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CONCISE REVIEWS OF PEDIATRIC INFECTIOUS DISEASES

EPIDEMIOLOGY AND PREVENTION OF HEPATITIS A VIRUS INFECTION

YONG POOVORAWAN, M.D.*

The prevalence of HAV infection, transmissible by oral-fecal route, reflects the standard of hygiene and socioeconomic conditions in any given country. In poor countries, the disease usually affects infants and young children among who it takes an entirely asymptomatic course leaving them with life-long immunity. India might serve as the best example for a country with high endemicity in that since 1982 near universal seroconversion has been shown to occur at a very young age. Developing countries, with sanitation and hygiene gradually improving, show moderate endemicity in that seroconversion occurs mainly among adolescents or young adults. The Philippines and Vietnam display age related seroprevalence patterns indicative of high to moderate endemicity whereas significant regional variation in HAV seroprevalence can be observed in Indonesia, Singapore, Thailand and Malaysia have undergone a decline in childhood and adolescent HAV seroprevalence typical of countries experiencing socioeconomic development countries, where due to good sanitation and hygiene, seroprevalence increases in direct proportion with age. Populations displaying age-related seroprevalence in parallel with socioeconomic improvement risk significant morbidity form active disease as the illness tends to take a more severe course among older individuals. Also, the probability of HAV epidemics increases due to a significant number of individuals susceptible to infection and variable conditions of sanitation conductive to water and food borne transmission. Moreover, most of Southeast Asian countries display a high prevalence of chronic liver disease not related to hepatitis A, an aggravating condition in cases of HAV superinfection. Hence, nationwide education campaigns geared towards improvement in sanitation and hygiene on an individual bases might improve prevention in normal populations, whereas vaccination is recommended to individuals, at high risk of infection, such as chronic liver disease patients without immunity to HAV, or individuals incapable of taking proper care of their personal hygiene.

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*Department of Pediatrics, Faculty of Medicine
Chulalongkorn University & Hospital, Bangkok 10330 Thailand

THE IMPACT OF HEPATITIS B VACCINATION

PING-ING LEE, M.D.*

Hepatitis B virus (HBV) infection is a global health problem and is endemic in many countries of Asia and Africa. The rate of hepatitis B surface antigen (HbsAg) carriage has been between 10-20% in Taiwan. Perinatal transmission has accounted for 40-50% of the carrier pool and most carriers acquire HBV infection before 2 years of age.

HBV vaccination at birth can effectively prevent perinatal transmission of HBV. A protective level of hepatitis B surface antibody (anti-HBs) develops in more than 90% of vaccine recipients. The protective efficacy of hepatitis B immune globulin and HBV vaccine at birth was approximately 90% for infants born to hepatitis B e antigen-positive carrier mothers. Possible causes of immunoprophylaxis failure include a high virus load from the mother, intrauterine infections, a genetical hyporesponsiveness to the vaccine antigen and a mutation at the "a" determinant of HbsAg. DNA sequence analysis of the "a" determinant had detected mutant HBV in 6 (22%) of 27 vaccinated children who had become carriers.

In Taiwan, current recommendations for HBV vaccination in neonates include 3 doses of recombinant HBV vaccine at 0, 1, and 6 months of age. A mass HBV vaccination program was launched in 1984. A serological survey in Taipei showed that the overall prevalence rate of HbsAg in children below 12 year old had dropped from 9.8% in 1984 to 1.3% in 1994. The prevalence rate of hepatitis B core antibody (anti-HBc) had also decreased significantly. A nation wide survey showed that the average annual incidence of hepatocellular carcinoma in children 6 to 14 years of age declined form 0.70 per 100.000 children between 1981 and 1986 to 0.57 between 1986 and 1990, and to 0.36 between 1990 and 1994.

Follow-up studies of vaccinated children without HbsAg demonstrated that seropositive rate of anti-HBs dropped from 99% at 1 year to 83% at 5 years, and to

*Department of Pediatrics, National Taiwan University Hospital
Taipei, Taiwan

67% at 10 years. Natural infections, as judged by the changes of anti-HBc, occurred in 12% of them. None of these episodes was associated with HbsAg positivity. In addition, cellular immunity to HbsAg could be demonstrated in most children 10 years after vaccination. These findings indicate that the protection afforded by HBV vaccine is excellent for at least 10 years.

HEPATITIS C VIRUS INFECTION IN CHILDREN

HTOSHI TAJIRI,M.D.*, ATSUSHI SAWADA, M.D.*, YURI ETANI,M.D.*, YOKO MIYOSHI, M.D.* KANAE TADA, M.D.*, SHINTARO OKADA, M.D.*

Hepatitis C virus (HCV) affects 1% of the world population. In this session issues on HCV infection in children including vertical transmission, natural course, interferon therapy and prevention will be discussed.

Transmission and natural course: Blood transfusion was one of the main transmission routes of HCV. However, since the introduction of screening with test for anti HCV, this route has been successfully prevented. HCV is also transmitted from mother to child and this mode of transmission is becoming a main route of HCV infection in children. We have investigated 8 cases of mother-to-child transmission of HCV who were diagnosed as such by using a homology analysis of the NS5B region of HCV genome. Five case underwent liver biopsies: 2 chronic persistent hepatitis, 2 chronic active hepatitis 2A, and 1 chronic active hepatitis 2B. All 8 children had mild to moderate abnormalities in liver function tests. We recommend that HCV infected children should be carefully followed up for liver disease.

Interferon therapy: The efficacy of interferon therapy was evaluated in 24 children with chronic hepatitis C. Six months after the end of interferon alpha therapy, 12 patients remained negative for serum HCV-RNA. Ten of these responders have remained so for more than two years. A liver biopsy was repeated in 7 responders and a marked improvement was noted in all patients. Serum levels of a fibrosis marker, 7S peptide of type 4 collagen, were decreased in half of virological non-responders as well as in most of virological responders. Interferon therapy in children with chronic hepatitis C may be beneficial as evaluated by sustained loss of viremia as well as by primary response.

