10.12998/wjcc.v7.i5.636.

92. Nolfi-Donegan D, Konar M, Vianzon V, et al. Fatal nongroupable *Neisseria meningitidis* disease in vaccinated patient receiving eculizumab. Emerg Infect Dis. 2018;24:1561–4. https://doi.org/10.3201/eid2408.180228.

93. O'Connor C, Collins A, Twomey E, Hensey C, Caird J, Gavin PJ. A case report of multiple cerebral abscess formation complicating serogroup B *Neisseria meningitidis* meningitis. BMC Infect Dis. 2019;19:863. https://doi.org/10.1186/s12879-019-4509-y.

94. Özdemir H, Kendirli T, Çiftçi E, Ince E. Purpura fulminans in a child due to *Neisseria meningitidis*. Infection. 2012;40:717–8. https://doi.org/10.1007/s15010-012-0286-x.

95. Ozenen GG, Sahbudak Bal Z, Ersayoglu I, et al. The first pediatric case of mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) associated with *Neisseria meningitidis*. Brain Dev. 2022;44:184–8. https://doi.org/10.1016/j.braindev.2021.09.002.

96. Pan J, Yao P, Zhang H, Sun X, He H, Xie S. The case of a new sequence type 7 serogroup X *Neisseria meningitidis* infection in China: may capsular switching change serogroup profile? Int J Infect Dis. 2014;29:62–4. https://doi.org/10.1016/j.ijid.2014.07.022.

97. Piet JR, Zariri A, Fransen F, et al. Meningitis caused by a lipopolysaccharide deficient *Neisseria meningitidis*. J Infect. 2014;69:352–7. https://doi.org/10.1016/j.jinf.2014.06.005.

98. Polat M, Parlakay AÖ. Meningococcemia due to nongroupable *Neisseria meningitidis* in a splenectomized child. Pediatr Infect Dis J. 2020;39:e57. https://doi.org/10.1097/inf.0000000000002608.

99. Pratt JJ, Connell TG, Bekhit E, Crawford NW. Splenic cyst and its management in a 21-month-old boy: a rare complication of invasive meningococcal disease. BMJ Case Rep. 2018;2018:bcr2018224613. https://doi.org/10.1136/bcr-2018-224613.

100. Rasoanandrasana S, Raberahona M, Milenkov M, et al. Resurgence of *Neisseria meningitidis* serogroup W ST-11 (cc11) in Madagascar, 2015–2016. Int J Infect Dis. 2017;55:1–3. https://doi.org/10.1016/j.ijid.2016.12.001.

101. Ray S, Riordan A, Tawil M, et al. Subdural empyema caused by *Neisseria meningitidis*: a case report and review of the literature. Pediatr Infect Dis J. 2016;35:1156–9. https://doi.org/10.1097/inf.0000000000001252.

102. Sahu S, Mohanty I, Narasimham MV, Pasupalak S, Parida B. Primary meningococcal arthritis of sacroiliac joint: a rare case report. Indian J Med Microbiol. 2013;31:87–9. https://doi.org/10.4103/0255-0857.108743.

103. Santos ACEZ, Luglio M, Delgado AF, et al. Acute petrified myocardium associated with meningococcal sepsis in childhood-onset systemic lupus erythematous: a fatal case. Rev Inst Med Trop Sao Paulo. 2019;61:e39. https://doi.org/10.1590/s1678-9946201961039.

104. Sekiya N, Sunagawa T, Takahashi H, et al. Serogroup B invasive meningococcal disease (IMD) outbreak at a Japanese high school dormitory: an outbreak investigation report from the first IMD outbreak in decades. Vaccine. 2021;39:2177–82. https://doi.org/10.1016/j.vaccine.2021.02.034.

105. Shanley LA, Durham MR. An adolescent female with fever, rash, and arthralgias. Clin Pediatr (Phila). 2013;52:475–8. https://doi.org/10.1177/0009922812466585.

106. Shinozuka J, Takahashi H, Masahiro M, Awaguni H, Imashuku S. Bacteremia and meningitis caused by a novel clone of *Neisseria meningitidis* serogroup B. Pediatr Int. 2018;60:1093–4. https://doi.org/10.1111/ped.13718.

107. Smith A, Zehetner A. Early onset neonatal serogroup B meningococcal meningitis and septicaemia. J Paediatr Child Health. 2013;49:158. https://doi.org/10.1111/jpc.12079.

108. Sorek N, Ashkenazi S, Livni G, Ben-Zvi H. *Neisseria meningitidis* and cytomegalovirus simultaneous detection in the filmarray meningitis/encephalitis panel and its clinical relevance. IDCases. 2019;17:e00516. https://doi.org/10.1016/j.idcr.2019.e00516.

