Objectives

- Describe the basic epidemiology of meningitis.
- Describe the presenting signs and symptoms of the disease.
- Describe the initial workup, pre-hospital care and safe transfer to hospital.
- Outline a prevention and infection control plan.
None of the presenters have conflict of interest disclosures.
Experts and Moderator

- Alfred Demaria, Jr., MD
  - Massachusetts Department of Public Health
- Jessica MacNeil, MPH
  - Centers for Disease Control
- Carol Sulis, MD
  - Boston Medical Center and Boston University School of Medicine
- David McBride, MD
  - Boston University Student Health Services and School of Medicine

Update on Meningococcal Disease
Patient story

Katie Hauser's Meningitis Story - Get Vaccinated

https://www.youtube.com/watch?v=68Fau_jGyG8

Courtesy of the National Meningitis Association (NMA)
Meningococcal Disease
Epidemiologic Considerations

Update on Meningococcal Disease
Proportions of the 1670 Cases of Bacterial Meningitis Reported in 2003–2007 Caused by Each Pathogen, According to Age Group.

Rate of Meningococcal Disease, by Year
United States, 1970–2011

Rates of Meningococcal Disease by Age Group and Burden of Disease, United States, Active Bacterial Core Surveillance System, 2003-2012

For more information visit: http://www.cdc.gov/abcs/index.html
Incidence of Invasive Meningococcal Disease in Massachusetts, 1988-2011
Invasive Meningococcal Disease in 5-24 Year-Olds Massachusetts, 1988-2011 and MCV4 Uptake in 13-17 Year-Olds, Massachusetts, 2006-2011

Update on Meningococcal Disease
Meningococcal Vaccines

- Conjugate vaccines
  - Menactra (MCV4-D)
    - Licensed 2005
    - Approved for use in those 9 months–55 years, IM
    - A,C,Y,W-135 conjugated to diphtheria toxoid
    - Does not require reconstitution
  - Menveo (MCV4-CRM)
    - Licensed 2010
    - Approved for use in those 2 months–55 years, IM
    - A,C,Y,W-135 conjugated to CRM197
    - Requires reconstitution
- Polysaccharide vaccine (MSPV4)
  - Licensed in 1978, for use in those ≥2 years of age, SC
  - Polysaccharide from A,C,Y,W-135
  - Requires reconstitution
Prevention and Control of Meningococcal Disease

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

APPENDIX B
Evaluation and Management of Suspected Outbreaks of Meningococcal Disease

As routine vaccination coverage among adolescents with MenACWY increases, the number of serogroup C and Y has declined (CDC, unpublished data, 2012). However, outbreaks might occur in age groups that are not routinely recommended to be vaccinated with MenACWY and deaths caused by meningococcal outbreaks can result in high levels of anxiety in a community (1). Mass vaccination might play a role protecting the population at risk during an outbreak. The decision to implement a mass vaccination campaign to prevent meningococcal disease depends on whether the occurrence of more than one case represents an outbreak or an unusual clustering of endemic disease. Because the number of cases in outbreaks is usually not substantial, this determination often requires evaluation and analysis of the patterns of disease occurrence. Mass vaccination campaigns are expensive, require a massive public health effort, and can create unwarranted concern among the public. However, mass vaccination campaigns might offer an opportunity to increase coverage in otherwise hard-to-reach populations (e.g., adolescents who have dropped out of school).

organization-based outbreaks is most useful for large organizations (e.g., universities). However, in the majority of organization-based outbreaks with three or even two cases of disease, the rate will be >10 cases/100,000 population. In such situations, public health officials might consider vaccination after only two primary cases are identified.

Attack Rate and Decision to Vaccinate

For a primary attack rate to be calculated, all confirmed cases (Box) of the same serogroup should be sumed; secondary cases should be excluded and each set of coprimary cases counted as one case. Because attack rates are calculated both to characterize the risk for disease among the general population and to determine whether overall rates have increased, related cases (secondary and coprimary) should not be included.

