Diagnosis of Meningococcal Infection and Clinical Management in Adults

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Introduction of meningococcus

Gram-negative, aerobic, encapsulated diplococcus

At least 13 serogroups were described, based on their polysaccharide capsular antigens

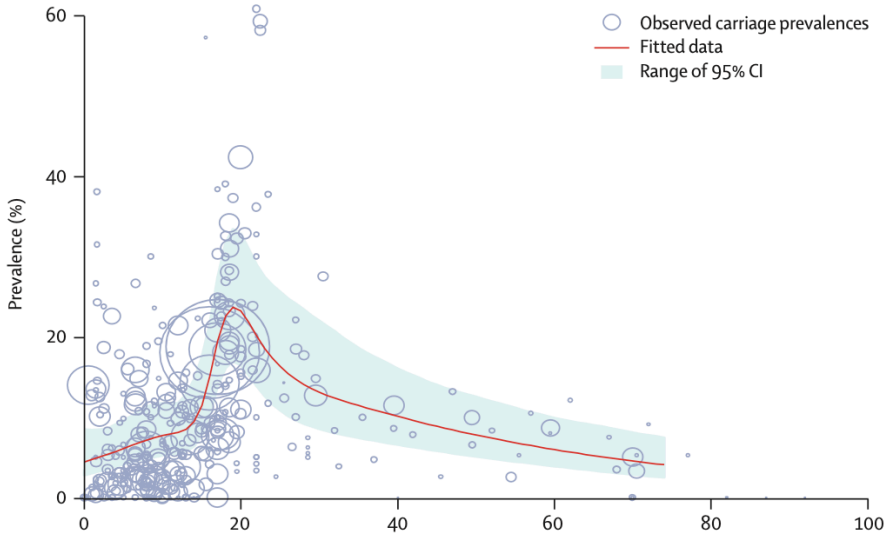
Serogroups A, B, C, W, X, and Y are responsible for over 95% of cases of meningococcal disease worldwide

Humans are the only natural reservoir

Asymptomatic nasopharyngeal carriage is common

Carriage rate was believed to be approximately 5%–10% of the population

Prevalence of meningococcal carriage by age



Can be transmitted from person-to-person through direct contact with droplet respiratory secretions or saliva of asymptomatic carriers and persons with invasive disease

Hannah Christensen et al. Lancet Infect Dis. 2010 Dec;10(12):853-61

Spectrum of meningococcal diseases

- **Meningitis**
- **Meningococcemia ± meningitis**
- Respiratory tract infection: pneumonia, epiglottitis, otitis media
- Other focal infection: conjunctivitis, septic arthritis, urethritis, purulent pericarditis

Clinical syndrome	No. (%)
Meningitis	**50.2%**
Bacteremia	**37.5%**
Pneumonia	9.2%
Septic arthritis	2.0%

One of the common causative organisms of bacterial meningitis in adults

Causative organisms	No. (%)
Neisseria meningitidis	**1089 (27%)**
Streptococcus pneumoniae	2157 (53%)
Haemophilus influenzae	112 (3%)
Listeria monocytogenes	154 (4%)
Other	548 (13%)

Causes acute, serious and potentially rapidly progressive and life-threatening infections

Incubation period: 2-10 days (mean 4 days)

Mortality

- Around 5-10% for meningitis with treatment
- Up to 40% for meningococcemia

Death can occur within hours of onset among patients with severe meningococcemia

N E Rosenstein et al. N Engl J Med. 2001 May 3;344(18):1378-88
Amanda C Cohn et al. Clin Infect Dis. 2010 Jan 15;50(2):184-91

Risk factors of meningococcal diseases

Host factors

- Anatomic or functional asplenia
- Terminal complement component deficiencies
- Advanced HIV infection
- Those who are receiving complement inhibitor, e.g. eculizumab or ravulizumab
- Active or passive smoking
- Recent upper respiratory tract infections

Environmental factors

- Crowded living conditions
- College freshmen residing in residence halls
- Close contact with patients with meningococcal disease, such as household members or daycare and preschool institutes
- Visit to areas with high prevalence or outbreaks

Diagnosis of meningococcal disease

Prompt diagnosis and treatment is important due to risk of severe morbidity and death