Prevention: The benefit of the screening for HCV was retrospectively assessed in 54 children with primary malignant disease. Before the introduction of blood screening with test for anti HCV, 15 of 35 patients seroconverted whereas none of 7 patients seroconverted after the screening was used. For patients who underwent bone marrow transplantation, the screening decreased the seroconversion rate from 7 to 11 patients to none of 6 patients. Screening with test for anti HCV has proven to be beneficial in preventing HCV infection in these high-risk children.

HEPATITIS E VIRUS (HEV) INFECTION IN CHILDHOOD

N K ARORA, M.D.*, PRASHANT MATHUR, M.D.*

Enterically transmitted hepatitis is widespread in regions lacking adequate sanitary and hygienic environment and safe drinking water. Both, hepatitis A and E viruses are enterically transmitted infections, and cause considerable morbidity and occasionally mortality in childhood.

HEV Infection in Children: Hepatitis E is caused by an RNA virus belonging to alciviridae group. The disease was initially described in adults ranging from sporadic cases to epidemics. It is only in the last few years that reports from several countries including India, Egypt, Sudan and Hong Kong have shown that children are also susceptible to the infection. The spectrum of the childhood infection ranges from asymptomatic to severe liver disease.

Acute hepatitis E: Clinical features are similar to acute hepatitis due to any of the known hepato-tropic viruses. HEV has been implicated in up to 60% of acute sporadic hepatitis from different regions of the world. Our own data shows that 12% (42 / 350) of all cases of acute sporadic hepatitis were isolated HEV infection and in another 35% (122 /350) children, mixed HEV and HAV infection was detected. It has also been shown as a cause of acute liver failure in 45% of patients mixed HEV and HAV infection was present in 27.5% of these patients. Acute hepatitis E infection maybe superimposed upon underlying chronic liver disease.

*Department of Pediatrics, Osaka University
Osaka, Japan

*Division of Pediatric Gastroenterology, Hepatology and Nutrition
All India Institute of Medical Sciences, New Delhi, India

HEV Epidemics: Small and large epidemics have mainly been described in young adults (15-40 years). In epidemic situations not many cases of symptomatic HEV infection were observed among children. In an epidemic of HEV infection near Delhi, the infection rate in children rate in childhood was 1.2% as compared to 2.9% among adults. Recently, we picked up an outbreak of HEV in a group of school children between the age of 13.4-13.8 years. The attack rate was 85% and 50% of them had clinical jaundice.

Asymptomatic HEV infections: Similar to HAV, asymptomatic HEV infection in childhood is not uncommon. Worldwide seroprevalence studies in children have estimated an overall anti-HEV IgG antibody prevalence between 0-36%. We carried out a study in 2013 healthy urban and rural children and the overall seroprevalence rates of anti-HEV IgG antibodies was 33% and 38% respectively till 10 years of age. The exposure occurred in early infancy and increased with advancing age.

Does Chronic HEV Infection occur?: Circulating HEV RNA has been described for up to 100 days after the appearance of first symptoms of acute viral hepatitis in a recent study. Recently, we came across a female child who had HEV-RNA circulating for over 36 months with persistently deranged liver functions without any other underlying liver disease. She had repeated episodes of encephalopahty and died 38 months after first onset of HEV disease.

Difficulties in Diagnosis: In addition to differences in the environmental hygiene and sanitary conditions, the reported variance in the prevalence of HEV infection in different studies may also be attributed to various HEV antigens used in the diagnostic methods and, regional as well as intra-regional differences in the prevalent HEV strains.

STREPTOCOCCAL PYOGENES – A RE-EMERGING PATHOGEN STREPTOCOCCAL PHARYNGOTONSILLITIS: TODAY'S CHALLENGES FOR THE OPTIMAL MANAGEMENT

GEORGE A. SYROGIANNOPOULOS, M.D.*

Worldwide group A ß-hemolytic streptococcal (GABHS) pharyngotonsillitis is a common pediatric infection. The "gold standard" for the management includes the identification of GABHS in culture of throat swab and treatment with penicillin, usually as a 10-day course of oral penicillin V. The epidemiology of GABHS pharyngotonsillitis is a changing and complex topic. The main challenges faced by pediatricians are: (1) the selection of patients with pharyngotonsillitis who require antibiotic treatment, (2) the use of a rapid test and/or culture of throat swabs for identification of GABHS, (3) the increased inability of penicillin to eradicate GABHS from the pharynx, (4) the rising incidence of erythromycin-resistant strains (5) alternative antibiotic treatments, and (6) questionable compliance of patients to the 10-day treatment regimen.

Although culture of throat swabs is relatively simple to perform, this approach may give equivocal results. In private practice and in countries with limited resources the culture of throat swabs often gives a quite lower rate of GABHS isolation. Rapid diagnostic tests, especially Strep A OIA, can provide useful information, but they require trained personnel and appropriate financial resources.

An area of concern is the decreased eradication of GABHS from the pharynx. Recent studies reveal a pharyngeal persistence of GABHS in 11 to 21% of patients following IM or oral penicillin. Efficacy of penicillin is decreased in toddlers and children, especially aged 2-5 years, and in patients ill for less than 2 days. Recurrent tonsillitis and the carrier state are two clinical conditions, which remain a subject of debate regarding etiology, clinical significance and proper management. Various theories have been suggested to explain this decreased eradication of GABHS from the pharynx, including poor patient's compliance, the prevalence in the oral microflora of ß-lactamase producing producing copathogens or decreased colonization with potentially protective flora, mainly a-hemolytic streptococci, a-hemolytic streptococci have interfering activity and produce a bacteriocin which inhibits GABHS. During the last decade, many reports favored the use of antibiotics, such as the cephalosporins, the macrolides and others when compared to penicillin in eradicating GABHS infection, even with shorter duration of treatment and more convenient daily dosages. The main arguments against the routine use of these alternative antibiotic treatments are the need to be better proved the effectiveness in preventing the non-possibility of development of microbial resistance.

