European Society for Paediatric Infectious Diseases Conference Review

Making Education Easy

8-12 May 2012, Thessaloniki, Greece

In this review:

Welcome to our review of the 30th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID), held in Thessaloniki in May 2012.

At ESPID, local and international experts discussed the latest advances and developments in the epidemiology, clinical presentation, diagnosis, prevention and treatment of paediatric infectious diseases. Participation of colleagues from not only Europe but also other continents ensured a rich environment for discussion of infectious disease problems in children all over the world. Dr Tony Walls attended ESPID 2012 and considered the following presentations to be particularly interesting. All articles presented at ESPID can be found online at http://www.kenes.com/espid2012/abstracts/.

We hope you find the conference review interesting and useful in your clinical practice.

Kind regards,

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Plasmodium falciparum malaria causes prolonged impairment of neutrophil oxidative burst activity

Authors: Cunnington A et al

Summary: This study evaluated neutrophil function in Gambian children with *Plasmodium falciparum* malaria. Neutrophil oxidative burst and degranulation were quantified using flow cytometric assays of samples taken in acute and convalescent states from 58 children. Two distinct populations of neutrophils were found; the major neutrophil population had reduced oxidative burst activity. The degree of oxidative burst impairment correlated significantly with markers of haemolysis. During an 8-week follow-up period, neutrophil function progressively normalised towards a single population of neutrophils with normal oxidative burst activity. In conclusion, the neutrophil dysfunction seen in children with *P. falciparum* malaria may explain their associated susceptibility to non-typhoid Salmonella infection.

Comment: Non-typhoidal Salmonella is the most common cause of community-acquired bacteraemia in many parts of Sub-Saharan Africa. Previous observations have suggested an association with persistent malaria infection but the mechanism of this effect has remained elusive. This study follows on from data from a mouse model showing that malarial infection leads to premature mobilisation of granulocytes from the bone marrow and defective killing of intracellular bacteria (*Nature Med* 2012;18:120-128).Tolerance to haemolysis due to persistent malarial infection and the production of haem oxygenase-1 appears to impair the immune response to salmonella infection and may explain the high rates of invasive infections in these children.

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http://www.kenes.com/espid2012/abstracts/PDF/713.pdf?zoom_highlightsub=cunnington

Analysis of polyfunctional T-cells can distinguish between latent and active tuberculosis in children

Authors: Tebruegge M et al

Summary: Current immunodiagnostic tests cannot distinguish between latent tuberculosis (TB) infection and active TB. This study investigated whether measurement of mycobacteria-specific, polyfunctional T cells can help distinguish between these two infection states. 82 children aged ≤18 years who were at risk for TB were tested by a tuberculin skin test (TST) and an interferon-gamma release assay. Intracellular cytokine assays were also performed by incubating whole-blood samples with PPD and the *Mycobacterium tuberculosis* RD1 antigens ESAT-6 and CFP-10. Cells were analysed by multi-colour flow cytometry. Six children were found to have active TB, 15 had latent TB infection and 61 were uninfected. Proportions of single-cytokine- (TNF-α+) producing, and double-cytokine- (IFN-γ+/TNF-α+) producing CD4+ T cells were significantly higher in TB-infected children than in uninfected children. In conclusion, measurement of polyfunctional T cells is a novel approach for distinguishing between latent TB infection and active TB.

Comment: Interferon-gamma release assays (IGRAs) seem to be almost as problematic as mantoux tests when it comes to identifying latent tuberculosis in children. Tuberculosis is a complicated disease immunologically and it has always seemed strange to me that we have assays that look at the production of just one cytokine from T-cells. This paper has used flow cytometry to look for a panel of intracellular cytokines produced by T-cells exposed to tuberculosis antigens. In this small sample the assay could differentiate between TB-infected and TB-uninfected children. More importantly it could distinguish between latent TB and TB disease. A lot more work needs to be done but this is an exciting innovation for TB diagnostics. Similar work in adults has recently been published (PLoS ONE April 2012;7(4):e36046).