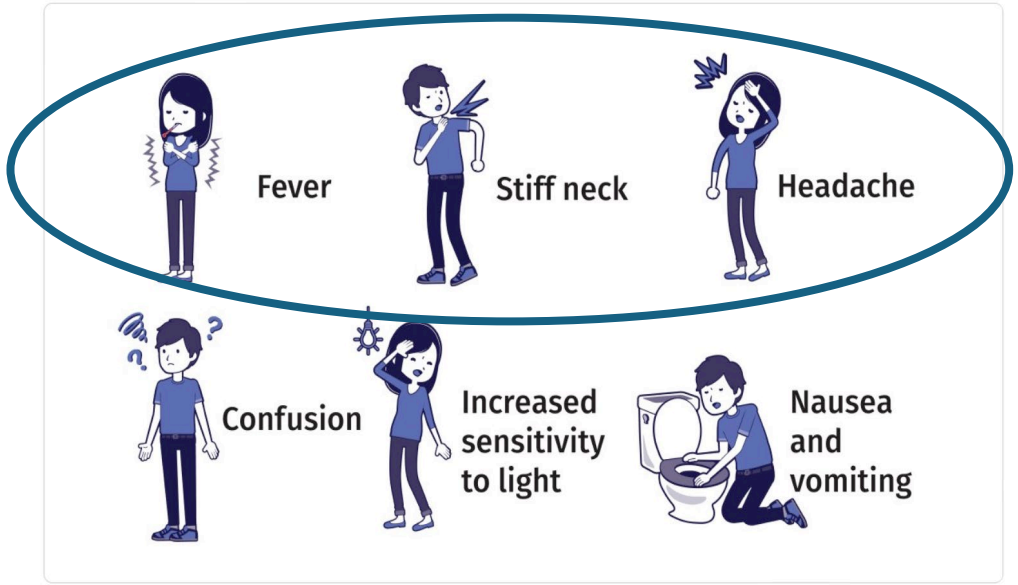
- **Compatible clinical features ± presence of risk factor**
- **Blood tests including culture**
- **Lumbar puncture and cerebrospinal fluid (CSF) tests**

Blood culture and lumbar puncture for collecting CSF should be done as early as possible, preferably before initiation of empirical antimicrobial therapy, unless there are specific contraindications or reasons for deferral

Clinical features

Symptoms and signs can be non-specific

Common symptoms of meningitis



Red flag combination: fever, headache, neck stiffness, and altered level of consciousness

Other neurological manifestations:

Seizure

Focal neurological deficits

Features in meningococcemia

Petechial or purpuric rash

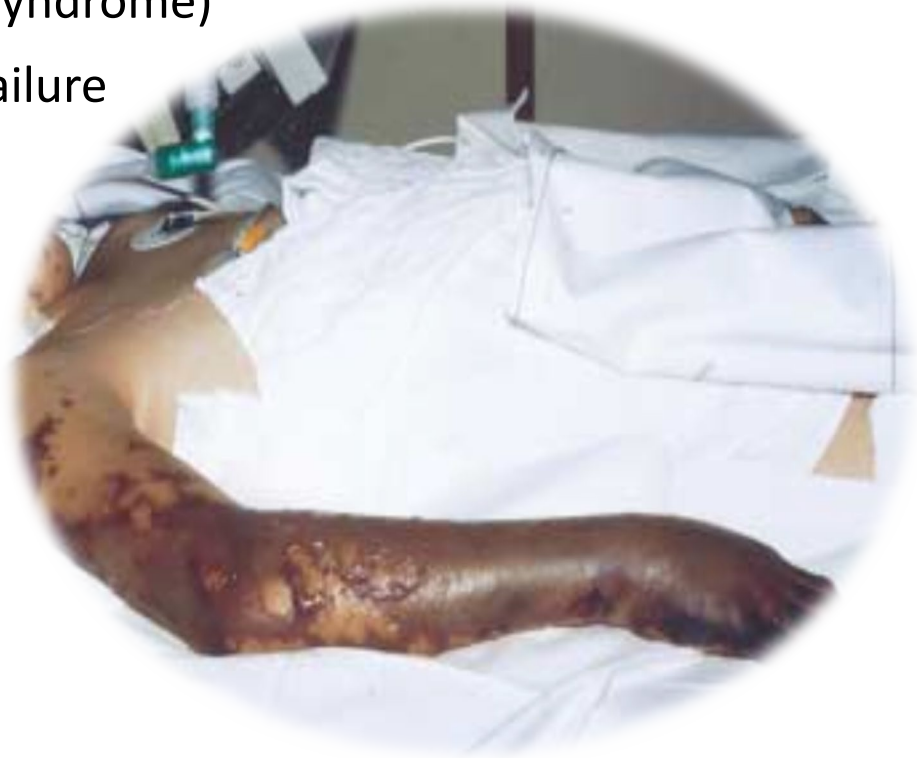
Shock

Disseminated intravascular coagulopathy (DIC)