*Department of Pediatrics, University of Patras, School of Medicine Patras, Greece

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Development of resistance to macrolides is currently a challenging issue in some geographic areas. Although it has been in the past a problem in Japan and Australia, during the last decade epidemics of macrolide-resistant GABHS occurred initially in Finland and later in Italy and Spain. Recently, according to our studies, 25-30% of GABHS isolates in Greece are erythromycin-resistant.

Finally, regarding penicillin and amoxacillin, which classically are considered as the first-line antibiotics for GABHS pharyngotonsillitis, there is accumulated evidence indicating that they can be used in more convenient regimens. Specifically, a twice-a-day regiment of penicillin has a similar efficacy with regimens providing a more frequent dosing schedule of this antibiotic. Moreover, recent reports suggest that amoxicillin may be more effective than penicillin in GABHS treatment because it can be administered on a once-a-day schedule and for a shorter period of time than penicillin.

EPIDEMIOLOGICAL CLUES TO THE PATHOGENESIS OF RHEUMATIC FEVER

JONATHAN R CARAPETIS, M.D.* BAST J CURRIE, M.D.*

Epidemilogical research during the 1930s to 1970s in North America, Europe and the Caribean improved our understanding of the pathogenesis of acute rheumatic fever (ARF). However, with the exception of recent outbreaks in some parts of USA, ARF is now uncommon in those regions, so further progress requires new studies in countries with high incidence today. The highest reported annual incidence of ARF is 224 to 508 per 100,000 in Aboriginal Australians of northern Australia. Other high incidence populations are found in the South Pacific, SE Asia, the Indian subcontinent, and sub-Saharan Africa. Recent work is challenging some basic assumptions about pathogenesis, and has important implications or primary prevention and vaccine development. For example, low throat carriage rates of group A streptococci (GAS) but hyper endemic streptococcal pyoderma, very high anti-Dnase B titers but inconsistently elevated anti-streptolysin O titers, and a lack of seasonal separation of ARF and glomerulonephritis in Aboriginal Australian cases are difficult to explain in view of the dogma that ARF only follows GAS infection of the upper respiratory tract. In New Zealand, serotypes of GAS associated with ARF are typical of skin strains in that population. Aboriginal Australians are exposed to an enourmous diversity of GAS strains, but the classical "rheumatogenic" serotypes are almost never seen. The chromosomal arrangement of emm genes which has been associated with nasopharyngeal carriage elsewhere (pattern A-C) is uncommon in strains from the Aboriginal population, even those isolated from the upper respiratory tract. Further studies are needed to determine if the dogma holds true, or if instead GAS strains originating in the skin may be linked of ARF pathogenesis. Other intriguing hypothesis yet to be used include the possibility that repeated infections are needed to sensitive the immune system for the subsequent development of ARF, and that groups C or G streptococci may have the potential to cause ARF.

*Royal Children's Hospital, Melbourne, Victoria Australia
Menzies School of Health Research, Darwin, Northern Territory Australia

SEVERE, INVASIVE GROUP A STREPTOCOCCAL DISEASE

KEITH GRIMWOOD, M.D.*

Group A ß-hemolytic streptococci (GABHS) are among the most common pathogenic bacteria isolated from children and they are associated with a wide variety of disease states. Since the mid 1980s there have been reports from several countries of an increased incidence of severe GABHS infections involving three overlapping clinical syndromes. These include streptococcal toxic shock syndrome, necrotising fasciitis and sepsis with or without and underlying clinical focus. Most invasive infections are sporadic with the greatest incidence being amongst young children, the elderly and those with underlying disorders. Varicella is a particularly important risk factor in previously healthy children and there is accumulating evidence that some non-steroidal anti-inflammatory drugs may have a causative role.

Streptococcal toxic shock syndrome is characterized by the early development of shock and multi-organ failure with severe focal infection

*Wellington School of Medicine, Wellington, New Zealand

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usually involving the skin and soft tissues. Necrotising faciitis is a deep-seated infection of the subcutaneous tissues, often at the site of a recent trivial injury in a previously well individual. It rapidly destroys fascia and fat, but may spare the skin and muscle. Bacteraemia may occur in isolation or be associated with a clinical focus such as pneumonia, empyaema, skeletal infection, cellulutis, myositis, peritonitis, wound infection of meningitis. Management includes intravenous fluids and inotropes to restore the circulation and parenteral antibiotic therapy. Prompt surgical exploration and debridement of suspected deep-seated infection are essential. Although GABHS remain exquisitely susceptible to penicillin, its efficacy is reduced for patients with overwhelming sepsis, necrotising faciitis or myositis. Experimental animal models indicate that clindamycin is superior to penicillin for the treatment of infections where large numbers of GABHS are present. This may be due to clindamycin's activity being unaltered by inoculum size, the suppression of bacterial toxins or its immunomodulatory properties. Even thought there are no controlled clinical trials, many experts now recommend that clindamycin is added to penicillin when treating severe invasive GABHS infections. Intravenous immunoglobulin therpay may also play an important role in streptococcal toxic shock syndrome. In spite of these measure 5-10% of children die from the illness or its complication.

Despite the observation that GABHS associated with invasive streoptococcal infection are found widely amongst asymptomatic carriers and those with pharyngitis or impetigo, cases of severe infection remain sporadic and an epidemic has not eventuated. This suggests that simple contact with a new invasive strain is not sufficient to cause severe disease. M protein contributes to invasiveness by its nati-phagocytic actions whereas streptococcal pyrogenic exotoxins have both toxic and super antigen properties. Both are important microbial virulence factor. The interaction between these factors and host immune system will determine clinical outcome. The absence of a high attack rate suggests the presence of substantial herd immunity against one or more of these virulence factors. It is therefore likely that the waxing and waning in the incidence of GABHS disease severity will continue as new clones emerge and population immunity increases following exposure to these variants.