If three or more cases have occurred in either an organization- or a community-based outbreak during ≤3 months (starting at the time of the first confirmed or probable case), a primary attack rate should be calculated. Rate calculations should not be annualized.
Meningococcal Vaccine Recommendations

- Routine vaccination of all persons aged 11-18 years with conjugate at the earliest opportunity
- MCV4 should be used in persons 2-10 years recommended to receive meningococcal vaccine
- Conjugate vaccine may be used in persons 11-55 years, polysaccharide vaccine should be used for higher-risk persons >55 years
- Conjugate vaccine also recommended for higher-risk persons aged 19-55 years:
  - college freshmen living in dorms
  - microbiologists routinely exposed to isolates of *N. meningitidis*
  - military recruits
  - travelers to or residents in countries in which *N. meningitidis* is hyperendemic or epidemic
  - those with terminal complement component deficiency or functional or anatomic asplenia (2 doses)
  - those with HIV infection “may elect vaccination”
# Recommended Meningococcal Vaccines for Use in Children and Adults

Advisory Committee on Immunization Practices (ACIP), United States, 2012

### Table 1: Recommended Meningococcal Vaccines

<table>
<thead>
<tr>
<th>Age group</th>
<th>Vaccine</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mos–10 yrs</td>
<td>MenACWY-D* (Menactra, Sanofi)</td>
<td>Not routinely recommended; see Table 7 for persons at increased risk</td>
</tr>
<tr>
<td></td>
<td>MenACWY-CRM† (Menevo, Novartis)</td>
<td>Not routinely recommended; see Table 7 for persons at increased risk</td>
</tr>
<tr>
<td></td>
<td>HibMenCY-TT§ (MenHibrix, GSK)</td>
<td>Not routinely recommended; see Table 7 for persons at increased risk</td>
</tr>
<tr>
<td>11–21 yrs</td>
<td>MenACWY-D or MenACWY-CRM</td>
<td>Primary:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Age 11–12 yrs, 1 dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Age 13–18 yrs, 1 dose if not vaccinated previously</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Age 19–21 yrs, not routinely recommended but may be administered as</td>
</tr>
<tr>
<td></td>
<td></td>
<td>catch-up vaccination for those who have not received a dose after their</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16th birthday</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Booster:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 1 dose recommended if first dose administered before 16th birthday</td>
</tr>
<tr>
<td>22–55 yrs</td>
<td>MenACWY-D or MenACWY-CRM</td>
<td>Not routinely recommended; see Table 7 for persons at increased risk</td>
</tr>
<tr>
<td>≥56 yrs</td>
<td>MPSV4, MenACWY-D, or MenACWY-CRM</td>
<td>Not routinely recommended; see Table 7 for persons at increased risk</td>
</tr>
</tbody>
</table>

Seroprotection Rates Following MCV Vaccination

% ≥ SBA 1:128

<table>
<thead>
<tr>
<th></th>
<th>3 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>75</td>
<td>55</td>
</tr>
<tr>
<td>Y</td>
<td>86</td>
<td>94</td>
</tr>
</tbody>
</table>

Years after MCV vaccination

MMWR 2009;58(No. 37):1042-3
Booster Dose Schedule

- **Ages 11 to 18:**
  - At age 16, if primary dose at age 11 or 12 years
  - At age 16 through 18, if primary dose at age 13 through 15 years
  - No booster needed if primary dose on or after age 16 years

- **At-risk, ages 2 to 55:**
  - Persons aged 2 through 6 years: after 3 years
  - Persons aged 7 years or older: after 5 years

Update on Meningococcal Disease
MenACYW Immunization Rates in U.S. Teens (11-15, 13-17 years old) National Immunization Survey (CDC)

Update on Meningococcal Disease
Distribution of Meningococcal Serogroups Among Invasive Meningococcal Disease Cases Reported in Massachusetts, 1988-2011 (% Serogrouped)

Shifting *Neisseria meningitidis* Serogroups Causing Invasive Disease Massachusetts, 1994-2011

1994-1999
- B: 27%
- Y: 32%
- C: 37%

2000-2005
- B: 28%
- Y: 28%
- C: 30%

2006-2011
- B: 39%
- Y: 41%
- C: 11%

Update on Meningococcal Disease
New vaccines on the horizon
Cross-Sectional View of the Cell Membrane

- **Capsule (serogroup)**
  - 13 types
  - 6 cause most disease globally (A, B, C, W, X, and Y)
  - Target for conjugate vaccines

- **Outer-membrane proteins**
  - Target for serogroup B vaccines
No MenB Vaccine Licensed in the US

- **Novartis:** Bexsero®, Recombinant MenB+OMV NZ (rMenB) Vaccine licensed in Europe, Australia and Canada in 2013
  - 2 dose series in adolescents
  - Contains 4 antigenic components (fHBP, NHBA, NadA, PorA)
  - Used in response to two outbreaks under a CDC-sponsored IND

- **Pfizer:** MenB vaccine currently in development
  - 3 dose series in adolescents
  - Contains 2 fHBP antigens
- Provide broad protection against multiple MenB strains
- Vaccines have received FDA Breakthrough Therapy designation
Process for Procuring rMenB Vaccine Under an Investigational New Drug (IND) Protocol