Focal gangrene (from vasculitis)

Acute adrenal hemorrhage (Waterhouse-Friderichsen syndrome)

Multi-organ failure (MOF)



Clinical features in adults with bacterial meningitis

Characteristic	No. of meningitis episodes, total =696 (%)
Duration of symptoms <24hr	317 (48)
Fever (body temp ≥38°C)	**522 (77)**
Headache	**544 (87)**
Neck stiffness	**569 (83)**
Nausea	449 (74)
Rash	176 (26)
Reduced GCS	**477 (69)**
Seizure	32 (5)
Focal neurologic deficits	233 (33)
Papilledema	13 (3)

The classic triad (fever, neck stiffness, and change in mental status) was only present in 44% of meningitic episodes

At least two of the four common signs (the classic triad plus headache) were present in 95% of meningitic episodes

Focal neurological deficits
Cranial nerve palsy
Aphasia
Hemiparesis

Among the patients with rash

- 89% of the rash was petechial
- 162 episodes of meningitis with rash were due to *N. meningitidis*

Diederik van de Beek et al. N Engl J Med. 2004 Oct 28;351(18):1849-59

Diagnosis of invasive meningococcal disease

- Compatible clinical features ± presence of risk factors)
- **Blood tests**
- Lumbar puncture and CSF tests

Blood culture

- **Without delay**
- **Before initiation of antimicrobial therapy**
- **Sensitivity can be up to ~75% prior administration of antimicrobial therapy**

Other blood tests	Interpretation
White blood cell count with differential count	can be low, normal or high, with marked left shift
Platelet count	Can be low due to DIC
Clotting profile	Look for coagulopathy
Kidney function	Can be impaired with MOF; look for electrolyte disturbance
Acid-base	Look for metabolic acidosis
Liver enzymes	Can for impaired with MOF
Creatinine kinase	Look for rhabdomyolysis

Diagnosis of invasive meningococcal disease

- Compatible clinical features ± presence of risk factors)
- Blood tests
- **Lumbar puncture and CSF tests**

Considerations before performing lumbar puncture

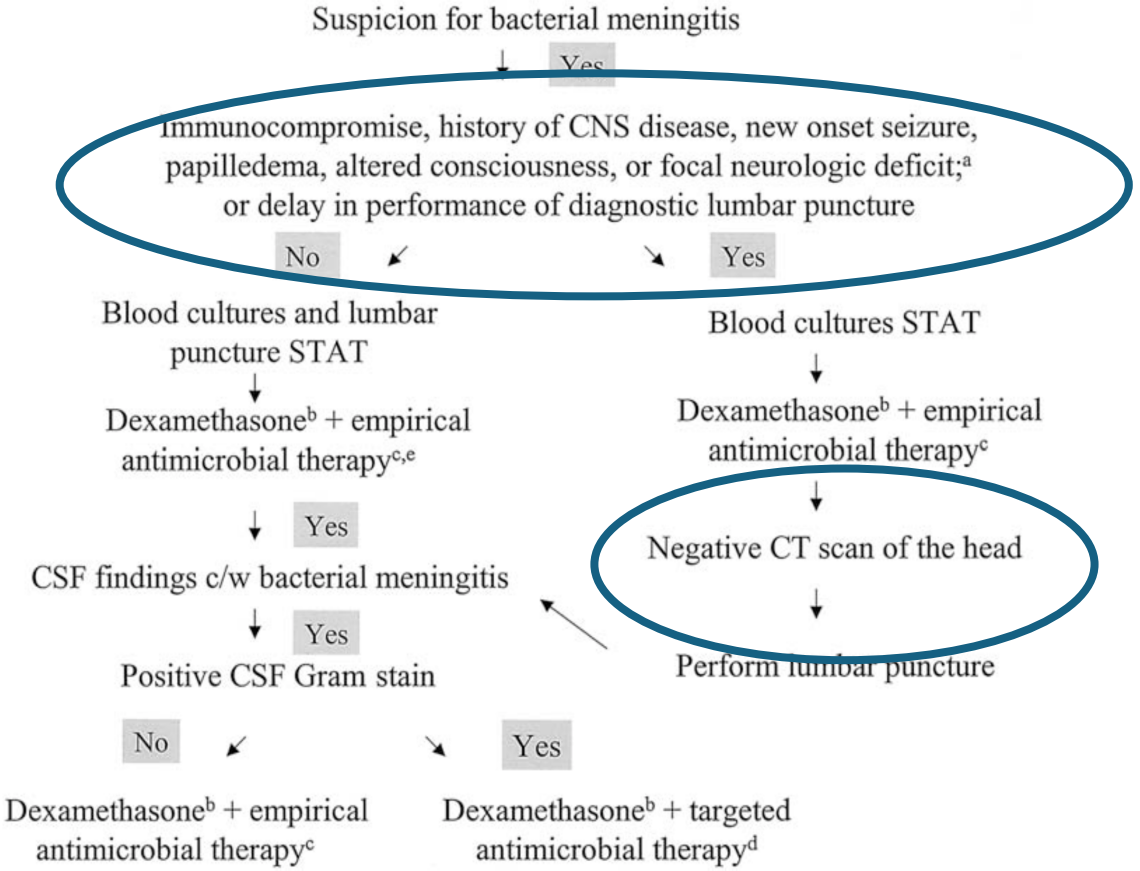
Risk factors for an evolving space-occupying lesion