STREPTOCOCCAL SUPER ANTIGEN-MEDIATED DISEASE

NIGEL CURTIS, M.D.*

Group A streptococci (GAS) produce a number of virulence factors that are important in the pathogenesis of invasive disease. Amongst the exotoxins produced by GAS are a number of superantigen toxins. Super antigens belong to a family of proteins that interact with the host immune system in a specific manner. A number of different organisms have been shown to produce superantigens including *Staphylococcus aureus*, GAS, *Yersinia spp*, Epstein-Barr virus and *Mycoplasma arthritidis*. In recent years, a number of new streptococcal and other superantigen toxins have been described.

Superantigens share a unique mode of action. They stimulate T cells without the requirement for processing by antigen presenting cells. Superantigen bind to the variable part of the ß chain (BV or V ß region) of the T cell receptor and, in conjunction with MHC class II antigens, cause activation and proliferation of T cells, that in turn leads to cytokine release from T cells and macrophages. In contrast to the highly specific interaction between conventional antigens and T cells, superantigen stimulation is limited only by the BV specificity of the T cell receptor. As all T cells belong to one of only 23 functional BV families, superantigens may activate a vast nuber of T cells up to 30% in vitro, and therefore induce an intense inflammatory response. This inflammatory response is believed to be responsible for the clinical and pathological features of superantigen toxin-medicated disease.

Superantigens are believed to play a role in the pathogenesis at staphylococcal toxic shock syndrome. It has also been suggested that these toxins are involved in the etiology of a number of other diseases, including atopic dermatitis, psoriasis, autoimmune disease and Kawasaki disease. Strains of GAS that produce superantigen toxins are associated with scarlet fever, streptococcal toxic shock-like syndrome and necrotising fasciitis. Although there has been a vast increase in the understanding of the immunology of superantigens, their role in the pathogenesis of invasive disease remains less clear. The various bacterial and

*Department of Pediatrics, University of Melbourne and Royal Children's Hospital, Melbourne, Australia

host factors that influence the development of invasive disease caused by superantigen toxins are gradually being unravelled. Understanding the contribution of these important virulence factors to the pathogenesis of invasive streptococcal disease provides opportunities for new targeted treatments and the possibility of future vaccine development.

TOWARDS DEVELOPING A VACCINE FOR GROUP A STREPTOCOCCUS

MICHAEL GOOD, M.D.*

Infection with group A streptococci (GAS) leads to acute and post-infectious pathology, the most serious of which is rheumatic fever/ rheumatic heart disease (RHD). The incidence of these disease is particularly high in developing countries, such as Australian's aboriginal population, who experience the highest incidence worldwide. A vaccine to prevent GAS infection would that lead to significant improvement in public health throughout the world. Immunity to GAS is mediated by antibodies to the M protein. However, this protein presents a fundamental obstacle for the immune system, inhibiting neutrophil-mediated phagocytosis. When opsonised by antibodies directed to its amino terminus, however, the organism can be phagocytosed and cleared. A further impediment to the immune system, is that the immunodominant antibody epitopes on the M protein display antigenic polymorphism delaying the eventual development of GAS immunity by 10-20 years.

Exposure to GAS thus leads to multiple infections which are terminated by the eventual development of strain-specific immune mechanisms or by chemotherapeutic intervention. Excessive exposure, particularly if associated with significant pharyngitis, can lead to rheumatic fever and rheumatic heart disease. While the pathogenesis of these conditions is not clear, accumulating evidence suggests that they are autoimmune disorders involving immunological cross-reactivity between GAS proteins and host tissues. Both antibodies and T cells have been implicated. These constraints have that severely hindered our ability to develop protective vaccines. However, different approaches have been developed to circumvent these obstacles.

Recent observations suggest that the carboxylterminal region of the protein which is highly conserved, may also lead to protective antibody response, although this region is less immunodominant than the aminoterminus. We have defined conserved regions of the protein which show great promise in vaccine development. Immunization of mice leads to the production of opsonic antibodies. Furthermore, we have been able to define a minimal epitope within the conserved region, which while stimulating opsonic antibody production, does not stimulate auto-reactive responses. This epitope forms the basis for a vaccine which will be tested in humans.

BATTLING DRUG RESISTANT MALARIA

MA. DORINA B. BUSTOS, MD, PHD.*

Malaria drug resistance is currently a serious global problem. Chloroquine resistance is widespread in most endemic areas around the world, and resistance is now emerging to sulfadoxine/pyrimethamine in African countries that have started using this drug. The current supply of anitimalarials affordable in developing countries is limited to two main drugs: chloroquine and sulfadoxine/pyrimethamine (SP). In the event of full resistance to these cheaper drugs, the use of more efficacious, second line drugs against multi-drug resistant P. falciparum malaria would pose an enormous fiscal burden in malaria endemic countries. Protecting the current and newly introduced drugs is, therefore, of utmost priority. The theoretical basis underlying the use of drug combination in preventing or delaying the emergence of drug resistance is well established and has been used successfully in diseases as tuberculosis, HIV and leprosy.

Developing a strategy against drug resistant malaria depends on three important elements. Firstly, defining the extent of the problem with the use of sensitive and specific methods for the early detection of resistance, and epidemiological mapping. Secondly, optimizing drug treatment to ensure both high efficacy and low toxicity with the aim of delaying the emergence of resistance. And thirdly, reviewing and implementing drug policies, based on sound clinical research data, which should be evaluated and revised

*Cooperative Research Centre for Vaccine Technology,
The Queensland Institute of Medical Research, Brisbane, Australia

*Research Institute for Tropical Medicine, Alabang,
Muntinlupa City, Philippines

with the changing epidemiology of drug resistance disease. So far, antimalarial drugs have been used alone (single agent chemotherapy) and exploited to the point where they become ineffective; then a new drug is introduced.

