Hot Topics in Pediatric Infectious Diseases

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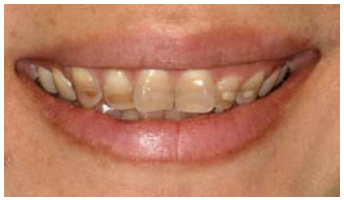
Conflict of Interest Disclosure Slide

In the past 2 years I have been an employee of	**University of Alberta**
In the past 2 years I have been a consultant for	my children only, and by the way, they never take my advice
In the past 2 years I have held investments in the following pharmaceutical organizations, medical devices companies or communications firms	none
In the past 2 years I have been a member of the Scientific advisory board for	none
In the past 2 years I have been a speaker for	no one who paid me
In the past 2 years I have received research support (grants) from	Pfizer, NIH
In the past 2 years I have received honoraria from	no one
I agree to disclose approved and non-approved indications for medications in this presentation.	YES
I agree to use generic names of medications in this presentation.	YES

Macrolide resistant *Mycoplasma pneumoniae* (MRMP) – Do we need to think about it?

- Widespread in Asia (>90% in some studies of outbreaks) with increasing reports from Europe and US
- Usually due to a mutation in V domain of 23S rRNA gene
- 11/96 *Mycoplasma pneumoniae* strains from Public Health Ontario Lab (11%) were MRMP (Eshagi S et al. Macrolide-resistant Mycoplasma pneumoniae in humans, Ontario, Canada, 2010-2011. Emerg Infect Dis 2013; 19:1525-8)
- Resistance is especially a concern in young children as quinolones  and tetracyclines  contraindicated.

But do antibiotics hasten the resolution of *Mycoplasma pneumoniae* anyway?

235 children hospitalized in China with pneumonia due to *Mycoplasma* - All treated with macrolides alone and all recovered. (Zhou Y et al. More Complications Occur in Macrolide-Resistant than in Macrolide-Sensitive Mycoplasma pneumoniae Pneumonia. Antimicrob Agents Chemother 2014; 58:1034-8)

Statistically significant results:

	MP susceptible to macrolides (N=29)	MP resistant to macrolides (N=206)
Severe pneumonia (British Thoracic Society definition)	**1 (3%)**	**38 (18%)**
Opacification > 1/3 of lung	**12 (41%)**	**127 (62%)**
Median days of fever after macrolide started	**3**	**5**
Median days in hospital	**6**	**8**
Extrapulmonary complications	**3 (10%)**	**61 (30%)**

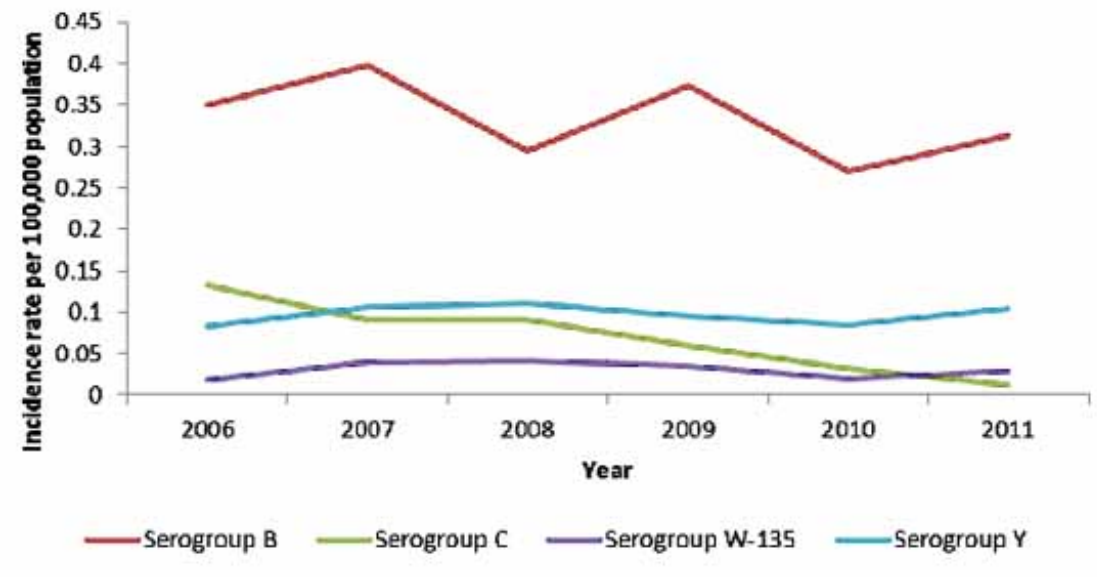
Does choice of antibiotic matter for MRMP?