Any clinical features which may indicate raised intracranial pressure

- New focal neurological features
- Abnormal pupillary reactions
- Progressive decline in level of consciousness

Role of neuroimaging

Management algorithm for suspected bacterial meningitis



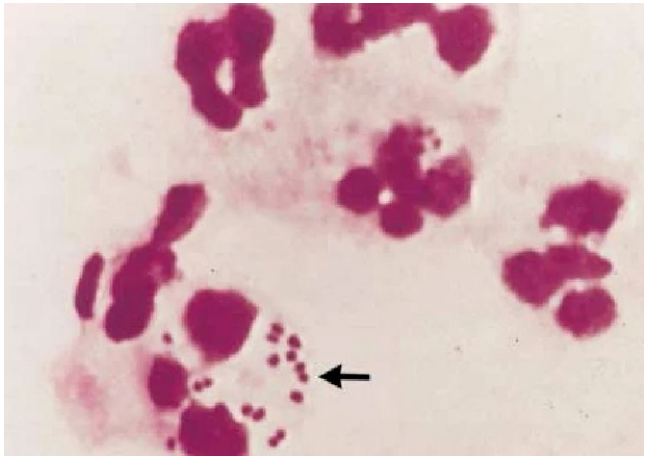
According to local recommendation, CT scan of brain should be performed first to exclude contraindications of lumbar puncture

Lumbar puncture and CSF results

Crucial to confirm the clinical suspicion of acute meningitis

CSF tests

- Cell count, including differential white cell count
- Total protein
- Glucose concentration (with concomitant blood glucose concentration)
- Lactate concentration
- Gram stain
- Microbiological culture, accompanied by antimicrobial susceptibility testing
- Antigen detection for specific serogroups
- Multiplex PCR for relevant pathogens



Diagnostic performance of acute bacterial meningitis

CSF tests	Sensitivity,% (95% CI)	Specificity, % (95% CI)
Gram stain	85 (55-96%)	99 (NA)
WBC count	77 (74-81%)	83 (75-92%)
Neutrophil count	82 (70-94%)	84 (77-90%)
Protein	86 (80-92%)	79 (70-88%)
Glucose	66 (52-79%)	85 (72-98%)
CSF-to-blood glucose ratio	88 (83-93%)	78 (52-100%)
Lactate*	94 (91-98%)	86 (74-98%)

However, none of these tests can be used alone to confirm or rule out a diagnosis of meningitis

Typical CSF abnormalities in bacterial meningitis and potential prognostic relationship

Bacterial meningitis	Viral meningitis
Increased opening pressure	Normal or mildly elevated opening pressure
Turbid or cloudy appearance	Clear appearance
Marked leukocyte pleocytosis	Moderate leukocyte pleocytosis
Neutrophilic predominance	Lymphocytic predominance
Low CSF-to-blood glucose	Normal CSF-to-blood glucose
Markedly increased protein	Normal or mildly increased protein
Increased lactate (prior to antibiotics)	Normal lactate