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http://www.kenes.com/espid2012/abstracts/PDF/513.pdf?zoom_highlightsub=tebruegge

A protein pattern in serum as a biomarker to diagnose active tuberculosis irrespective of HIV status

Authors: Eleftherohorinou H et al

Summary: The clinical and radiological features of TB do not discriminate it from a range of other HIV-associated opportunistic infections in individuals with HIV. This study aimed to identify a protein pattern that distinguishes active TB from other conditions, irrespective of HIV status. Serum samples were collected from 1200 children and adults from sub-Saharan Africa who had active TB, latent TB or other infections with clinical features resembling TB. SELDI proteomic profiling of the serum samples identified approximately 700 proteins that were differentially expressed in patients with active TB compared with patients with latent TB or other infections, regardless of HIV status. In conclusion, SELDI analysis identified serum biomarkers of active TB that may be a diagnostic signature of the disease.

Comment: It has long been recognised that we need better diagnostic tests for tuberculosis, especially in children where only 20% of cases are confirmed microbiologically. The risk of developing TB following infection is high in children, and even higher in those who are immunocompromised. This study combines proteomics and advanced bioinformatics to identify protein profiles from serum that distinguish children and adults with active TB from those with latent TB. This approach appears to also be able to differentiate TB from other infections that in children present in a similar way to TB. By analyzing the protein patterns present in the serum of patients they found specific signatures of TB infection. This process appears to have great potential, but the challenge will be making it simple enough to use in a routine clinical setting – watch this space.

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http://www.kenes.com/espid2012/abstracts/PDF/302.pdf?zoom_highlightsub=Eleftherohorinou

Long-term outcomes of congenital cytomegalovirus (CMV) infection in Sweden and the United Kingdom

Authors: Townsend C et al

Summary: This study evaluated the long-term outcomes associated with congenital CMV infection. 176 congenitally infected infants were identified from >50,000 screened infants born in Sweden and the UK between 1977 and 1986. These infants (cases) were matched with 214 controls and were followed for 5+ years. 83% of CMV-infected children followed up to age 5 had no developmental problems; 7% had mild, 3% moderate and 6% had severe impairment. 56% of children who were symptomatic as neonates had some impairment, compared with 14% of those who were asymptomatic (p=0.007). All serious outcomes were identified by age 2. Four controls had sequelae. In conclusion, 9% of children with congenital CMV had moderate or severe long-term outcomes.

Comment: Congenital CMV infection is the leading cause of sensorineural deafness and of mental retardation in children. Even children who are asymptomatic at birth can have significant sequelae including progressive hearing loss. This is the largest long-term follow up study of infants with congenital CMV. The strength of the study is that a high proportion (86%) of children completed follow up to age 5 years. Although a significant proportion of children who were asymptomatic at birth had subsequent problems, reassuringly only a small proportion of asymptomatic infants did. Given the concerns over progressive sensorineural hearing loss in infected children it was reassuring to see that no serous outcomes developed beyond age 2 years. Interestingly, 8 out of 14 infants with moderate/severe outcomes had mothers with probable non-primary infection.

Oral presentation: Neonatal infections session

http://www.kenes.com/espid2012/abstracts/PDF/20.pdf?zoom_highlightsub=townsend

For more information about ESPID 2012 go to

http://www2.kenes.com/espid/pages/home.aspx

Elucidating the perfect storm: multiple pneumococcal serotypes and bacterial species at high density and with near-universal rhinitis in young children

Authors: Rodrigues F et al

Summary: This Portuguese study examined nasal ecology in young children. The investigators swabbed the nasopharynges of 586 children aged between 6 months and 6 years who were attending 6 nurseries in Coimbra in 2010. Swabs were cultured for pneumococcus, *M.catarrhalis*, *H.influenzae* and *S.aureus*. 56% of children had symptoms of rhinitis. Rates of colonisation were 45.7% for pneumococcus, 68.8% for *M.catarrhalis*, 51.7% for *H.influenzae* and 15.5% for *S. aureus*. Colonisation rates were highest in youngest children (except *S. aureus*) and were associated with age (all $p \leq 0.05$). Pneumococcus density was associated with symptom score, independently of age ($p < 0.001$). 62.8% of children had multiple bacterial species and 90% of those with pneumococcus also carried another species. 29 pneumococcus serotypes were detected, including vaccine types 3, 7F, 18C (previously undetected), 19A and 19F. In conclusion, drivers of pneumococcal transmission (colonisation density and rhinitis symptoms) are mutually associated and may be important determinants of disease.