Okada T et al. Rapid effectiveness of minocycline or doxycycline against macrolide-resistant Mycoplasma pneumoniae infection in a 2011 outbreak among Japanese children. Clin Infect Dis 2012; 55:642

176/202 (87%) MRMP – Observational study - Those with MRMP who received tetracyclines as secondary therapy defervesced faster and had a more dramatic drop in NPS bacterial load than did those who received quinolones or those who continued on macrolides ($p<0.05$).

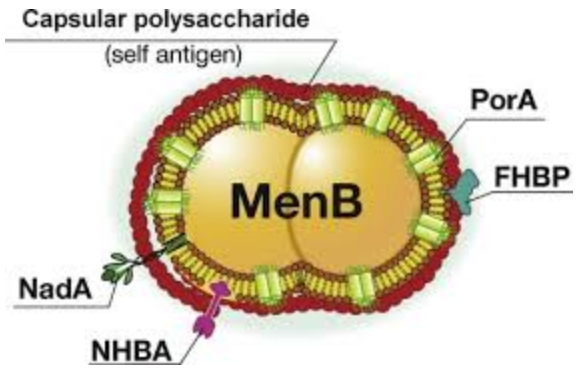
Some of the children we see with pneumonia who are slow to respond to therapy have MRMP, but their outcomes are likely to be good even if we are not smart enough to think of that possibility. Tetracyclines may be more effective than quinolones for MRMP.

What's new with meningococcal vaccines in Canada?



So where are we with a vaccine for serogroup B?

- The 4-component vaccine 4CMenB or Bexsero (contains the sub-capsular proteins neisserial heparin-finding antigen, factor H-binding protein, neisserial adhesion A and Por A) was licensed in Canada in Dec 2013 for ages 2 months through 17 years and became available Feb 2014 at a cost of $101/dose.



- Good initial immunogenicity has been established after 3 doses in the first 6 months of life, 2 doses at 12-15 months of age, or 2 doses at 11-17 years of age or in adulthood

US post-secondary outbreaks of meningococcal serogroup B infection

- Decided to use 4CMenB despite the vaccine not being approved in US:
  - 9 cases starting March 2013 at Princeton University and 4 cases in Nov 2013 at University of California, Santa Barbara

What is the new evidence on 4CMenB efficacy ?

- The Meningococcal antigen testing system (MATS) is an in-vitro ELISA assay used to see if Men B strains have at least one of the four vaccine antigens in sufficient quantity that vaccine-induced antibodies would be predicted to protect against that strain.
- This was the case for 66% of recently circulating B strains in Canada (but only 49% in children <1 year of age) (Bettinger JA et al. Diversity of Canadian meningococcal serogroup B isolates and estimated coverage by an investigational meningococcal serogroup B vaccine (4CMenB). Vaccine 2013; 32:124-30) versus 70% in the UK and 91% in US.

What is the new evidence on 4CMenB efficacy ?

- A study from the UK showed that even though MATS predicted coverage for only 70% of the strains tested, human serum bactericidal antibody assay with human complement (the surrogate correlate of protection for meningococcal disease) predicted 88% coverage.

Frosi G et al. Bactericidal antibody against a representative epidemiological meningococcal serogroup B panel confirms that MATS underestimates 4CMenB vaccine strain coverage. Vaccine 2013; 31:4968-74

What is the new evidence on the duration of protection with 4CMenB?