Prior antibiotic use or known/suspected immunodeficiency has to be taken into account

Multivariate Analysis of Factors Associated with an Unfavorable Outcome

Characteristic	Favorable Outcome (N=459)	Unfavorable Outcome (N=237)	Odds Ratio (95% CI)†	P Value
Indexes of inflammation in the CSF				
White-cell count — no./no. evaluated (%)††				
<100/mm³	23/428 (5)	39/217 (18)	3.43 (1.64–7.20)	0.001‡
100–999/mm³	56/428 (13)	66/217 (30)	2.82 (1.59–4.78)	<0.001‡
1000–10,000/mm³	238/428 (56)	87/217 (40)	1.00 —¶	—
>10,000/mm³	111/428 (26)	25/217 (12)	0.55 (0.30–1.01)	0.05‡
Protein — g/liter	4.8±4.7	5.4±3.9	1.03 (0.99–1.07)	0.17‡
CSF:blood glucose ratio — mg/dl	0.18±0.2	0.15±0.2	0.91 (0.70–1.17)	0.44‡

Diederik van de Beek et al. N Engl J Med. 2004 Oct 28;351(18):1849-59

Diagnosis of invasive meningococcal disease

	Culture	PCR
Advantages	- **The gold standard test for diagnosis** - Virtually 100% specificity - Valuable for serogrouping - Allow monitoring of antimicrobial susceptibility	- Rapid test - High sensitivity and specificity
Disadvantages	- Fastidious growth requirements - **Poor sensitivity in specimens from patients who have received antibiotics**	- Fails to determine antimicrobial resistance

Overall sensitivity of culture prior to antimicrobial therapy

- Blood 50-60%
- CSF 80-90%
- Skin biopsy 36-56%

PCR is useful for detection of *N. meningitidis* from clinical samples, particularly when patient was treated with antibiotics prior to specimen collection

Shimon Takada et al. Intern Med. 2016;55(6):567-72

Case Definitions of
Statutory Notifiable Diseases

Meningococcal infection (invasive)

Description

An acute bacterial disease, characterized by sudden onset of fever, intense headache, nausea and often vomiting, stiff neck and, frequently, a petechial rash with pink macules or, very rarely, vesicles. Delirium and coma often appear; occasional fulminant cases exhibit sudden prostration, ecchymoses and shock at onset. Other forms of invasive disease (e.g. septic arthritis) are less common.

Laboratory criteria

Any one of the following:

- Isolation of *Neisseria meningitidis* from a normally sterile site such as in blood or CSF
- A positive antigen test for *Neisseria meningitidis* in a normally sterile site
- A positive nucleic acid test (e.g. polymerase chain reaction) for *Neisseria meningitidis* in a normally sterile site

Confirmed case

- Clinically compatible case that is laboratory confirmed

Probable case

- Clinically compatible illness with Gram-negative diplococci identified in any sterile fluids such as CSF

General management of invasive meningococcal disease

Invasive meningococcal disease can be rapidly fatal and should always be viewed as a medical emergency

Initiate empirical antimicrobial therapy promptly, prior to presence of diagnostic test results

- **Droplet and contact precaution**
- **Supportive treatment**
- **Empirical antibiotic therapy**
- Eradication of nasopharyngeal carriage
- Post-exposure prophylaxis
- Vaccination

Supportive treatment

- Unprotected airway
- Respiratory compromise
- Shock
- Uncontrolled seizures
- Bleeding risk

ICU care may be indicated

- Hemodynamic or respiratory compromise
- Seizures
- Altered mental status
- Other life-threatening complications, including DIC, septic shock or multiorgan failure

Empirical antimicrobial therapy for suspected bacterial meningitis

Considerations of initiating antibiotic therapy

- Clinical features
- Epidemiological risk
- Initial CSF characteristics
- Underlying medical history
- Antimicrobial penetration into CSF
- Bactericidal effect of antimicrobials

Any deferral of diagnostic investigations should not delay therapy administration

"1-hour window" is generally regarded as the golden time period to initiate empirical antibiotic therapy for patients with suspected bacterial meningitis

Empirical antimicrobial therapy for suspected bacterial meningitis (before knowing the causative organism)