- **Initial proposal to FDA**
  - Generic proposal with background on MenB outbreaks, rationale for use of MenB vaccine, and specific questions for FDA

- **Official submission of IND protocol**
  - Testing of isolate by Novartis for vaccine antigen matching
  - Epidemiologic investigation to define eligible population for vaccination
  - Consents, vaccine information sheets, data collection instruments developed

- **CDC Institutional Review Board approval and FDA Safe-to-Proceed letter issued**

- **Contractual agreements finalized between CDC, Novartis and Princeton University**
Safety Follow-Up

- Mandatory reporting of all serious adverse events (SAEs) to FDA
  - Include death, a life-threatening adverse event (AE), hospitalizations, substantial disruption in the ability to conduct normal life functions, or a congenital anomaly/birth defect

- To date, rate of SAEs reported is 2.0/1,000 vaccinees at Princeton University
  - One SAE determined to be “possibly related” to rMenB

- No concerning patterns among other types of AEs reported

- No cases of MenB among vaccinated persons
Challenges

- IND preparation process and vaccine procurement process takes time
- Unable to determine when additional cases may occur
- Need for clear guidance about when to initiate process
Clinical Presentation

- “Flu-like” illness
  - Fever
  - Headache
  - Sore throat
  - Coryza
  - Nausea/vomiting
  - Myalgias
  - Meningismus
  - Altered mental status

“Classic triad” occurs in only 25% of patients with meningococcal meningitis as compared to over half of patients with pneumococcal meningitis.
Meningococcal associated rash
Meningococcal Disease

- **Meningococcal rash**
  - Rash may be initially pink and blanching and on the trunk and extremities
  - Progressing to erythematous/violaceous and non-blanching
  - Petechiae typically seen initially on ankles, wrists, axillae, mucosal surfaces and conjunctivae and then spreading
<table>
<thead>
<tr>
<th>Rapidly progressive cases</th>
<th>Subset of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>• DIC</td>
<td>• Cutaneous hemorrhage</td>
</tr>
<tr>
<td>• Multi-organ failure</td>
<td>• Purpura fulminans</td>
</tr>
<tr>
<td>• Septic shock</td>
<td></td>
</tr>
</tbody>
</table>
N. meningitidis on throat culture
Transfer of care, office to hospital

- **KEY POINT:** Parenteral antibiotics must be started as soon as possible.
  - Evidence of pre-hospital antibiotics is inconclusive.
Pre-admission antibiotics for suspected cases of meningococcal disease (Review)

Sudarsanam TD, Rupali P, Tharyan P, Abraham OC, Thomas K

Authors’ conclusions

We found no reliable evidence to support or refute the use of pre-admission antibiotics for suspected cases of non-severe meningococcal disease. Evidence of moderate quality from one RCT indicated that single intramuscular injections of ceftriaxone and long-acting chloramphenicol were equally effective, safe and economical in reducing serious outcomes. The choice between these antibiotics would be based on affordability, availability and patterns of antibiotic resistance.

Further RCTs comparing different pre-admission antibiotics, accompanied by intensive supportive measures, are ethically justifiable in participants with severe illness, and are needed to provide reliable evidence in different clinical settings.
Administer pre-hospital antibiotics if...

- Urgent transfer to hospital is not possible
- Presence of “red flag” symptoms...
  - Early signs of shock
  - Altered mental status, tachycardia or labored breathing
  - Petechial or rapidly evolving rash
  - Hypotension in a patient with suspected meningitis
- Recent outbreaks in the community may warrant consideration of pre-hospital antibiotics

Update on Meningococcal Disease
Transfer with droplet precautions

Update on Meningococcal Disease
Notify the transfer facility!
Initial workup and diagnosis

- Focus physical on hemodynamic stability, neurological findings, mental status and skin examination
- Cultures of oropharynx and blood
- Examination of CSF with culture
  - Antigen testing can be performed even if antibiotics have been started
  - Do not delay treatment while awaiting culture results
Antibiotic choice

- Ceftriaxone 2 g IV q 12 hours
- Fluoroquinolones may be considered in the case of severe beta-lactam allergy, but consult with Infectious Disease before making this choice
Practice Guidelines for the Management of Bacterial Meningitis

Allan R. Tunkel,1 Barry J. Hartman,2 Sheldon L. Kaplan,3 Bruce A. Kaufman,4 Karen L. Roos,5 W. Michael Scheld,6 and Richard J. Whitley7