Snape M et al. Persistence of bactericidal antibodies following early infant vaccination with a serogroup B meningococcal vaccine and immunogenicity of a preschool booster dose. CMAJ 2013; 185: E715-24

- A dose was given at 40 to 44 months of age to children with various previous immunization schedules.
- For each of the 4 components, the range of presumed adequate titres **prior to the booster** was from 41% to 76% for those immunized at 2, 4, 6, and 12 months, from 0 to 38% for those immunized with one dose at 12 months and from 0 to 65% in controls.

Anamnestic response noted with the booster

Conclusion

Does 4CMenB alter the incidence of meningococcal carriage?

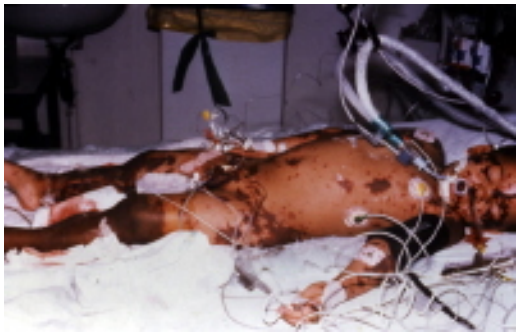
There was only a 16.5% (95% CI 1.5 to 29.2) decline in carriage rates in immunized university students in the UK.

(Read RC, Baxter D, Chadwick DR, et al. Impact of a quadrivalent conjugate (MENACWY-CRM) or a serogroup B (4CMENB) meningococcal vaccine on meningococcal carriage in English university students. Abstract 1472. European Society for Paediatric Infectious Disease Annual Conference. Milan, May 28 to June 1, 2013)

Using MATS, it appears that 4CMen B may also work for serogroup X, which is possibly increasing in incidence in the meningitis belt in Africa

(Hong E. Could the multicomponent meningococcal serogroup B vaccine (4CMenB) control Neisseria meningitidis capsular group X outbreaks in Africa? Vaccine 2013; 31:1113-6)

What should we do in Canada with 4CMenB?



What did NACI say?

Immunization of individuals (≥2 months of age) should be considered under the following circumstances:

1. If they are at high risk of meningococcal disease
2. If they have been in close contact with a case of invasive meningococcal disease caused by serogroup B
3. If they are at risk during outbreaks caused by serogroup B or the emergence of hyperendemic and/or hypervirulent *N. meningitidis* strains that are predicted to be susceptible to the vaccine based on MATS testing.

Encephalitis in Children

MAJOR ARTICLE

Case Definitions, Diagnostic Algorithms, and Priorities in Encephalitis: Consensus Statement of the International Encephalitis Consortium

A. Venkatesan,[1] A. R. Tunkel,[2] K. C. Bloch,[3,4] A. S. Lauring,[5] J. Sejvar,[6] A. Bitnun,[7] J-P. Stahl,[8] A. Mailles,[9] M. Drebot,[10] C. E. Rupprecht,[11] J. Yoder,[12] J. R. Cope,[12] M. R. Wilson,[13,14] R. J. Whitley,[15,16,17,18] J. Sullivan,[19] J. Granerod,[20] C. Jones,[21,22] K. Eastwood,[23] K. N. Ward,[20,24] D. N. Durrheim,[25,26] M. V. Solbrig,[27] L. Guo-Dong,[28] and C. A. Glaser,[29] on behalf of the International Encephalitis Consortium

Clin Infect Dis. 2013 Oct;57(8):1114-28.