Meningitic dose of antimicrobials has to be given in intravenous route

Treatment options

- **3rd generation cephalosporin**, e.g. ceftriaxone 2gm Q12H or cefotaxime 2gm Q4H
- **Ampicillin or amoxicillin** for patients with risk factors for *Listeria monocytogenes* infection (in addition to ceftriaxone or cefotaxime)
- **Vancomycin** (should be considered to cover penicillin or third-generation cephalosporin resistant *Streptococcus pneumoniae)*

Specific antimicrobial therapy for invasive meningococcal infection

Treatment options

- **Ceftriaxone IV 2gm Q12H** or **cefotaxime 2gm Q4-6H** (to cover penicillin-resistant *N. meningitidis*)
- **Penicillin IV 3-4 MU Q4H** or ampicillin IV 2gm Q4-6H (could be used if the isolate is penicillin susceptible or penicillin-resistance is not a concern)
- **Alternatives: aztreonam, meropenem, moxifloxacin, chloramphenicol**

(can be considered as alternative therapy for patients with beta-lactam allergy)

In **outpatient setting**, when invasive meningococcal infection is suspected, empirical therapy should be considered prior to hospitalization or on admission to emergency departments

Option: **Ceftriaxone IV or IM 2gm**

Alternative: benzylpenicillin IV or IM 1.2gm

Concern on drug-resistance of meningococcus

Antimicrobial resistance in bacterial meningitis caused by *N. meningitidis* (2010–24): a systematic review and meta-analysis

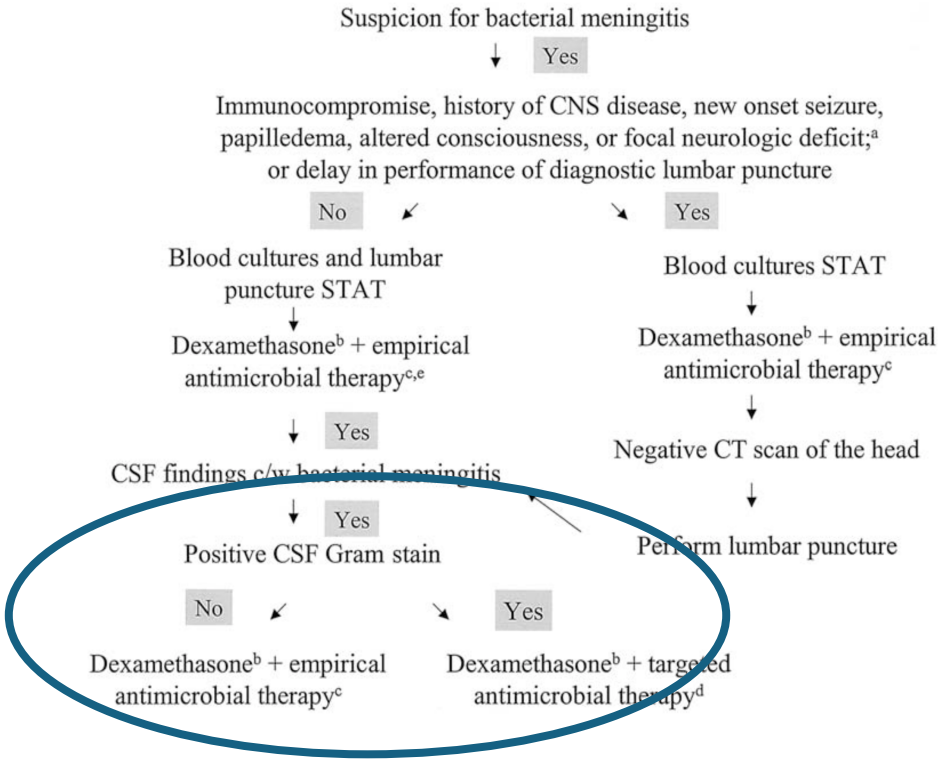
Global and regional prevalence estimates of antimicrobial resistance

