

Secondary bacterial infections following viral respiratory infection

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Introduction

Bacterial superinfection in viral respiratory disease is a clinically well documented phenomenon. However, the frequency with which this occurs and the pathogenic mechanisms involved remain poorly understood. Respiratory pathogens like *Streptococcus pneumoniae* and *Haemophilus influenzae* are often carried in the nasopharynx in healthy individuals. Physical damage to respiratory tract may lead to opportunistic invasion of these bacteria. Enhancement of bacterial adherence by the infected respiratory cells may play an important role. The epidemiological evidence, in vitro and in vivo experimental data on the predisposition of bacterial infections

in viral respiratory illness are presented and recent postulations that help to explain this phenomenon are discussed.

Epidemiological Evidence

The incidence of secondary bacterial pneumonia varied from 2% - 18% during the influenza pandemics in 1918 - 1919 and 1957-1958 (1). A three-fold increase in incidence of pneumonia due to *S. aureus* during the influenza pandemic of 1968-9 compared to a non-epidemic period was observed (2). Other organisms documented included *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and other alpha- haemolytic streptococci. However, the relative frequency with which these different organisms cause secondary pneumonia during or after influenza has not been determined.

In a prospective, population-based surveillance study on 8851 children <15 year's old for community acquired pneumonia (CAP) in Finland (3), it was shown that 39% (20/51) of the children with CAP with confirmed viral aetiology also had bacterial involvement. Conversely, among cases with bacterial pneumonia, only 24% (20/82)

cases had serological confirmation of viral co-infection. The commonest mixed viral-bacterial agents were RSV (respiratory syncytial virus) with *S. pneumoniae*. However, a drawback from this study was that during the surveillance period, no positive serologically confirmed cases of influenza virus infection was detected and

thus secondary bacterial infections subsequent to influenza could not be evaluated.

In 2000, O'Brien (4) at the CDC, Atlanta performed a case-control study to determine if preceding influenza (H1N1) infection was associated with severe pneumococcal pneumonia. She demonstrated that patients with severe pneumococcal pneumonia were significantly more likely than controls to experience an influenza-like illness preceding admission (OR 12.4; 95% CI, 1.7-306), and had positive influenza A convalescent serology to controls (OR 3.7; 95% CI, 1.0-18.1). This further supported that severe bacterial complications occurred in viral respiratory infections.

Evidence from in vitro and in vivo Experimental Data

Enhanced bacterial adherence effects of *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Staphylococcus aureus* have consistently been demonstrated in experimental conditions in monolayers of epithelial cells, including Madin-Darby canine kidney (MDCK), HEp-2, and HeLa, infected at separate experiments with influenza A, rhinovirus, RSV and adenovirus.

Enhanced adherence of both *Staphylococcus aureus* and Group B *Streptococcus* have also been shown in the nasopharynx of ferrets pre-infected with influenza A virus (5). In addition, using the chinchilla otitis media model, it has been demonstrated that in the group co-infected with both influenza A virus and *Streptococcus pneumoniae*, otitis media was documented in 67% of cases versus 21% and 4% for those infected with *S. pneumoniae* or influenza A virus alone (6).

Pathogenic Mechanisms of Bacterial Adherence during Viral Infection

Previously, impaired local defence and the physical damage to the local respiratory tract epithelium with exposure of the basement membrane were thought to enhance bacterial adherence and invasion. RSV has been shown to induce ciliary injury, with ciliostasis, clumping and loss of cilia from bronchial cells in vitro (7). Necrosis of the bronchial epithelial lining occurred in influenza A virus infection (8).

Experimental studies increasingly indicate that different mechanisms for increased bacterial adherence induced by viruses are operating for specific viral-bacterial combinations. Bacterial-cellular interactions occur at the host cell membrane. Viral glycoproteins, such as glycoprotein G, neuraminidase, and haemagglutinin, expressed on host cell may act as bacterial cell receptors for adherence. Virus-induced changes on host cell membrane may also mediate binding of bacterial cells. Upregulation of pre-existing receptors: CD14 and CD15 in RSV-infected HEp-2 cells have been associated with enhanced adherence of non-piliated *Neisseria meningitidis* (9). Subsequent finding demonstrated that the use of monoclonal antibodies to CD14 receptors significantly reduced binding of *N. meningitidis* ($p < 0.001$) (10). In addition, extracellular matrix provides bacterial binding to virus-infected cells. Fibrinogen enhanced the adherence of Group A streptococcus to influenza A-infected cells, by binding directly to neuraminidase or haemagglutinin. (11).