Table 1. Diagnostic Criteria for Encephalitis and Encephalopathy of Presumed Infectious or Autoimmune Etiology

Major Criterion (required):
Patients presenting to medical attention with altered mental status (defined as decreased or altered level of consciousness, lethargy or personality change) lasting ≥24 h with no alternative cause identified.
Minor Criteria (2 required for possible encephalitis; ≥3 required for probable or confirmed[a] encephalitis):
Documented fever ≥38° C (100.4°F) within the 72 h before or after presentation[b]
Generalized or partial seizures not fully attributable to a preexisting seizure disorder[c]
New onset of focal neurologic findings
CSF WBC count ≥5/cubic mm[d]
Abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new from prior studies or appears acute in onset[e]
Abnormality on electroencephalography that is consistent with encephalitis and not attributable to another cause.[f]

Table 3. Diagnostic Algorithm for Initial Evaluation of Encephalitis in Children[a]

ROUTINE STUDIES
CSF[b]
Collect at least 5 cc fluid, if possible; freeze unused fluid for additional testing
Opening pressure, WBC count with differential, RBC count, protein, glucose
Gram stain and bacterial culture
HSV-1/2 PCR (if test available, consider HSV CSF IgG and IgM in addition)
Enterovirus PCR
SERUM
Routine blood cultures
EBV serology (VCA IgG and IgM and EBNA IgG)
Mycoplasma pneumoniae IgM and IgG
Hold acute serum and collect convalescent serum 10–14 d later for paired antibody testing
IMAGING
Neuroimaging (MRI preferred to CT, if available)
NEUROPHYSIOLOGY
EEG
OTHER TISSUES/FLUIDS
Mycoplasma pneumoniae PCR from throat sample
Enterovirus PCR and/or culture of throat and stool
When clinical features of extra-CNS involvement are present, we recommend additional testing (eg, biopsy of skin lesions; bronchoalveolar lavage and/or endobronchial biopsy in those with pneumonia/pulmonary lesions; throat swab PCR/culture in those with upper respiratory illness; stool culture in those with diarrhea); also see below
CONDITIONAL STUDIES
HOST FACTORS
Age <3 y—Parechovirus PCR (CSF)
Immunocompromised—CMV PCR, HHV6/7 PCR, HIV PCR (CSF); cryptococcal antigen; *Toxoplasma gondii* serology and/or PCR; MTB testing[c]; fungal testing[d]; WNV testing[e]
GEOGRAPHIC FACTORS
Africa—malaria (blood smear); trypanosomiasis (blood/CSF smear, serology from serum and CSF); dengue testing[e]
Asia—Japanese Encephalitis Virus testing[e]; dengue testing[e]; malaria (blood smear); Nipah virus testing (serology from serum and CSF; PCR, immunohistochemistry, and virus isolation in a BSL4 lab can also be used to substantiate diagnosis)
Australia—Murray Valley encephalitis virus testing[e]; Kunjin virus testing[e], Australian Bat Lyssavirus (ABLV) testing[f]
Europe—Tick-borne Encephalitis Virus (serology); if Southern Europe, consider WNV testing[e], Toscana virus testing[e]
Central and South America—dengue testing[e]; malaria (blood smear)
North America—Geographically—appropriate arboviral testing (eg, WNV, Powassan, LaCrosse, Eastern Equine Encephalitis viruses,[e] Lyme (serum ELISA and Western blot)
SEASON AND EXPOSURE
Summer/Fall: Arbovirus[e] and tick-borne disease[g] testing
Cat (particularly if with seizures, paucicellular CSF)—Bartonella antibody (serum), ophthalmologic evaluation
Tick exposure– Tick borne disease testing[g]
Animal bite/bat exposure—rabies testing[f]
Swimming or diving in warm freshwater or nasal/sinus irrigation– *Naegleria fowleri* (CSF wet mount and PCR[h])
SPECIFIC SIGNS AND SYMPTOMS
Abnormal behavior (eg, new onset temper tantrums, agitation, aggression), psychotic features, seizures or movement disorder–NMDAR antibody (serum, CSF), oligoclonal bands, IgG index, rabies testing[f]
Behavior changes followed by myoclonic spasms/jerks: measles IgG (CSF and serum)
Vesicular rash—VZV PCR from CSF (sensitivity may be low; if test available, consider CSF IgG and IgM); VZV IgG and IgM from serum
Rapid decompensation (particularly with animal bite history or prior travel to rabies-endemic areas)—rabies testing[f]
Respiratory symptoms—chest imaging (chest X-ray and/or CT scan); respiratory virus testing[i]; *Mycoplasma pneumoniae* PCR (CSF)
Acute flaccid paralysis—Arbovirus testing[e]; rabies testing[f]
Parkinsonism –Arbovirus testing[e]; Toxoplasma serology
Nonhealing skin lesions—*Balamuthia, Acanthamoeba* testing[h]
Prominent limbic symptoms—Autoimmune limbic encephalitis testing[j], HHV6/7 PCR (CSF)