It is the aim of this paper to focus on the second element, the use of highly efficacious drugs in areas where malaria drug resistance is a problem. It is not a question of inappropriate treatment alone. In remote areas where physicians may not always have the best available facilities nor resources to help their patients, with effective treatment as their primary objective, we cannot also overlook the risks of over treatment and reactions to irrational drug combinations in the absence of pharmacokinetic knowledge of these compounds.

In parts of Asia and the Southwest Pacific, i.e. Laos, Philippines, Malaysia and Indonesia, Pf resistance to chloroquine and SP is variable. Chloroquine resistance in P. vivax has also been reported in Irian Jaya, Myanmar, Papua New Guinea and Vanuatu. On the western and eastern borders of Thailand, P. Falciparum has developed resistance to choroquine, SP and mefloquine, and with declining efficacy to quinine (multi-drug resistance). In some areas, treatment failure rates to high-dose mefloquine in children with acute malaria have reached 50%. The addition of artemisinin derivatives, artesunate and artemether, has substantially improved the efficacy of mefloquine, and with 3-5 day courses of combined treatment, cure rates still exceed 85%. Studies on the use of combination therapy in malaria are currently being done in some countries to look at the benefits of adding artemisine derivatives to existing first-line therapy, a UNDP/ World Bank/WHO TDR Project. This paper shall discuss the appropriate recommended antimalaria regimen depending on the degree of resistance and source of infection of the patient.

SCHISTOSOMIASIS – The Philippine experience

GEMILIANO ALIGUI, M.D.

Schistosomiasis has been a major problem in the Philippines for more than 50 years since the first large-scale field surveys in 1940. At that time, it was estimated that there were about 300,000/ Although death from this disease was estimated to be less than 1% the disability from hepatosplenic pathology was usually more than 90%. Today, the estimate is approximately 500,000 but the disability from hepathosplenic injury is approximately 7%. Prior to 1980, the prevalence of schistosomiasis was generally above 50% and since then significant efforts and money have been allocated to combat the problem. Three approaches were tried (usually in combination), namely: chemotherapy (using praziquantel), molluscicide (using niclosamide) and environmental sanitation. Of these, only chemotherapy remains to be the most cost-effective method of schistosomiasis control which brought significant improvements in community health. Given this accomplishment, there are still important issues related to subtle morbidities which need to be addressed: (1) the timing and frequency of chemotherapy and (2) the elucidation of the immunologic mechanism of disease that are relevant in the development of vaccines. We found evidence of growth stunting in infected children during adolescence. Cognitive dysfunction remains to be studied in Filipino children in endemic areas. Our studies on cytokine response in a defined population indicate that acquired resistance can develop at mid to late teens. Although we do not predict that an effective vaccine might be realized in the next 5 years, we confirm that recombinant pramyosin can induce alpha interferon response suggesting that the molecule can be a promising vaccine candidate. Immediate concerns must be focused on surveillance most especially on the performance of field diagnosis since our mathematical modeling indicate that the current practice and testing procedure underestimate true prevalence by as much as 50%. In response to this situation, we are currently developing a "dipstick" method of schistosomiasis diagnosis by measuring urine cathodic antigen, specific for *S. japonicum*. The exposure model that we have developed for *S. japonicum* also contradicts the classical functional form of exposure model for the two other species, suggesting that there are behavioral and ecological factors that differentiate the transmission pattern-at least in the Philippine setting. For thirty years we believe water buffalos to be a significant reservoir of the disease, now, we found that none of the water buffalos we examined in 4 strategic locations in the Philippines were infected. This demonstrates that animals may be less of a priority for intervention in order to reduce transmission and might not be a good target of first-line vaccination trials because or their role in transmission is less important than that of humans. As an applied epidemiologic tool, we have started to develop surveillance methods for the new

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set of control strategies for schistosomiasis using geographic information system. Thus we show that the Philippines have made significant strides in the scientific community as regards the study and control of *Schistosomiasis japonicum.*

CONTROL OF FILARIASIS

Vicente Y. Belizario, Jr., MD, MTM &H*

Lymphatic filariasis remains as a major public health problem in the developing countries. It poses significant social and economic burden, affecting over 120 million people in 73 countries. It is the second leading cause of permanent long-term disability worldwide. About 20% of the world's population live in areas where they continue to be at risk of infection. *Wuchereria bancrofti* comprise about 90% of infections, while *Brugia malayi* about 10% of them . Almost half of all people with lymphatic filariasis have overt clinical disease. The rest are asymptomatic, but with internal damage undetected and untreated. Among the easily recognized clinical manifestations are lymphedema and elephantiasis of renal limbs or genitals, hydrocele, lung disease, and chyluria. Pre-clinical, internal damage to lymphatic and renal systems as well as abnormalities of renal function have been estimated to occur in millions of people. In the past several years, there have been significant advances which have led to a much better understanding of the severity and burden of disease, new diagnostic and monitoring tools, and new treatment and control methods. Control of lymphatic filariasis is based on controlling transmission of the parasite and preventing or easing the consequences of disease. Diethylcarbamazine (DEC) and ivermectin are drugs that kill microfilariae in the blood which then prevents transmission on the parasite. The drugs may be given alone or in combination, in a single dose once a year. Ivermectin given with albendazole single dose also results in a very marked reduction of microfilaria counts. The use of table salt fortified with DEC has been shown to completely interrupt transmission, but this works best in areas where the delivery salt can be well-regulated. Practicing simple hygiene has been shown to significantly reduce elephantiasis and associated infections. Certain measures help in preventing the development of lymphatic disease in infected individuals who are still asymptomatic and in stopping disease progression in individuals with slight lymphatic damage. These measures also stand to benefit those with advanced lymphedema of elephatiasis since collateral lymphatic channels can re-established lymph flow if secondary infection is avoided.