	Global	African region	Region of the Americas	South-East Asia region	European region	Eastern Mediterran-ean region	Western Pacific region
Ceftriaxone	7·8% (0·0–31·7)	32·2% (0.0-100)	0·0% (0·0–0·1)	---	0·0% (0·0–0·9)	17·0% (0·0–100)	0·0% (0·0–3·2)
Cefotaxime	2·1% (0·0–17·4)	17·1% (0·0–100)	---	---	0·0% (0·0–0·9)	0·93% (0·0–3·6)	0·0% (0·0–3·2)
Ciprofloxacin	3·7% (0·0–25·9)	17·1% (0·0–100)	0·0% (0·0–0·2)	---	---	0·0% (0·0–0·9)	10·5% (0·0–100)
Benzyl-penicillin	24·7% (5·3–52·3)	44·9% (0·0–100)	38·0% (24·0–53·2)	---	29·0% (15·1–45·4)	9·4% (7·2–11·8)	9·4% (0·0–100)
Rifampicin	0·7% (0·0–2·4)	---	0·1% (0·0–0·4)	---	0·4% (0·0–3·0)	1·9% (0·2–5·3)	20·0% (2·3–48·8)

Data are % (95% CI)

Lancet Microbe. 2026 Feb;7(2):101238.

Role of corticosteroids for bacterial meningitis



Subgroup	No. of Patients	No. of Deaths*	Relative Risk of Death in the Dexamethasone Group (95% CI)	P Value
Streptococcus pneumoniae	55	5	—¶	0.028‖
Other cause	368	37	0.92 (0.49–1.73)	0.797
S. suis	116	3	—¶	0.070‖
Other cause	307	39	0.86 (0.46–1.58)	0.624
Gram-positive bacteria	218	17	0.06 (0.01–0.45)	0.006
Gram-negative bacteria	56	11	1.65 (0.52–5.21)	0.391
Bacteria not seen or cultured	149	19	3.16 (0.88–11.31)	0.078

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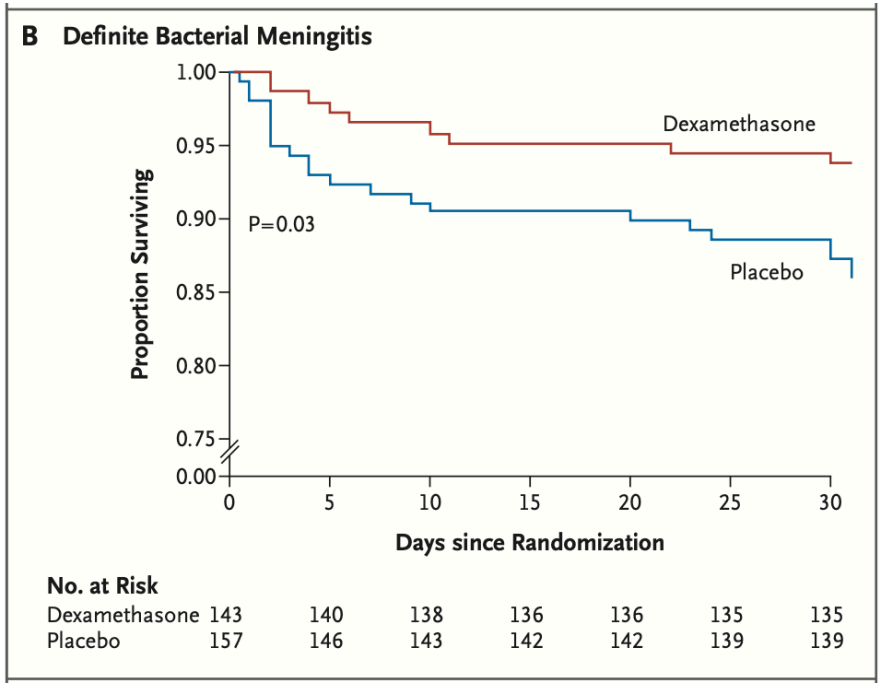
Dexamethasone in Vietnamese Adolescents and Adults with Bacterial Meningitis



Corticosteroids is not routinely recommended to patients with meningococcal disease

Take home messages

- *Neisseria meningitidis* can cause acute, potential rapidly progressive and life-threatening infection
- Diagnosis rely on compatible clinical features and isolation of the organism or positive nucleic acid test in normally sterile site, e.g. blood, CSF
- Investigations including blood culture and lumbar puncture for CSF collection (if not contraindicated) should be performed as early as possible
- Prompt antimicrobial therapy is crucial for invasive meningococcal infection, and should not be delayed by any deferral of investigations
- 3rd generation cephalosporin, ceftriaxone or cefotaxime, was the treatment of choice

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