European Society for Paediatric Infectious Disease Conference Review

Making Education Easy

4–8 May 2010 Nice, France

In this issue:

Welcome to our review of the 28th Annual Meeting of the European Society for Paediatric Infectious Disease (ESPID) held in Nice, France in early May 2010.

ESPID forms the basis for European investigators interested in infectious diseases in children and infection prevention in childhood. Annual ESPID meetings offer the latest information on epidemiology, diagnosis, prevention, treatment, and clinical presentation of important paediatric diseases. The following abstracts from ESPID were selected and reviewed by Emma Best (Paediatric Infectious Diseases Consultant at Starship Children's Hospital and Senior Lecturer in Infectious Diseases in the Department of Molecular Medicine, University of Auckland), Neil Poskitt (Rotorua GP and Clinical Leader in Child Health for the Rotorua Area Primary Health Service), Elizabeth Wilson (Paediatric Infectious Diseases Consultant at Starship Children's Hospital) and Sharon Wong (General Paediatrician at Waitemata DHB and Honorary Clinical Senior Lecturer, Department of Paediatrics: Child and Youth Health, University of Auckland). We hope you find them interesting.

Kind regards,

Dr Chris Tofield
Medical Advisor, Research Review
christofield@researchreview.co.nz

Prevention and therapy of Group B streptococcus

Prevention and therapy of perinatal group B streptococcal infection: can we do more?

Presenters: L Weisman and Alison Bedford Russell

Comment: Group B streptococcus, also known as *Streptococcus agalactiae* infection remains a leading cause of neonatal morbidity and mortality. Universal prenatal screening of women at 35-37 weeks for vaginal and rectal GBS and subsequent intrapartum antibiotics has been effective in reducing early onset neonatal GBS infection by 65% and maternal GBS sepsis by 21%. However failure of this screening process still occurs. A US study of 4696 pregnant women was presented. Seventy seven percent had prenatal swabs taken. Of those with a GBS positive prenatal swab only 50% were still GBS positive at delivery. Of those with a negative prenatal swab, 8% were GBS positive at time of delivery. Eighty-two percent of cases of neonatal GBS infection came from women who were GBS negative on prenatal swabs. No prevention strategy is 100% effective nor is a vaccine imminent. CDC guideline revisions are pending. *NP*

Febrile illness in children without apparent source

Children with fever: challenges for paediatricians and methodologists

Authors: Oostenbrink R

Summary: Children presenting to an emergency department with fever pose a diagnostic challenge because their fever may be symptomatic of a number of illnesses, ranging from a self-limiting viral disease through to a life-threatening infection. We therefore need discriminators for presence or absence of serious conditions to help triage patients when they present. Several prediction rules have been developed for children with fever, but validation studies have shown limited results. Several issues therefore need to be addressed to successfully proceed with diagnostic research in children suspected of serious infections. [1232]

Diagnostic value of symptoms and signs in assessing the risk for serious bacterial infections in children with fever without source

Authors: Thompson M et al

Summary: This abstract reported the findings of 2 studies of the diagnostic value of symptoms and vital signs in children with acute infection. A primary care study compared the symptoms of 924 children with acute infection with existing data on symptoms in 345 children with meningococcal disease. This study found that symptoms of leg pain, cold extremities, photophobia, neck pain/stiffness, confusion and rash were all highly specific for meningococcal disease. A cohort study of 700 children presenting to a paediatric assessment unit found that 1 or more of temperature ≥ 39˚C, saturations ≤ 94%, tachycardia and tachypnoea was 80% sensitive and 39% specific for serious or intermediate infection. In conclusion, some key symptoms should be diagnostic `red flags' for clinicians in acute paediatric settings. [1233]

Comment: The early recognition of the signs and symptoms associated with sepsis requires a thorough history and examination. Vital signs including temperature, heart rate, respiratory rate and oxygen saturations should always be evaluated in a child in whom a serious bacterial infection is included in the differential diagnosis. In New Zealand clinicians must still remain vigilant despite the decline in meningococcal disease following the meningococcal serogroup B vaccination campaign, as the classic features of disease often develop late in the illness. This session highlighted the importance of obtaining basic clinical information to aid decision making. *SW*

Interpretation of a single laboratory test to discriminate between viral and bacterial infections in children with fever without source?