*Department of Parasitology, *Associate Professor and Former Chair,* College of Public Health University of the Philippines Manila

CONTROL OF JAPANESE B ENCEPHALITIS THROUGH IMMUNIZATION IN KOREA: PAST, PRESENT AND FUTURE

YOUNG MO SOHN, M.D.*

The expanded JE immunization program resulted in the significant reduction of the incidence of JE in Korea, together with the improvement of environment, sanitation and higher standard of living. Although the inactivated mouse brain derived-JE vaccine has been used successfully for twenty years in Korea, there are still some questions about its adequate immunization schedule including uncertain policies on age and schedule of primary and booster administration. Two doses 4 weeks apart with a booster one year later has been recommended as a primary immunization and thereafter boosters given annually through out primary school. Total 12 boosters were recommended until 15 years of age. However, the duration of immunity after serial annual boosting is not well known. After starting EPI against JE, JE occurred in adults rather than children for last 10 years – two third of patients (12/18) was adults middle aged persons. Although there is no active surveillance study to find out adult JE cases, JE is becoming a disease of adults in Korea. Adult group is seems to be beyond of the protection with waning immunity. We should consider if there is a need to maintain the long-term immunity by old ages to protect secondary vaccine failure.

The booster immunization schedule has been a burden to the public, because of limited period of vaccination, mass immunization with inappropriate clinical practice, uncertain effect of the long-term immunity in the old age group, poor recognition of adverse events and uncertain guarantee of vaccine quality in Korea. In 1994, the cluster of severe systemic adverse events after JE vaccination was reported spontaneously. Two sudden deaths were attributed to anaphylaxis after vaccination and four cases of severe

neurological illness including encephalopathy and acute disseminated encephalomyelitis. The causal relation between JE vaccine and the cluster of severe adverse events has not been completely determined. But the potential causality and retrodictive causality including timing of events, characteristics of the adverse reactions, susceptibility, alternative etiologic agents showed no evidence of the rejection of causal relation. The evidence might be thought rather in favor of the acceptance of causality. Concern over the adverse reaction in the public and medical community led to refuse the vaccination. The public concern turned out to the decreased coverage rate. There was a public debate regarding JE immunization schedule. In 1995, the Advisory Committee of National Immunization Program announced that there would be a need to improve the JE immunization program with regard to the schedule, age, booster and vaccine strain. At first, the annual booster schedule was temporarily changed to once-in-every two years. Recently the governmental authority began to re-evaluate the safety and quality of vaccine produced in this country and the Advisory Committee of National Immunization Program evaluated the JE national immunization program regarding the public burden and the effort of running the program.

In 1996, seroprevalence study took place to evaluate indirectly the efficacy of JE immunization program for primary school children. Plaque reduction neutralizing antibody test was conducted at the Department of Virology, United States Army Medical Components-Armed Forces Research Institutes of Medical Sciences (Bangkok, Thailand). According to the time interval from the last booster injections in 311 children, the neutralizing antibody titers gradually decreased as the duration of booster intervals increased – 239.2 for 6 months, 187.9 for 18 months, 133.7 for 30 months. The seropositivity rate was 98.1% (152/155), 99% (103/104) and 95.6% (43/45) for 6 months, 18 months and 30 months, respectively. However, seropositivity rate for more than 42 months was 71.4% (5/7).

Attenuated SA 14-14-2 Japanese encephalitis vaccine has been administered safely and deffectively to more than 100 million children in China since 1988 and recently, licensure of the vaccine in Korea has been sought. In the first clinical evaluation of the vaccine outside of China, side effects ion 84 children were monitored and antibody responses to a single dose given as primary JE vaccination were evaluated in 68 children, 1-3 years old (mean age 27 months). No significant adverse events were noted. Neutralizing antibodies (GMT of 188) were produced in 96% of the 28 subjects. In 10 other children who previously has been immunized with two or three doses of inactivated JE vaccine, the booster administration of SA 14-14-2 vaccine produced an anamnestic response in all, with a GMT of 3378. In a comparison group of 25 children previously immunized with two doses of inactivated vaccine, neutralizing antibody titers were detected in 16(64%). Viral specific IgM was detected in nine primary vaccines (13%) but in others, IgM may have declined to undetectable levels in the four week post immunization sample.

Our preliminary observations show that a single booster with SA 14-14-2 vaccine is enough to elicit high neutralizing antibody titers in the children and more effective secondary immune response than the Nakayama vaccine in Korea. A single booster with SA 14-14-2 vaccine might be one of the possible ways not only to decrease the frequency of booster vaccination and the risk of vaccine adverse events but also reduce the economic burden and public concern in Korea.

ANTIBIOTIC RESISTANCE-TRENDS AND POLICIES

MIEKE HOOGKAMP-KORSTANJE, M.D.*

Resistance is the result of mutation of acquisition of resistance genes, often induced by bacterial stress as an answer on e.g. pollution of the environment, contact with heavy metals, nitric oxid, drugs and antibiotics. To get insight in the significance of resistance many surveillance programs are initiated all over the world. However data produced are often isnapshots and give no information on incidence of species, distribution, shifts and trends in time. Over more most data are from developed countries, collected within multi-centre studies, hospital-associated and from undefined patient groups. Very few is known from susceptibility patterns of commensals in healthy subjects. Only ongoing surveillance in a well-defined population with well-defined indicator micro-organisms can provide useful information on trends.

Within urinary pathogens Esherichia coli is the most important microorganisms. From surveillance we observed that E. coli isolated from uncomplicated UTI, complicated UTI or from faeral flora have quite

*University Hospital St. Radboud, Nijmegen, The Netherlands

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different susceptibility patterns. This may reflect use of certain antibiotics and is directive for the choice of empiric therapy in specific patient groups.