Comment: It is generally considered that the development of invasive pneumococcal disease in children is preceded by carriage of the organism in the child's nasopharynx. Traditionally studies of pneumococcal serotypes carried in the nasopharynx of children have selected only a few colonies from agar plates and assumed this is representative of the overall population of organisms present. This study has demonstrated that in young children not only is it common for them to carry multiple bacterial species, it is very common for them to carry multiple serotypes of pneumococcus. Children with rhinitis were more likely to be colonised and interestingly, the carriage of multiple pneumococcal serotypes was not affected by recent pneumococcal vaccination or antibiotics.

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http://www.kenes.com/espid2012/abstracts/PDF/567.pdf?zoom_highlightsub=Rodrigues

Severe pertussis among infants <90 days of age admitted to pediatric intensive care units. Southern California, September 2009–June 2011

Authors: Murray E et al

Summary: This study evaluated the features of critically ill infants with pertussis. Data for infants ≤90 days of age who were admitted to a paediatric intensive care unit (PICU) with pertussis between September 2009 and June 2011 in Southern California were reviewed. Outcomes in infants with more severe infections (they died or were diagnosed with pulmonary hypertension) were compared with those with less severe infections. 31 infants were included (55% female, 94% Hispanic) of whom 8 had more severe infections. Infants with more and less severe infections were demographically similar, and there were no significant between-group differences in time from illness onset to initial medical care. Those with more severe infections had higher peak white blood cell counts (WBC; $p<0.01$) and their WBC exceeded 30,000 more rapidly after illness onset (5.1 vs 14.6 days; $p<0.01$). They were also more likely to have a 50% increase in WBC within 24 hours. In conclusion, infants with more severe pertussis were more likely to have higher WBC and more rapid increases in WBC than infants with less severe infections.

Comment: This is a timely reminder of how severe pertussis infection can be in infants. The study involved a small group of children with severe pertussis admitted to PICU. Children who died or had pulmonary hypertension were classified as having severe disease, whereas the others were classified as less severe. It appears a very high or rapidly rising WBC may be a marker for more severe disease and may identify a subset of infants who may require exchange transfusion.

Oral presentation: Emerging infections session

http://www.kenes.com/espid2012/abstracts/PDF/31.pdf?zoom_highlightsub=murray

Why did early fluid resuscitation increase mortality in African children with severe febrile illness and shock in the Feast trial?

Authors: Gibb D et al

Summary: This study examined the impact of early fluid boluses in African children with severe febrile illness. 3141 children who presented to African hospitals with febrile illness, impaired consciousness or respiratory distress and signs of impaired perfusion were randomised to receive boluses (20-40 ml/kg) of 5% albumin or 0.9% saline, or to a control group. At presentation, 69% of children had severe acidosis/shock, 26% had respiratory and 41% had neurological presentation syndromes (alone or combined). Excess mortality was apparent in bolus versus control groups for all syndromes. Shock resolved more frequently within 1 hour in bolus vs control groups (43% vs 32%, p<0.001), but excess mortality in bolus arms occurred irrespective of shock resolution. 9% and 7% of children in bolus and control groups, respectively, developed hypoxia within 1 hour (p=0.06), but this did not explain the excess mortality seen in the bolus group. Excess terminal clinical events with boluses were mainly due to cardiovascular collapse. In conclusion, excess mortality from boluses occurred in all subgroups and was mostly a result of cardiovascular collapse rather than fluid overload.

Comment: This important study of the administration of fluid boluses in severely ill African children has probably raised more questions than it answers. It showed that children presenting with severe febrile illness randomised to receive fluid boluses early in treatment had a higher mortality than those in the control group (*NEJM* 2011;364:2483). Here the authors re-analysed the data to determine any identifiable reasons for the excess mortality that occurred in children who received fluid boluses. The worse outcomes for these children occurred across in all subgroups and deaths appear to be more related to cardiovascular collapse than fluid overload per se. The exact reason for this still remains unknown.