Clin Infect Dis. 2013 Oct;57(8):1114-28.

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis

- Second only to acute demyelinating encephalomyelitis (ADEM) as an autoimmune cause of encephalitis
- Initially described in women with ovarian teratomas in 2005
- Combining all age groups, about 80% are female and about 40% have a neoplasm
- However, only 60% of those < 12 years of age are female and <10% in this age group have a neoplasm
- Worth making the diagnosis (by looking for NMDAR antibodies in CSF or blood) as immunotherapy may hasten improvement – about 80% of children and adults have a good outcome at 24 months

(Titulaer M et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 2013; 12:157-656)

Clues to the diagnosis of anti-NMDA-receptor encephalitis

- Adults often present with psychiatric symptoms but 50% of children present with movement disorders or seizures (Titulaer M et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 2013; 12:157-656)
- Hyperkinetic movement disorder in 85%+ of pediatric cases (Baizabel-Carvallo JF et al. The spectrum of movement disorders in children with anti-NMDA receptor encephalitis. Mov Disord 2013; 28:543-7)
- Hypoventilation less common in children than in adults

Is there a relationship between anti-NMDAR and herpes simplex encephalitis?

ANNALS of Neurology

AN OFFICIAL JOURNAL OF THE AMERICAN NEUROLOGICAL ASSOCIATION AND THE CHILD NEUROLOGY SOCIETY

Original Article

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N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis

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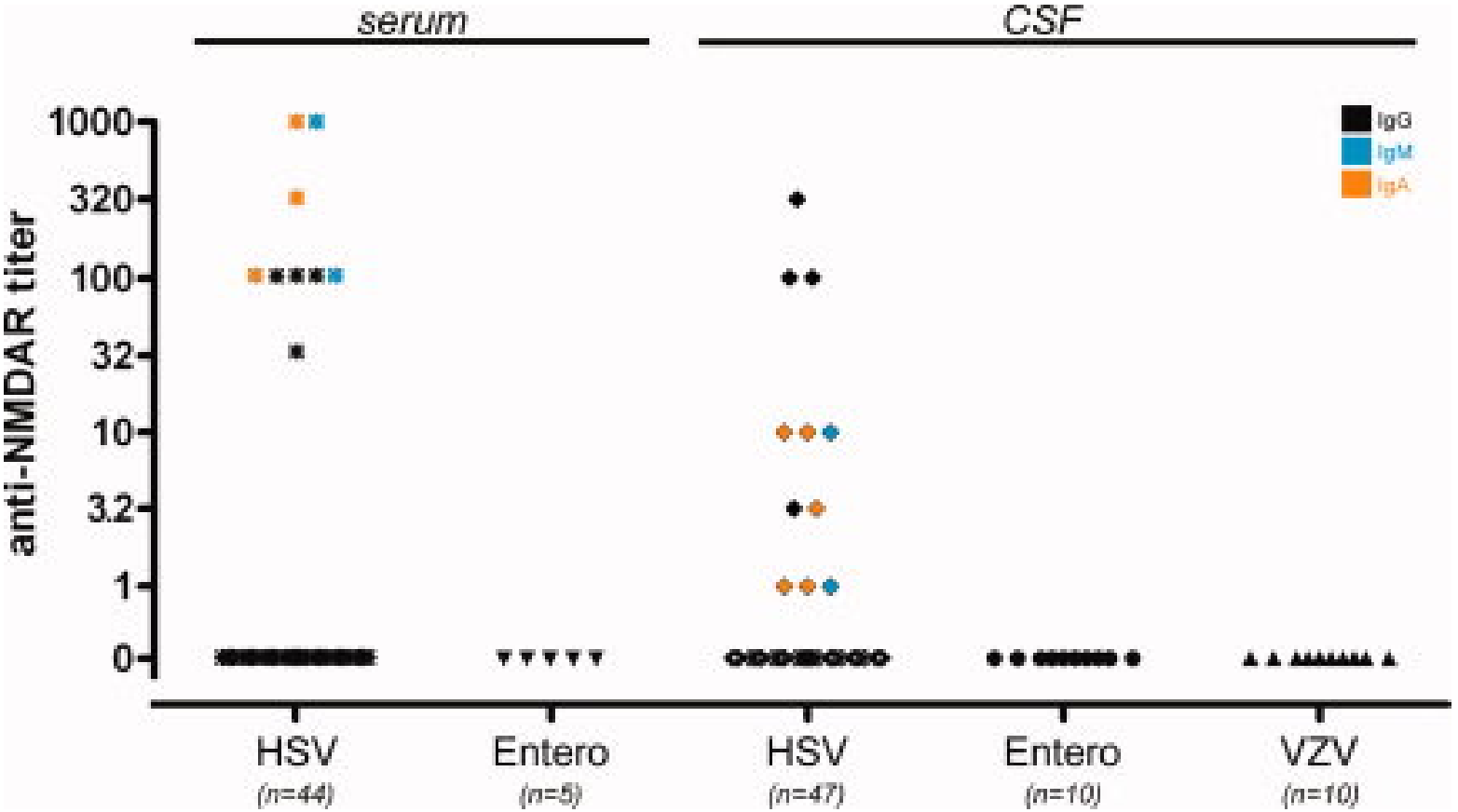
N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis



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http://onlinelibrary.wiley.com/doi/10.1002/ana.23689/full#fig4

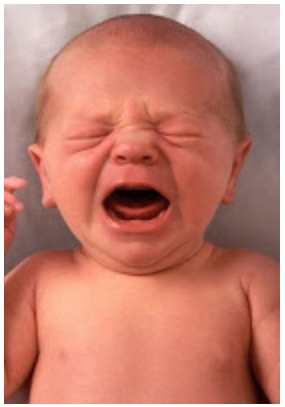
NMDAR antibodies detected in "recurrence" of HSV encephalitis:

- *Leypoldt F et al.* Herpes simplex virus-1 encephalitis can trigger anti-NMDA receptor encephalitis: case report. Neurology 2013; 81:1637 **= 1 adult**
- *Desena A et al.* Herpes simplex encephalitis as a potential cause of Anti-N-methyl-d-aspartate receptor antibody encephalitis: Report of 2 cases. JAMA Neurol 2014; ePub **= 1 infant and 1 adult**
- *Armangue T et al.* Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. J Pediatr 2013; 162: 850-6 **= 1 child**

Two possibilities:

- Some cases of HSV encephalitis and some apparent recurrences are related to NMDAR encephalitis so may respond to immunotherapy.

- NMDAR antibodies are non-specific.



Why do infants < 90 days of age with pyelonephritis commonly have CSF pleocytosis? Could the problem be a concomitant viral infection?

- 1% to 2% of infants < 90 days of age with UTI also have bacterial meningitis
- Sterile pleocytosis in infants with UTI was first described in 2001 (Finkelstien Y et al. Concomitant aseptic meningitis and bacterial urinary tract infection in young febrile infants. PIDJ 2001;20:630-2) and occurs in 5 to 18% of cases (depending how pleocytosis is defined)
- This creates a diagnostic dilemma if an LP is performed after the infant received antibiotics.