In a recent study using the mouse model, McCullers JA and his study group (12) demonstrated that the timing of exposure between the influenza virus and *S. pneumoniae*, and the infective dose of the pathogens were critical in the outcome of the infections; in terms of the severity, rapidity of progression of the disease and survival. He challenged mice pre-infected with a mouse-adapted influenza virus with an encapsulated strain of *S. pneumoniae* at different times relative to the influenza infection. He demonstrated that the effect was most severe when the pneumococcal challenge was given 7 days post-influenza infection; with 100% mortality and mean duration of survival for < 24 hours. Pathological findings in the lungs were also extensive with

widespread consolidation and obliteration of alveolar architecture. A gradual improvement on percentage and mean duration of survival were observed when the pneumococcal challenge was administered after 9 to 21 days of influenza infection. The explanation for this was that the virus infection altered the host in such a way that it was most susceptible to pneumococcal infection at Day 7, but this alteration returned to normal within 2-3 weeks of infection. One postulation was that the alteration occurred at the level of pneumococcal receptor(s), allowing for spread of pneumococcus beyond that of a focal, lobar process. This was further supported by a study from Tong HH et al (13) using the chinchilla otitis media model, that terminal sialic acid residues are removed from Neu5Ac(a2-6)Gal receptors on the endotracheal epithelial cells during the influenza infection and GlcNAc(p1-4)Gal, a component of pneumococcal receptor, becomes exposed in the epithelium. He found that combined influenza A and *S. pneumoniae* infection significantly altered the cell surface carbohydrate structure of the epithelium beyond that by the individual pathogen alone. The removal of sialic acid residues is from the action of neuraminidase, but the contribution of this by the two pathogens require further evaluations. Increasing data is available to interpret at the cellular level, how bacterial superinfection interplay in viral respiratory diseases. The mechanisms involved are likely to be multifactorial and complex. Viral infection induces profound systemic effects in the human host with modulation of the host immune response. The modulation of cytokines and chemokine secretions are likely to play an important role and already, suppression of neutrophil chemoattractants e.g. IL8 (14) and defective chemotaxis and phagocytic function (15) have been demonstrated to occur and increase the host susceptibility to bacterial infection.

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An update on tuberculosis therapy
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In April 1993, WHO declared TB as a global emergency. In its website recently, WHO reiterated the persistence of the TB threat and called for strengthening of control measures. In August 2002, WHO estimated that between 2002 and 2020, approximately 1000 million people will be newly infected, over 150 million people will get sick, and 36 million will die of TB.

Back in the 2000 World Health Assembly, the Global Partnership to Stop TB was formed and the following targets were set: by 2005, 70% infectious TB cases will be diagnosed, and the treatment success rate will reach beyond 85%. The Global Partnership was supported by a structured organization consisting of various working groups, forums, coordinating board, secretariat, technical advisory groups and TB fund and drug facility. Among these, there is a Working Group on TB Drugs Research & Development promoting studies of new drugs.

To fight tuberculosis, DOTS (directly observed treatment, short course) remains the cornerstone of the control strategies. DOTS consists of five components: government commitment, use of smear microscopy for case detection, standardized short course treatment under direct observation, regular supply of quality drugs, and a monitoring and reporting system. Hence, DOTS expansion would mean not only enhancement of treatment success, but also improvement of case detection. However, with the rising importance of drug resistant TB, additional measures were considered necessary. In 2000, WHO set up guidelines for the establishment of DOTS-plus pilot projects, which encompasses three additional components: regular application of drug susceptibility tests, continuous surveillance of drug resistance pattern, and modification of drug regimen according to susceptibility tests.

Currently available anti-tuberculosis agents include a number of first and second line drugs. However, the development of more new drugs are necessary, and ideally, they should have the following properties and characteristics: shortening the total duration of treatment, increasing the

dosing interval of intermittent regimens, higher efficacy including activity against drug-resistant organisms, less expensive, less side effects, and suitable for use under special circumstances, e.g., in AIDS patients. Some drugs of particular interest are described in the following paragraphs.