Authors: Gervais A

Summary: Although most children who present to the ED or paediatrician with fever have benign and self-limiting illness, a few are at risk for developing a severe bacterial infection such as bacteraemia, meningitis or pyelonephritis. Signs and symptoms of severe bacterial illness are often nonspecific so laboratory blood markers of infection should be used. There is no single test that can discriminate between viral and bacterial infections so combinations of clinical and laboratory criteria are needed. Regardless of which laboratory or clinical marker is used, it's sensitivity and specificity to a specific disease is important. The likelihood ratio (LR) combines the sensitivity and the specificity of a test, and improves the estimated risk of having a particular disease. The higher the LR, the higher the probability of having the disease. [1280]

Comment: No single laboratory test can distinguish between viral and bacterial infections. The clinical context determines the usefulness of different tests. However, in terms of ruling out serious bacterial infection the most useful tests are procalcitonin (PCT) followed by C-reactive protein (CRP) followed by white blood cell count. *NP*

Development and validation of clinical prediction rules in children with fever without source

Authors: Chalumeau M et al

Summary: No single test offers high sensitivity and specificity for distinguishing between viral and bacterial infections in children presenting with fever. Therefore, `clinical prediction rules' that combine clinical and laboratory criteria have been developed by various groups. The rules must be developed according to standards proposed by the Evidence Based Medicine Working Group and need to consider the following: the selection of the population to derive the rule; the definition of the outcome; the independence between the predicted variable and the predictors used; the reproducibility of the variables; the mathematical techniques used to derive the rule; validation of the rule. However, no rule will be able to detect a bacterial superinfection that has started during a viral infection. [1251]

Comment: Combinations of clinical and lab criteria have been used to develop 'clinical prediction rules' for children with fever without source. None of these tools are 100% sensitive in ruling out serious bacterial infection. Duration of bacterial infection is important for the performance of bacterial markers. Only observation over time can detect secondary bacterial infections with children seen initially with a viral illness. *NP*

Treatment options for CMV disease

New trends in diagnosis and treatment of congenital CMV infections

Authors: Sharland M

Summary: This abstract discussed antiviral therapy options for cytomegalovirus (CMV) disease. Ganciclovir was first studied 20 years ago but the optimal regimen for many children still remains unclear; virtually no studies have assessed its use in premature infants or teenagers. The oral prodrug valganciclovir is now licensed by the EMA but only for patients over 18 years of age. There have been no comparative studies of IV ganciclovir vs oral valganciclovir, mostly because of the difficulty of recruitment into clinical trials and the lack of a surrogate marker for successful treatment. The duration of treatment of valganciclovir (6 weeks vs 6 months) is being currently evaluated in a US trial in children with symptomatic congenital CMV. There have been only small studies on the use of cidofovir and foscarnet in children with CMV and there are almost no new antiviral agents in the pipeline for CMV. [1239]

Comment: With availability of antiviral agents active against CMV the decision needs to be made as to whom to treat. The need for ganciclovir to be given intravenously (e.g. for 6 weeks) has made treatment of mildly affected infants unappealing because of drug toxicity and risks of central lines. However, if the trials discussed in this talk show safety and benefit of oral valganciclovir use, treatment may become the norm for more infected infants. Long-term sequelae are more likely in infants with petechiae, IUGR, microcephaly, and those with high urine viral load are more likely to suffer hearing loss even if asymptomatic. Such infants may soon become candidates for treatment. A European congenital CMV treatment register has been established to capture data on infants being treated outside clinical trials. *EW*

Independent commentary was organised by Dr Emma Best.