Within respiratory pathogens Haemophilus influenzae and Streptococcus pneumoniae play a major role. Since 1977 resistance to ampicillin in H. influenzae has spread over the world, but there is a considerable difference between countries; resistance prevalence varies from 10->50%. This is also observed with penicillin-resistance in S. pneumoniae (0->50%) and in methicillin-resistance in Staphylococcus aureus: 0->80%.

Convinced that antibiotic use and policy are important determinants for development of resistance we introduced antibiotic policies in many hospitals in The Netherlands during the last 25 years. Mainstays are: any policy better than no policy, restricted arsenal (1 drug per antimicrobial group, 1 drug for 1 indication and 1 alternative for exceptions, same drug for same indication, no permit for drugs not listed in the guide book, control by pharmacist and microbiologist), ban on certain antibiotics, isolation of patients with multi-resistant strains, surveillance of indicator micro-organisms. Commitment and solidarity with colleagues of many disciplines and intensive escort of medial microbilogist, infectious disease specialist and pharmacist are mandatory. This has resulted in an overall low percentage of resistance in hospitals. Examples of the 1998 multi-centre surveillance in % are: MRSA <1, penicillin-resistant S. pneumoniae <1, ampicillin-resistant H. influenzae 10, vancomycin-resistant enterococci <1, amoxicillin-resistant E. coli 40, cotrimoxazole-resistant E. coli 34, nitrofurantoin-resistant E. coli 2, ciprofloxacin-resistant E.coli 3, gentamicin-resistant Pseudomonas aeruginosa 2, ciprofloxacin-resistant P. aeruginosa 4. No significant increase in resistance was observed over the years.

EFFECT OR ANTIBIOTIC TREATMENT ON THE SPREAD OF RESISTANT RESPIRATORY TRACT PATHOGENS (RTP)

RON DAGAN, M.D.*

In the presence of increasing resistance among RTP, it is important to attempt to answer to relate but different question with regard to antibiotic treatment: 1) Is the increasing antibiotic-resistance among RTP related to increasing bacteriologic and clinical failure rate? And 2) Does the use of antibiotics promote the carriage and spread of antibiotic resistance pathogens? Those two question differ significantly: The first addresses the issue of the impact of resistance on the individual whereas the latter addresses the antibiotic effect of the treatment on the society as a whole.

When a antibiotic is administered the drug is absorbed and distributes to all body compartments, including the nasopharynx, where it rapidly reduces the concentration of organisms that are susceptible to the drub. A rapid replacement occurs with either the already existing organism that are more resistant to the drug or by acquisition of new resistance organisms. This presentation will concentrate on the example of Streptococcus pnuemoniae (Pnc) carried in the nasopharynx as a representative example.

Most children are often colonized with Pnc during their first years of life. Today, many of the Pnc are resistances to various antibiotic drugs, mainly to penicillin. A large body of evidence has been accumulated showing that the carriage of antibiotic resistance Pnc is associated with recent antibiotic treatment. A series of news studies was able to reveal some the early processes that occur in the nasopharynx during and in theimmediate post-treatment period of cases of respiratory tract infections, in regard to antibiotic-resistant Onc. Those studies could correlate the following: 1) Most studied drugs (amoxicillin/clavulanate, cefpodoxime, cefuroxime-axetil, azithromycin and trothoprim/sulfamethoxazole [TMP/SMX]) had a substantial effect on the nasopharynx and were able to eradicate on the reduce the carriage of pneumococci that were susceptibel to the drugs. 2) For all drugs, only little, if any, effect was seen when the organisms has reduced susceptibly tot he administered drug. 3) Some drugs, such as azithromycin and TMP/SMX seemed to promote colonization with resistant S. pneumoniae in general and penicillin non-susceptible S. pneumoniae in particular (amoxicillin/clavulanate, cefuroxime-axetil) had stronger effect on S. pneumoniae colonization was rapid and was observed when tested already after 3-4 days of treatment.

*The Pediatric Infections Disease Unit, Soroka University Medical Center And the Faculty of Health Science, Ben-Gurion University of the Neges, Beer-Sheva, Israel

Furthermore, antibiotic drugs were able select new pneumococcal strains either by overgrowth of strains that were masked by other organisms or that were rapidly acquired initiation of treatment. The main drugs associated with such a phenomenon were the long acting macrolides/azalides and trimethoprim/ sulfamethoxozole.

Thus, the widespread use of antibiotics for AOM in the era of prevalent resistance in associated not only with reduced bacteriologic and clinical responses in the individual patient, but also increases in the nasopharyngeal carriage of resistant organisms, which in turn facilitates their spread to others in the society, especially tot he age group in which AOM in most prevalent. This creates a vicious cycle that is difficult, if at all possible, to overcome (Figure 10). The presence of such a vicious cycle poses a real challenge to society and innovative approaches must be tested to reduce this phenomenon. Efforts should be made to reduce antibiotic use, to study the possibilities of preventing colonization by various non-antibiotic substances, and to study vaccines against pathogens predisposing or causing AOM.

PHARMACODYNAMICS AND PHARMACOKINETICS – NEW STRATEGIES TO PREDICT EFFICACY

MICHAEL R. JACOBS, MD, PHD*

To understand the relationship between drug dose and efficacy, pharmacokinetic (PK) and pharmacodynamic (PD) characteristics need to be integrated. Patterns of antimicrobial activity generally fall into one of two patterns: time-dependent killing (seen with many antibiotic classes, including β-lactams and macrolides) and concentration-dependent killing (seen with aminoglycosides, quinolones and azalides).