Retrospective study from Utah looked at infants < 90 days of age with a UTI (defined as ≥ 5 X 10^7 cfu/L of at least one pathogenic organism) who had CSF enterovirus (EV) PCR testing performed

- 162 infants (mean 36 days old) fit the criteria.
  - 57 had CSF pleocytosis (defined as >18 WBCs in first 28 days of life or > 9 WBC/HPF after that):
    - 16 bloody taps excluded (1 had EV)
    - 1 had definite *E. coli* meningitis and 3 others were treated for *E. coli* meningitis
    - **37 (23%) had sterile pleocytosis**
      - **4 had EV (median 387 cells/µL; interquartile range 151–965)**
      - **33 were EV negative (median 21 cells/µL; interquartile range 12–28)**

Doby EH et al. Cerebrospinal fluid pleocytosis in febrile infants 1-90 days with urinary tract infection. PIDJ 2013;32:1024

EV is not the usual cause of sterile CSF pleocytosis in infant with UTIs

What are other theories as to why CSF pleocytosis occurs with infant UTIs?

1) Venous drainage of the urogenital system results in inflammation in the subarachnoid space.
2) The pleocytosis is due to systemic inflammation and cytokine release.
3) We should be looking for a different virus

How can one avoid the diagnostic dilemma?

- You have to decide at the initial assessment if the infant needs an LP.
- One should only do an LP after antibiotics if there is a new clinical indication – not just because the infant has documented bacteremia. After all, infants with UTIs were probably all bacteremic at some point.

How long should community-acquired pneumonia (CAP) be treated with antibiotics?

- No previous randomized trials in children other than those done in developing countries, often in children with no CXR
- Double-blind randomized trial in Israel of outpatients 6-59 months old with alveolar pneumonia on CXR, fever and WBC > 15,000/mm3

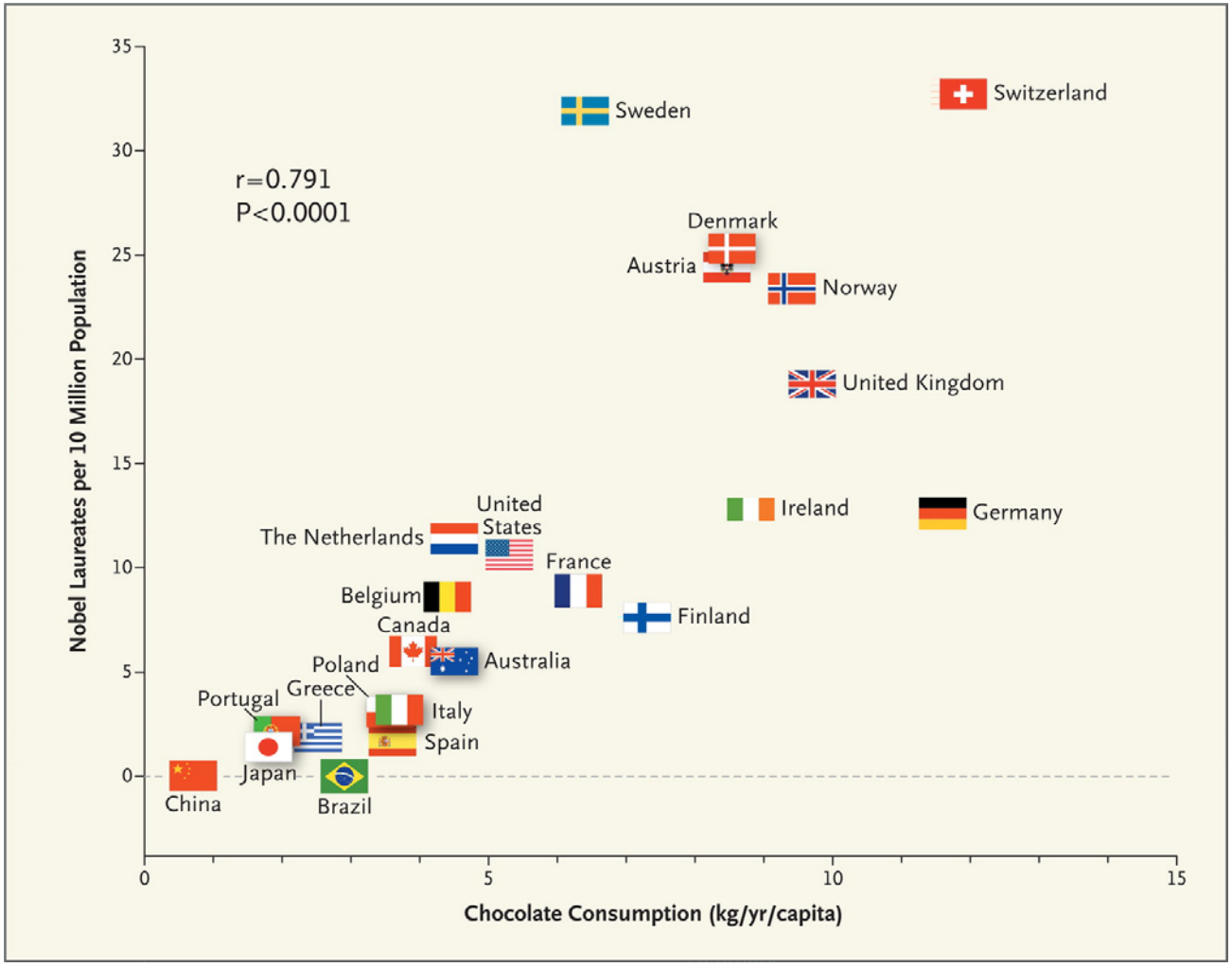
  (Greenberg D et al. Short-course Antibiotic Treatment for Community-acquired Alveolar Pneumonia in Ambulatory Children: A Double-blind, Randomized, Placebo-controlled Trial. PIDJ 2014; 33:136-42)