Dr Emma Best is a Paediatric ID consultant at Starship Children's Hospital and a Senior Lecturer in Infectious Diseases in the Department of Molecular Medicine, University of Auckland. Dr Best attended ESPID this year and presented a poster on nasopharyngeal Streptococcus pneumoniae *serotypes and antibiotic susceptibilities amongst South Auckland children aged under 2 years prior to conjugate pneumococcal vaccine in New Zealand.*

Do teenagers need HepB booster?

Are boosters necessary for teenagers immunized against hepatitis B in infancy?

Authors: Pokorsks-Lis M

Summary: This study investigated the level of immunity against hepatitis B in 130 children aged 10–12 years who had been immunised against hepatitis B with recombinant vaccine (10µg at 0, 1, 2, 12 months) as infants. Humoral immunity (anti-HBs antibodies) and cellular memory (anamnestic response to booster given in children without protective anti-HBs titers) were determined. 102 out of 130 children (78%) were found to have protective levels of anti-HBs. 28 children (22%) did not have humoral immunity and antibodies were undetectable in 9 children (7%). Anamnestic memory was seen in 8 out of 11 children (73%) tested. Overall, 97% of children were found to have immunity against hepatitis B. In conclusion, these results suggest there is no need for routine boosters in teenagers immunised against hepatitis B in infancy. [240]

Comment: Protection in Polish teens was evaluated in this study. Despite lack of protective antibody (Hep B surface antibody titre < 10) in 22%, the anamnestic response was found in the majority of serologic responders implying likely immunity in most regardless of antibody measure. However, a proportion had also encountered wild hepatitis B virus infection post vaccination (demonstrated serologically in a small percent of the cohort). Ongoing boosting via exposure to endemic HBV may also have enhanced immunity in this population. Similar information on our adolescent population is required before we can interpret this information in the New Zealand context. *EB*

What causes vaccine failure?

Protein-polysaccharide conjugate vaccine failure

Authors: Pollard AJ

Summary: Protein-polysaccharide conjugate vaccines protect young children against invasive disease caused by *Haemophilus influenzae* type b (Hib), serogroup *C Neisseria meningitidis*, and *Streptococcus pneumoniae*. Vaccine failure is a rare event in immunised populations but may occur after poor vaccine storage, incorrect administration, interaction with coadministered vaccines, and inadequate host responses. The age of the individual may also affect the strength of the vaccine response, as immunity declines rapidly in early childhood. Booster doses of conjugates can protect patients with a poor initial response or whose immunity has waned, but booster schedules need to be designed carefully to protect during the period of greatest disease risk. [1229]

Comment: Vaccine failures do not present with more severe clinical disease. However true vaccine failures are more likely to occur in those with co-morbid conditions for example preterm, trisomy 21, immunosuppression. For conjugate vaccine failure the rates of co-morbid conditions can vary between vaccine/disease. Amongst vaccine failures following conjugate pneumococcal vaccine [*Park et al. J Pediatrics 2010;156 (3):478-83*] or HiB vaccine [*Pladhani S et al; abstract 299*], up to 40% of children had co-morbid conditions identified. However men-C conjugate vaccine failures identified co-morbid conditions in less than 8%. For the clinician the investigation of underlying abnormalities following true vaccine failure should always be considered. *EB*

Single nucleotide polymorphisms in MAL/TIRAP and interleukin-10 genes are associated with invasive haemophilus inflenzae B (Hib) infection in immunised children

Authors: Pladhani S et al

Summary: Hib vaccine failure is rare, and is probably due to a genetically determine inadequate immune response. This study investigated single nucleotide polymorphisms (SNPs) known to affect function in biologically plausible genes in relation to the risk of Hib disease. 323 families of UK children who had Hib vaccine failure between 1992-2005 were approached and 260 completed a questionnaire; the final cohort comprised 172 families of Caucasian children. 19 functional SNPs in 14 immune response genes were investigated. The recessive homozygous genotype for an SNP in the TIRAP (or MAL) gene was strongly associated with non-meningitis cases of Hib vaccine failure (odds ratio 5.6; 95% CI 2.7–11.5) and the recessive homozygous genotype for an SNP in the interleukin-10 (IL10) gene was associated with epiglottitis only (odds ratio 5.8; 95% CI 2.4–14.2). In conclusion, failure of the Hib vaccine is in part genetically determined. [299]