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http://www.kenes.com/espid2012/abstracts/PDF/711.pdf?zoom_highlightsub=gibb

Postmarketing surveillance of intussusception following mass introduction of the attenuated human rotavirus vaccine in Mexico

Authors: Velázquez F et al

Summary: This postlicensure study evaluated the potential association between vaccination with the attenuated human rotavirus vaccine (Rotarix™; GlaxoSmithKline Biologicals) and intussusception in Mexican infants. 753 episodes of intussusception were reported among 750 infants aged <1 year at221 hospitals across Mexico from January 2008 to October 2010. The temporal association between vaccination and intussusception was assessed by self-controlled case-series analysis. 701 of the 750 infants were vaccinated. The relative incidence of intussusception within 31 days of vaccination was 1.75 post-dose 1 (p=0.001) and 1.06 post-dose 2 (p=NS), and within 7 days of vaccination was 6.49 post-dose 1 (p< 0.001) and 1.29 post-dose 2 (p=NS). Clustering of intussusception within 7 days of vaccination was observed postdose 1. In conclusion, a small temporal increase in risk for intussusception was seen within 7 days after the first dose of vaccine but it remains unclear whether rotavirus vaccination has any impact on the overall incidence of intussusception in infants.

Comment: Rotavirus vaccine is not presently funded in New Zealand despite the WHO recommending its use. Experience with rotavirus vaccines in Australia and elsewhere have shown significant reductions in hospitalisations due to gastroenteritis in infants. However, several studies have now shown there does appear to be a very small increase in the risk of intussusception in infants within 7 days of receipt of the first vaccine. In NZ this would roughly equate to 1-2 potential additional cases a year (with our birth cohort of about 65,000, with a 90% uptake). In countries where there is significant mortality associated with rotavirus gastroenteritis the benefits of rotavirus vaccination far outweigh the risks. However in New Zealand the presence of a small increase in the rate of intussusception could make parents think twice about vaccinating their children. Providing clear and accurate information about the risks and benefits of rotavirus vaccine to parents is essential. Unfortunately this study was unable to evaluate the impact of vaccination on the overall risk of intussusception throughout childhood. In Australia there has been no increase in the rate of intussusception after the introduction of the vaccine.

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http://www.kenes.com/espid2012/abstracts/PDF/777.pdf?zoom_highlightsub=Velazquez

Bactericidal antibody persistence two years following meningococcal B vaccination at 6, 8 and 12 months in 40 month old children

Authors: Philip J et al

Summary: This extension study evaluated the persistence of the antibody response to meningococcal B vaccination. 60 infants were given a serogroup B meningococcal vaccine containing recombinant-proteins alone (rMenB) or the proteins with an outer-membrane vesicle (4CMenB) at 6, 8 and 12 months. In this extension study they had serum bactericidal antibody (SBA) titres evaluated before and after booster doses of the vaccines at 40 months. Age-matched Men B naïve children (n=40) served as a control group. Prior to the booster, the proportions of 4CMenB recipients with SBA titres ≥1:4 were 36% for strain 44/76-SL, 100% for 5/99, 14% for NZ98/254 and 79% for M10713. These percentages ranged from 14 to 29% for infants who received rMenB, with the exception of strain 5/99 (93%). For controls, percentages were ≤3% for all strains except M10713 (53%). When evaluated 1 month after the booster dose, ≥93% of 4CMenB recipients had SBA titres ≥1:4 for all 4 strains. In conclusion, bactericidal antibodies appear to wane after infant immunisation with rMenB or 4CMenB and booster doses may be necessary to maintain immune protection throughout childhood and adolescence.

Comment: Persistence of serum bactericidal antibodies is important for ongoing protection against meningococcal disease. It is encouraging that the new meningococcal B vaccine (4CMenB) produces good anamnestic responses in children at age 40 months who have received a 3-dose primary immunisation schedule. However the levels of antibodies prior to this are fairly disappointing for several of the strains, including the NZ strain, which suggests that frequent booster doses would be required to maintain adequate protection in young children.

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http://www.kenes.com/espid2012/abstracts/PDF/793.pdf?zoom_highlightsub=philip

Independent commentary by Dr Tony Walls

Dr Tony Walls is a Senior Lecturer in the Department of Paediatrics, University of Otago, Christchurch and a Paediatric Infectious Diseases Specialist. He has an ongoing interest in childhood vaccinations, and his current research includes a study on the aetiology and impact of pneumococcal vaccination on otitis media with effusion in New Zealand children.

Research Review publications are intended for New Zealand health professionals.