Rifapentine is a derivative of rifamycin B with complete cross-resistance with rifampicin. Compared with rifampicin, it has a half life of around 13 hours, about five times as that of rifampicin. 95% of the drug is protein-bound compared with 80% for rifampicin. The first internationally reported randomized clinical trial on rifapentine was conducted in Hong Kong. The Hong Kong Trial consisted of three arms, all employing the same drugs in the initial phase for two months, including streptomycin, isoniazid, rifampicin, and pyrazinamide given thrice weekly (SHRZ₃). In the subsequent four months' of continuation phase, the first arm consisted of isoniazid and rifapentine 600 mg once per week (HRp₁), the second arm consisted of isoniazid and rifapentine 600 mg once per week but given for 2 weeks out of every 3 weeks (HRp_{1(2/3)}), and the third arm was the control regimen using isoniazid and rifampicin thrice weekly (HR₃). Results showed that the rifapentine-containing regimens had a high relapse rate of around 10% as compared with 4% for the control regimen. It was concluded that the rifapentine dosage was probably too low as a high proportion of the drug was protein-bound with a low percentage of free active drug. Adverse outcome in terms of failure or relapse was associated with extensive disease shown on the pretreatment radiographs.

Subsequently, CDC (Centers for Disease Control and Prevention) of the United States reported an essentially similar study but which contained only 2 arms: the study arm using HRp₁, (isoniazid and rifapentine 600 mg once weekly) and the control arm using HR₂ (isoniazid and rifampicin twice weekly) in the continuation phase. Again, the rifapentine-containing regimen showed a high relapse rate similar to that of the Hong Kong study. Factors independently associated with increased risk of failure or relapse included persistence of positive sputum culture at 2 months, presence of cavitation on chest radiograph, and bilateral pulmonary involvement. It was concluded that rifapentine once a week was safe and effective for the treatment of

pulmonary TB in HIV-negative people without cavitation on CXRs, and that clinical, radiographic, and microbiological data helped to identify patients with TB who are at increased risk of failure or relapse when treated with either regimen.

In view of the unsatisfactory results when 600 mg rifapentine was used, CDC further conducted a study on the tolerability of higher doses of rifapentine given at 900 mg and 1200 mg. Rifapentine 900 mg once weekly appeared to be safe and well tolerated, and has been evaluated in Phase III efficacy trials of treatment of latent TB infection. The safety and tolerability of rifapentine 1200 mg would require further studies and evaluation.

Fluoroquinolones are another group of drugs under active research and development. Most have excellent oral bioavailability with favourable pharmacokinetic profiles for TB treatment. Moxifloxacin, a long-acting third generation fluoroquinolone with a half-life of around 12 hours, is tested for safety and tolerance for long-term use as well as efficacy in the CDC TB Trials Consortium Study 27. It has the potential of being used at a dosing interval of once per week when paired with rifapentine. A local study has retrospectively reviewed the roles of levofloxacin and ofloxacin in the treatment of 99 cases of multidrug resistant tuberculosis. The overall treatment success rate for those treated with levofloxacin-containing regimens was 90.0% compared with 79.7% for those treated with ofloxacin-containing regimens. Three factors were found to be independently associated with adverse outcomes in the form of treatment failure or relapse, namely, bacillary resistance to ofloxacin, poor adherence, and radiographic extent of disease more than the area of one lung. More detail analysis showed that the treatment success rates were better in the levofloxacin group than the ofloxacin group in the presence of 1 or 2 such adverse factors. However, the outcomes were equally good or equally bad in both groups with no or with 3 adverse factors respectively.

Fluoroquinolones have been recommended for use in a number of international guidelines for the management of community-acquired pneumonia (CAP). However, this raises the concern of possibly masking TB signs and symptoms leading to delayed diagnosis and

treatment of TB cases. In fact, this has already been reported recently by some small-scale studies. In addition, the emergence of tuberculosis resistant to fluoroquinolones will be another concern with the widespread use of this group of compounds in CAP. The TB Reference Laboratory of the Department of Health in Hong Kong has recently analysed the rates of drug resistance to ofloxacin in service sample specimens for the years 1999 and 2000: 0.7% among strains fully sensitive to the 4 first line anti-TB drugs, 7.4% among strains with resistance to one or more of the 4 first line drugs, 21% among multidrug resistant strains, and 4.5% overall.

Isocitrate lyase inhibitors belong to a novel group of compounds with potential activity against non-multiplying or semi-dormant bacilli, as recent studies showed that these bacilli are probably metabolizing lipid-rich host cell debris utilizing the glyoxylate shunt which involves the enzyme isocitrate lyase. Thus, it would be attractive to assess these drugs as sterilizing agents with a view to shorten the duration of anti-tuberculosis treatment.

Thiolactomycins are chemicals isolated from a soil *Nocardia* species. They target at cell wall synthesis by interfering fatty acid and mycolic acid metabolism. They are effective against isoniazid-resistant strains of *Mycobacterium tuberculosis* and are under active research activities.