Comment: In contrast to the study by Pollard et al [abstract 1229], researchers following HiB vaccination in England found that most children with HiB vaccine failure were previously healthy. However genetically acquired immune defects not able to be tested by conventional methods may be increasingly recognised in the future as underlying these children with vaccine failure and remains an exciting area of research. *EB*

Viremic spread of VZV after vaccination

Viremic spread of varicella zoster virus (VZV) following vaccination and natural infection

Authors: Gershon A et al

Summary: This study investigated whether viremic spread of VZV occurs in vaccinated children. PCR, in situ hybridization and immunocytochemistry of children autopsied after sudden death showed latent VZV in bilateral ganglia at multiple levels in vaccinated children and in children with a history of varicella infection. Latent VZV was also found in surgical gut specimens. Some of the vaccinated children were found to have wild-type VZV. In conclusion, viremic spread of VZV occurs after vaccination. [210]

Comment: Virologic investigation of post-mortem paediatric patients appears to support the theory that viremia occurs after vaccination for most including immunocompetent children. It is already recognised that the Oka/Merck strain of VZV in the vaccine can establish latent infection and clinically reactivate as zoster indistinguishable clinically from wild-type VZV. However the risk of zoster in children (immunocompromised or immunocompetent) who receive varicella vaccine appears to be less. As vaccine recipients get older the risk and manifestation of vaccine strain zoster in older persons who are at greater risk for zoster complications can be evaluated more thoroughly. The authors note that the new combination measles mumps rubella and varicella (MMRV) vaccine has a larger viral load of varicella Oka strain compared with the monovalent VZV vaccine. *EB*

New and old antibiotics to treat resistant bacteria

New and old antibiotics to treat resistant bacteria: linezolid

Authors: Pulcini C

Summary: The novel oxazolidinone antibacterial agent linezolid has demonstrated activity against antibiotic-resistant aerobic Gram-positive cocci, including MRSA, and has almost 100% oral bioavailability. The drug has been approved in a number of countries for the treatment of community-acquired and nosocomial pneumonia, skin and soft-tissue infections, and infections caused by MRSA and vancomycin-resistant enterococci. Evidence suggests it may also be useful in febrile cancer patients with neutropenia, and in patients with infective endocarditis, tuberculosis, nocardiosis, or anaerobic infections. Adverse events reported with prolonged use of the drug in adults include neuropathy, hematological abnormalities and hyperlactatemia. Efficacy and tolerability data in children are limited. [1307]

Comment: Linezolid (available with special authority) has activity against aerobic gram positive cocci including methicillin resistant *Staphylococcus aureus*, penicillin resistant *Streptococcus pneumoniae* and vancomycin resistant enterococci. The drug has excellent oral bioavailability and good tissue penetration achieving 30-40% of serum levels in CSF, eye fluids and bone. Accumulating literature supports paediatric use and it has an established role in treatment of resistant pneumonia and skin or soft tissue infections. However, its side effect profile limits long term usage. Side effects include peripheral neuropathy, optic neuritis and haematologic abnormalities, most frequently affecting platelets followed by haemoglobin and white cells.