109. Spence Davizon E, Soeters HM, Miller L, Barnes M. Two cases of meningococcal disease in one family separated by an extended period — Colorado, 2015–2016. MMWR Morb Mortal Wkly Rep. 2018;67:366–8. https://doi.org/10.15585/mmwr.mm6712a4.

110. Stefanelli P, Fazio C, Neri A, et al. Imported and indigenous cases of invasive meningococcal disease W:P1.5,2:F1-1: ST-11 in migrants' reception centers. Italy, June–November 2014. Adv Exp Med Biol. 2016;897:81–3. https://doi.org/10.1007/5584_2015_5006.

111. Sterrey J, Abedi F, Henderson TR. Bilateral primary meningococcal conjunctivitis in an Indigenous child. Med J Aust. 2018;209:370. https://doi.org/10.5694/mja18.00415.

112. Straticiuc S, Ignat A, Hanganu E, Lupu VV, Ciubara AB, Cretu R. *Neisseria meningitidis* serogroup C causing primary arthritis in a child: case report. Medicine (Baltimore). 2016;95:e2745. https://doi.org/10.1097/md.0000000000002745.

113. Toubiana J, Heilbronner C, Gitiaux C, et al. Pachymeningitis after meningococcal infection. Lancet. 2013;381:1596. https://doi.org/10.1016/s0140-6736(13)60315-3.

114. van den Broek B, Coolen JPM, de Jonge MI, et al. *Neisseria meningitidis* serogroup Z meningitis in a child with complement C8 deficiency and potential cross protection of the MenB-4C vaccine. Pediatr Infect Dis J. 2021;40:1019–22. https://doi.org/10.1097/inf.0000000000003259.

115. van den Heuvel N, O'Leary C, Gwee A. Meningococcal meningitis complicated by ventriculitis in an

infant. J Paediatr Child Health. 2018;54:213–4. https://doi.org/10.1111/jpc.13831.

116. Van Gysel D, De Raeve H, De Wit M. Chronic malaise and a persisting skin rash in an adolescent. Pediatr Dermatol. 2016;33:559–60. https://doi.org/10.1111/pde.12943.

117. Wang X, Xia A, Wang C, et al. Clinical and molecular characterization of the first culture-confirmed pediatric fulminant meningococcemia case caused by a serogroup Y clonal complex 23 strain in China. Vaccine. 2021;39:4261–5. https://doi.org/10.1016/j.vaccine.2021.06.019.

118. Xu Z, Zhu B, Xu L, Gao Y, Shao Z. First case of *Neisseria meningitidis* capsule null locus infection in China. Infect Dis (Lond). 2015;47:591–2. https://doi.org/10.3109/00365548.2015.1010228.

119. Yusuf IH, Sipkova Z, Patel S, Benjamin L. *Neisseria meningitidis* endogenous endophthalmitis with meningitis in an immunocompetent child. Ocul Immunol Inflamm. 2014;22:398–402. https://doi.org/10.3109/09273948.2013.854392.

120. Zhou H, Shao Z, Li Q, et al. *Neisseria meningitidis* strain of unknown serogroup, China. Emerg Infect Dis. 2011;17:569–71. https://doi.org/10.3201/eid1703.101329.

121. Staels F, Meersseman W, Stordeur P, et al. Terminal complement pathway deficiency in an adult patient with meningococcal sepsis. Case Rep Immunol. 2022;2022:9057000. https://doi.org/10.1155/2022/9057000.

122. Kiral E, Yetimakman AF. Clinical and laboratory findings of 12 children with invasive meningococcal disease in pediatric intensive care unit. Crit Care Res Pract. 2021;2021:9713918. https://doi.org/10.1155/2021/9713918.

123. Colobran R, Franco-Jarava C, Martín-Nalda A, et al. Novel mutations causing C5 deficiency in three North-African families. J Clin Immunol. 2016;36:388–96. https://doi.org/10.1007/s10875-016-0275-4.

124. Dellepiane RM, Dell'Era L, Pavesi P, et al. Invasive meningococcal disease in three siblings with hereditary deficiency of the 8th component of complement: evidence for the importance of an early diagnosis. Orphanet J Rare Dis. 2016;11:64. https://doi.org/10.1186/s13023-016-0448-5.

125. Brostowski LE, Graf EH. The brief case: meningococcemia leading to a diagnosis of complement deficiency in a 23-month-old. J Clin Microbiol. 2019;57:e01513–18. https://doi.org/10.1128/jcm.01513-18.

126. Centers for Disease Control and Prevention (CDC). Outbreak of meningococcal disease associated with an elementary school – Oklahoma, March 2010. MMWR Morb Mortal Wkly Rep. 2012;61:217–21.

127. Medeiros I, Reis Melo A, Baptista V, Ribeiro A. Meningococcemia: rare but life-threatening. BMJ Case Rep. 2018;2018:bcr2018226914. https://doi.org/10.1136/bcr-2018-226914.

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