Prevention of perinatal Group B streptococcus (GBS) disease: effectiveness and cost of GBS intrapartum PCR screening strategy

Authors: El Helali N et al

Summary: This French study evaluated the cost and effectiveness of an intrapartum PCR screening strategy implemented in France in 2010 to prevent perinatal GBS and compared it with the antenatal lower-vagina culture screening strategy in place in 2009. Early-onset GBS disease in newborns was monitored and direct costs (including screening test costs and hospital costs) for deliveries of healthy versus GBS-infected newborns were estimated. Among 5575 screened mothers, the vaginal GBS colonisation rate was 11.7% based upon antenatal GBS culture screening in 2009 and 16.7% based on intrapartum PCR testing in 2010. The overall probabilities of neonatal GBS disease were 0.9% and 0.5%, respectively, and the average total costs per delivery were €1,390 and €1,386. The severity of early-onset GBS disease was higher in 2009 than in 2010. In conclusion, intrapartum PCR screening for GBS was cost-neutral compared with the antenatal lower-vagina culture screening, and was associated with a significant decrease in early-onset GBS disease.

Comment: Screening for GBS infection in pregnant women has always been problematic, with a slow turn around time for cultures meaning they need to be done well in advance of delivery. Rapid diagnosis at the time of delivery with PCR is a very attractive screening strategy with results being available within a few hours. This means a woman can be screened at the time she goes into labour. Introducing such a strategy could be potentially very costly however. It was pleasing to see that the introduction of PCR screening in France was cost-neutral and that they had higher detection rates of maternal infection. More importantly there was a significant decrease in the rate of early-onset GBS disease in infants between the two years. Hopefully this strategy can lead to sustained reduction in the rates of GBS disease in infants.

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http://www.kenes.com/espid2012/abstracts/PDF/262.pdf?zoom_highlightsub=El%2BHelali%2Bprevention

Human beta defensin 2 (HBD2) serum levels may predict susceptibility to infections in preterm neonates

Authors: Olbrich P et al

Summary: This study measured levels of HBD2 in cord blood of preterm infants and evaluated its role in infant immunity. 31 preterm neonates (median gestational age 30 weeks) were enrolled. 11 of them had late-onset sepsis, and organisms were isolated in 7/11 patients: *S. epidermidis* (n=4), *K. pneumonia* (n=2) and *E. faecalis* (n=1). Neonates with late-onset sepsis had significantly lower HBD2 serum levels in cord blood than those without late-onset sepsis (median 556 vs 1552 pg/ml; p=0.01), irrespective of birthweight, gestational age, chorioamnionitis or the use of corticosteroids before birth. In conclusion, low HBD2 levels at birth might be a predictor of increased susceptibility to neonatal infections in preterm neonates.

Comment: This is one of those interesting observational studies that may or may not have stumbled upon something. It's well known that neonates have impaired innate immunity in the first few weeks of life but this study has identified an antimicrobial peptide HBD2 that is significantly reduced in neonates who go on to develop late-onset sepsis. This was a small study and clearly more work needs to be done to back up this observation.

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http://www.kenes.com/espid2012/abstracts/PDF/293.pdf?zoom_highlightsub=olbrich

Effectiveness of the pneumococcal *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) against invasive pneumococcal disease (IPD) in infants: FinIP trial

Authors: Palmu A et al

Summary: This Finnish study investigated the vaccine effectiveness (VE) of the 10-valent PHiD-CV (Synflorix™, GlaxoSmithKline Biologicals) against IPD when given to infants in a 3+1 or 2+1 schedule. 47,369 children <19 months of age were cluster randomised to receive 10-valent PHiD-CV or control vaccine (hepB vaccine or hepA vaccine). To assess the effectiveness of different schedules in infants aged <7 months at enrollment, half of infants received 4 doses (3+1) and the other half received 3 doses (2+1). In 30,528 infants aged <7 months at enrollment who received at least 1 dose of the vaccine assigned to their cluster, VE for vaccine type IPD was 100% with the 3+1 schedule and 92% with the 2+1 schedule. The only vaccine-type IPD in the PHiD-CV groups was diagnosed 12 days after the 1st dose in the 2+1 group. In conclusion, the FinIP trial demonstrated excellent effectiveness of PHiD-CV against IPD.

Comment: This study is directly relevant to New Zealand because PHiD-CV vaccine (Synflorix) was introduced into our vaccine schedule in July 2011. It is the largest ever trial of pneumococcal vaccine. The effectiveness of the vaccine was excellent, preventing 93% of all culture proven invasive pneumococcal disease in children < 7 months of age at enrollment. It was interesting to see that a 2+1 schedule also performed very well. No information was provided about the spectrum of pneumococcal serotypes causing IPD in Finland prior to the introduction of the vaccine.

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