Daptomycin (not available in New Zealand) is a cyclic lipopeptide particularly useful in MRSA and vancomycin resistant *Staphylococcus aureus* although there is a distinct lack of paediatric data regarding its use. At present it has indications in treatment of endocarditis with resistant *S. aureus* and has some data showing it is more effective than vancomycin. In addition daptomycin is able to penetrate biofilms important in foreign body infections, particularly bone and joint.*EB*

Oral communications sessions

Possible harms of oseltamivir-interpreting safety in context of the H1N1 09 pandemic

Authors: Khandaker G

Summary: This observational study evaluated the incidence of vomiting associated with oseltamivir in children with influenza. 220 consecutive children aged <15 years who were admitted to the Children's Hospital at Westmead, Sydney with laboratory confirmed influenza (86% H1N1 09) were assessed. 85 children (39%) had vomiting at presentation to hospital; 104 (47%) were treated with oseltamivir. Of 64 children without vomiting on presentation who were then given oseltamivir, only 1 child subsequently developed vomiting. Oseltamivir did not exacerbate vomiting in any of the children who had vomiting prior to treatment. In conclusion, these observations indicate a lower rate of vomiting associated with oseltamivir than suggested by clinical trials, and support its use in children. [971]

Comment: Oseltamivir has been associated with increased vomiting in one meta-analysis of community treatment of influenza in children. [*Shun-Sin et al. BMJ 2009; 339*] However in this Sydney study of hospitalised children, investigators observed lower rates of vomiting following oseltamivir treatment of novel-H1N1 in 2009. The drug was tolerated extremely well by children and the overall duration of hospital stay was equal or shorter amongst those treated with oseltamivir despite the higher likelihood that oseltamivir was given to those with more severe symptoms at presentation.*EB*

Characteristics of H1N1 infection in children admitted to St Mary's Hospital, London

Authors: Herberg J et al

Summary: This study examined the clinical and laboratory characteristics of children presenting to a major paediatric centre in London with H1N1 infection. Data were analysed for 43 patients aged <16 years who were admitted between June and December 2009 with confirmed H1N1 infection. 20 of the 43 patients (47%) had a primarily respiratory presentation. 22 patients had a risk factor for severe disease including neurodevelopmental delay, immunosuppression, chronic lung disease and sickle cell disease. Eleven patients were admitted to the intensive care unit: 5 of them died (3 from ARDS/respiratory failure, 1 from refractory shock and 1 from sepsis/multi-organ failure). Two of the patients who died were previously healthy. Bacterial superinfection was documented or suspected in 17 children. [432]

Comment: It is recognised that children <5 years have the higher incidence, complication and hospitalisation rates from influenza A. Amongst hospitalised children, more severe disease during the novel H1N1 pandemic was seen particularly in those with neurodevelopmental co-morbidities and there was a high frequency of seizure occurring in these children at presentation. In the context of recent concerns about association between influenza vaccine and benign febrile convulsions in Western Australia, it is important that children with co-morbid conditions particularly with neurologic and metabolic conditions are still encouraged to receive flu vaccine as they may be at more risk of severe disease.*EB*

Seroprevalence of pertussis in The Netherlands: increased circulation of pertussis among adults

Authors: de Greeff SC

Summary: This population-based study estimated the seroprevalence of pertussis infection in adults in The Netherlands in 2006–2007. IgG levels against pertussis toxine (PT) were measured in a multiplex bead-based fluorescent immunoassay. Overall, 9.3% of individuals had a titer above 62.5 EU/ml (suggestive of infection in the past 12 months) and 3.4% had a titer above 125 EU/ml (suggestive of infection in the past 6 months). The highest prevalence of pertussis infection in the past year was seen in people aged 75–79 years (14.4%), followed by those aged 40–44 years (13.4%). Levels of presumptive pertussis infection had increased 5.5-fold compared with data from 1995–1996. [1066]

Comment: Good pertussis vaccination coverage of young children, yet a vaccine which does not give lifelong immunity, has shifted the epidemiology of pertussis. For many countries this has meant that adults and adolescents are now important sources of infection for vulnerable infants. In New Zealand this is being combated by the recent introduction of adolescent booster pertussis vaccination. The burden of pertussis disease is increasingly noted in elderly populations in the developed world. Recommendations regarding adult booster pertussis vaccination and 'cocooning' infants by vaccinating adult carers (including grandparents) will be important strategies to consider in the future.*EB*