The efficacy of animicrobials showing time-dependent killing is dependent on the duration of exposure of a pathogen to the antimicrobial. The major PK/PD parameter correlating with efficacy of time-dependent animicrobials is the serum concentration present for 40-50% of the dosing interval. Based on this, PD Breakpoints can be calculate as the serum concentration maintained for at least 40-50% of a dosing interval by particular dosing regimens of antimicrobial agents. Therefore, if an agent is to be useful for empirical therapy, the MIC against a pathogen must be less than or equal to the PD breakpoint. The efficacy of concentration-dependent killing is depended on the antimicrobial concentration at the site of infection. The major PD/ PK parameter correlating with the efficacy of these antimicrobials is the 24 hour area under the curve to MIC ratio, which should de $\geq$25 for immunocompetent patient and $\geq$ 125 in immunocompromised or in life threatening infections PD breakpoints for such agents can, therefore, be calculate from the formula AUC ÷ 25 for immunocompetent patients. As for time dependent killing, the MIC of concentration-dependent antimicrobials against a pathogen needs to be less than or equal tot he PD breakpoint for the agent to be useful empirically.

In designing effective treatment regimens, the ability of an antimicrobial dosing regiment to meet these PK and PD parameters against pathogens should be considered. Using PD parameters, MIC breakpoints predictive of clinical outcome can be defined. These PD breadpoints can be used in conjunction with MIC data from local surveillance studies to predict antibiotic efficacy in an empirical setting. This is particularly important for oral dosing regimens for the treatment of emerging resistant respiratory tract pathogens in many parts of the world.

These findings emphasize the need for continue epidemiological monitoring of animicrobial resistance round the world and for reassessing current antimicrobial practice.

BACTERIAL AND CLINICAL SUCCESS-RECOMMENDATIONS FOR JUDICIOUS ANTIBIOTIC USE

URS SCHAAD, M.D.

Increasing antibiotic resistance has a negative impact on the treatment of respiratory tract infections (RTIs), but the true extent of this impact has remained largely unqualified. Recent studies in acute otitis media (AOM) have established the double tap methodology (tympanocentesis before and during treatment) as in effective clinical model, allowing investigation of the link between antibiotic resistance and antibiotic efficacy, as determined by

*Professor of Pathology and Medicine, Case Western Reserve University and University Hospital of Cleveland, USA

successful bacterial eradication,and clinical efficacy. Bacteriological eradication on Day 3-6 of therapy gives 93% chance of clinical success, whereas bacteriological failure results in 63% of patients (Marchant et al. J Pediatr 1992;120:72). The model can also indicate differences in the efficacies of amoxycillin/clavulanate and azithromicin in the treatment of AOM (Dagan et al., in press). The results of this study will be presented during the symposium.

This clinical model confirms that the efficacies of different antimicrobials vary and highlights the need to used potent agents that are able to eradicate the pathogen for the site of infection. Recent guidelines for the treatment of AOM from the Centers for Disease Control and Prevention (CDC) recommended oral amoxycillin as the first-line treatment, followed by oral amoxycillin/clavulanate, cefuroxime axetil or intramuscular ceftriaxone if treatment failure is apparent after 3 days.

CURRENT ABSTRACT

BACTERIAL MENINGITIS IN CHILDREN LESS THAN FIVE YEARS OF AGE AT A PROVINCIAL HOSPITAL IN THE PHILIPPINES

E. ABUCEJO, M.D.*, S. LUPISAN, M.D.*, B. QUIAMBAO, M.D.*, L. SOMBRERO, M.D.* M. LUCERO, M.D.*, R. CAPEDING, M.D.*, J. ARCAY, M.D.*, E. HERVA, M.D.*, P. RUUTI, M.D.*

Objective: To describe the clinical and laboratory profile of bacterial meningitis in children less than five years of age at a provincial hospital in the Philippines

Methods: To increase the previously infrequent use of lumbar tap for CSF samples, a guideline based on combination of neurologic symptoms and signs was develop. Blood and CSF samples were cultured for bacteria, and CSF agglutination was done for pnemococcus, meningococcus (A.C) and Haemophilus influenzae type b. Clinical and laboratory data of children less than five years old were collected from January 1995 to December 1998.

Age in months	No. of Patients	Etiologic agents
<2	6	S. pneumoniae (2), S. typhi (1), E coli (1), P. aeruginoza (1), e. cloac (1)
2-6	20	H. influenzae b (13), S. pneumoniae (3), S. pyogenes (3), Enterobacter sp. (1)
7-11	8	H. influenzae b (4), S. pyogenes (2), E. cloase (1)
12-23	4	S. pneumoniae (1), S. aureus (2), Non-typhoidal Salmonella (1)
24-59	6	H. influenzae b (2), S. aureus (2), K. pneumoniae (1) Enterobacter sp. (1)
Total	44	

Results: Six hundred seventy five patients fulfilled the criteria for CSF sampling, out of which 469 (69%) had CSF sample. Bacterial pathogens were identified in 44 (9.4%) cases (table. The frequent presenting signs and symptoms were convulsion (79%) fever (68%) drowsiness/lethargy (43%), bulging anterior fontanel (41%), neck rigidity (41%), and vomiting (34%). Male: female ratio is 1.3:1 Six (13%) patients died.

The most common pathogens identified were H. influenzae type b, 19 (43%) and S. pneumoniae, 7 (16%). The findings were made in both blood and CSF culture, 21 (48%), CSF culture alone . 14 (32%), CSF latex agglutination test alone, 3 (7%), and blood culture alone with concomitant CSF pleocytosis, 6 (13%). Fourteen (32%) had history of previous antibiotic intake. All strains of S. pneumoniae and H. influenzae type b were sensitive to chloramphenicol, cotrimoxazole and amipicillin.
Conclusion: S. pneumoniae and H. influenzae type b are the most common bacterial causes of meningitis specially in patients less than 1 year old.

*Research Institute for Tropical Medicine Manila, Philippines