  - **10 children received 3 days amoxicillin – 4 failures**
  - **42 children received 5 days and 56 children received 10 days amoxicillin – 0 failures**

Vancomycin levels in children

- Trough of 15-20 mcg/mL required in adults to attain an AUC/MIC > 400 for MRSA with MIC=1
- Study showed that with 15 mg/kg q6H dosing, a trough of 7-10 mcg/mL usually achieves this same AUC/MIC in children (Frymoyer A et al. Desired vancomycin trough serum concentration for treating invasive methicillin-resistant Staphylococcal infections. PIDJ 2013; 32:1077-9.)
- Those who know more than I do debate which formula to use for creatinine clearance in children, which alters the AUC (Chhim RF et al. Vancomycin dosing practices, trough concentrations, and predicted area under the curve in children with suspected invasive staphylcocccal infections. JPIDS 2013;2:292)
- Benefits of measuring vancomycin levels in children who presumably have normal renal function remain unproven

Correlation between Countries' Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population



Messerli FH. N Engl J Med 2012;367:1562-1564.

Clostridium difficile infection (CDI) – How are children different?

- Complications are rare
  - Retrospective study from SickKids 2008-2012 (Schwartz KL et al. Severe clinical outcome is uncommon in Clostridium difficile infection in children: a retrospective cohort study. BMC Pediatrics 2014; 14:28)
  - 299 cases (26% community-associated) – 8.3/10,000 patient days with no change over time
  - 40% had malignancy – 10% had IBD
  - 17% relapse rate
  - 5 ICU admissions due to CDI – one death post-HSCT but also had *Enterobacter* sepsis – no colectomies
  - 11% NAP1; 24% NAP4 – more relapses with NAP4

Before we congratulate ourselves on solving the meningococcal serogroup C problem with our infant vaccine programs, we need to consider that US graphs look similar and they have only ever had routine adolescent programs.

How many cases of invasive meningococcal disease are we actually talking about?

- There were a mean of 194 cases per year in Canada 2007-2011.
- A mean of 111 of these were serogroup B of which a mean of 22 cases were in children < 1 year of age and 21 cases were in children 1 through 4 years of age.

(National Microbiology Laboratory and Centre for Immunization and Respiratory Infectious Diseases - Public Health Agency of Canada. National Enhanced Invasive Meningococcal Disease Surveillance System)