1Drexel University College of Medicine, Philadelphia, Pennsylvania; 2Weill Cornell Medical Center, New York, New York; 3Baylor College of Medicine, Houston, Texas; 4Medical College of Wisconsin, Milwaukee; 5Indiana University School of Medicine, Indianapolis; 6University of Virginia School of Medicine, Charlottesville; and 7University of Alabama at Birmingham

OBJECTIVES

The objective of these practice guidelines is to provide clinicians with recommendations for the diagnosis and treatment of bacterial meningitis. Patients with bacterial meningitis are usually treated by primary care and emergency medicine physicians at the time of initial presentation, often in consultation with infectious diseases specialists, neurologists, and neurosurgeons. In contrast to many other infectious diseases, the antimicrobial therapy for bacterial meningitis is not always based on randomized, prospective, double-blind clinical trials, but rather on data initially obtained from

In this guideline, we will review our recommendations for the diagnosis and management of bacterial meningitis. Recommendation categories are shown in table 1. The guideline represents data published through May 2004.

INITIAL MANAGEMENT APPROACH

The initial treatment approach to the patient with suspected acute bacterial meningitis depends on early recognition of the meningitis syndrome, rapid diagnostic evaluation, and emergent antimicrobial and adjunctive therapy [1]. Our management algorithm for infants and
Outcomes
### Case-Fatality Ratio by Serogroup and Age-Group, United States, 1997-2011

<table>
<thead>
<tr>
<th>Serogroup</th>
<th>&lt;5 years</th>
<th>5-10 years</th>
<th>11-19 years</th>
<th>20 years</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>4%</td>
<td>22%</td>
<td>15%</td>
<td>23%</td>
<td>13%</td>
</tr>
<tr>
<td>C</td>
<td>13%</td>
<td>9%</td>
<td>12%</td>
<td>16%</td>
<td>13%</td>
</tr>
<tr>
<td>Y</td>
<td>0%</td>
<td>13%</td>
<td>13%</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>W</td>
<td>&lt;1%</td>
<td>0%</td>
<td>0%</td>
<td>10%</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>5%</strong></td>
<td><strong>12%</strong></td>
<td><strong>15%</strong></td>
<td><strong>15%</strong></td>
<td><strong>12%</strong></td>
</tr>
</tbody>
</table>

ABCs cases from 1997-2011 estimated to the US population
Prophylaxis and control measures
Chemoprophylaxis of Close Contacts

- **Close contacts include:**
  - Household members, daycare center classmates, and teachers
  - Anyone directly exposed to oral secretions

- **Treat as soon as possible**

- **Secondary cases rare**
<table>
<thead>
<tr>
<th>Drug</th>
<th>Age group</th>
<th>Dosage</th>
<th>Duration and route of administration*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin†</td>
<td>Children aged &lt;1 mo</td>
<td>5 mg/kg every 12 hrs</td>
<td>2 days</td>
</tr>
<tr>
<td></td>
<td>Children aged ≥1 mo</td>
<td>10 mg/kg every 12 hrs</td>
<td>2 days</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>600 mg every 12 hrs</td>
<td>2 days</td>
</tr>
<tr>
<td>Ciprofloxacin§</td>
<td>Adults</td>
<td>500 mg</td>
<td>Single dose</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Children age &lt;15 yrs</td>
<td>125 mg</td>
<td>Single IM dose</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Adults</td>
<td>250 mg</td>
<td>Single IM dose</td>
</tr>
</tbody>
</table>
Control of an Outbreak

- Define vaccination group
- Protective antibodies in 7-10 days
- High vaccine coverage necessary
- Mass chemoprophylaxis not effective in most settings
- Community and physician education
Decision to vaccinate

- Vaccination should be considered if the attack rate is >10 cases/100,000
  - Majority of organization-based outbreaks with 2-3 cases will have an attack rate above the threshold to vaccinate, thus vaccination may be considered after only 2 cases identified

- In organization based outbreaks the vaccination group usually includes the whole population at risk, and potentially even persons outside of the population at risk
Other control measures

- Mass chemoprophylaxis not recommended to control large outbreaks, as often impractical and unlikely to succeed
  - May be considered in some cases, such as outbreaks involving limited populations, particularly serogroup B outbreaks

- If mass chemoprophylaxis is undertaken, should be administered to all targeted persons at same time

- Interventions not recommended: restricting travel to outbreak areas, closing schools, canceling events

- Educating communities, physicians, and other health-care personnel is important and should be initiated as soon as an outbreak is suspected