PA-824 belongs to the group of nitroimidazopyran compounds. It is still in the preclinical phase of development and is found to target mycobacterial enzyme systems more effectively than rifampicin. There is no cross-resistance with current anti-tuberculosis drugs and it has potential in the treatment of drug-resistant tuberculosis, shortening TB therapy, as well as treatment of latent TB infection.

Many more other new agents are under active development. Apart from drugs targeting the tubercle bacilli, agents for immunomodulation are also potentially useful, such as recombinant BCG vaccine, *Mycobacterium vaccae*, interferon-gamma, and levamisole. Moreover, active research activities are ongoing in the area of TB/HIV coinfection as there are concerns of higher relapse rate, drug-drug interactions with the anti-retrovirals, drug malabsorption, as well as immune reconstitution

syndrome.

With the availability of therapeutic drug monitoring (TDM), the evaluation of new or existing drugs is greatly facilitated, particularly when treatment compliance, drug absorption or other pharmacokinetic problems are in question.

Research studies in tuberculosis have been seen to flourish in recent years. It is interesting and worthwhile to keep abreast with the availability of such new information. With the accumulation of new scientific data and knowledge in tuberculosis, we should be able to arm ourselves with more and better tools in the fight against this important global infectious disease.

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Acinetobacter infection

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Acinetobacter has emerged as an important nosocomial pathogen imposing a great challenge to clinical management and infection control.

At least 9 Acinetobacter species and 23 DNA groups (genomic species) have been recognized. Strains from genomic species 2 (*A. baumannii*), 3, and 13 sensu Tjernberg and Ursing (13TU) are frequently isolated from clinical specimens and are associated with nosocomial outbreaks; they belong to the *A. baumannii* complex. Together with genomic species 1 (*A. calcoaceticus*), they form the *A. calcoaceticus*-*A. baumannii* complex. Acinetobacter species are ubiquitous environmental organisms, present both inside and outside the hospital. They have been found in vegetables, fish, meat and soil. They can survive on moist surfaces such as respiratory therapy equipments, and on dry surfaces including the hands of healthcare staff. Their ability to survive under dry conditions for up to four months is unusual for gram-negative bacilli. In the hospital, Acinetobacter species have been isolated from tap water, sink traps, floors, angiography catheters, blood collection tubes, plastic urinals, pillows, mattress, bedside cupboards, curtains and air in the intensive care unit (ICU).

In hospitalized patients, *Acinetobacter* species have been isolated from the gastrointestinal (GI) tract, respiratory tract, skin and oral cavity. Colonization of hospitalized patients with Acinetobacter species after admission occurred rapidly, usually during the first week of stay. These bacteria appear to be the normal flora in oropharynx, skin, respiratory tract or GI tract of a small number of healthy people. In Hong Kong, the skin carriage of *Acinetobacter* species in healthy subjects was characterized by variation in genospecies and strains (1).

An Emerging Nosocomial "Superbug"

Multidrug-resistant Acinetobacter has caused outbreaks in different parts of the world including the United States, Europe, Middle East, South America and Far East Asia. In some areas of the United States,

Acinetobacter species has accounted for 10% of all nosocomial gram-negative isolates. In Europe, *A. baumannii* has become the fifth most commonly isolated Gram-negative pathogen from the ICUs. In Hong Kong, *Acinetobacter* infection was reported to be endemic and have a higher incidence of nosocomial infection, including bacteremia and pneumonia, than elsewhere (2-5).

Seasonal Pattern

Siau et al described an increased isolation rate of *Acinetobacter* species in Hong Kong during summer (5). The Centers for Disease Control and Prevention (CDC) also described a seasonal pattern of *Acinetobacter* infections with an infection rate that was twice as high in late summer as in the early winter (8). Temperature and humidity changes were discussed as the possible reasons for this finding.

Clinical Impact

Acinetobacter species can cause a wide spectrum of nosocomial infection in susceptible patients. They include respiratory tract infection, urinary tract infection, wound infection (especially burn wound), septicemia, endocarditis, peritonitis and meningitis. Septicemia due to *Acinetobacter* species was reported to have a mortality rate as high as 32-36%. Intravascular catheter and lower respiratory tract were the leading infection sources of *Acinetobacter* in Hong Kong (3,4).

Acinetobacters are opportunistic pathogens. Patients with malignancy, burns, trauma and surgery are susceptible groups in the hospital. Immunosuppression (including splenectomy, corticosteroid, antineoplastic therapy, organ transplantation or AIDS) increases the risk of *acinetobacter* bacteremia. In Hong Kong, the ICU was reported to be the commonest location of acquisition of *Acinetobacter* bacteremia (3). Catheter, tube insertion, and artificial devices especially mechanical ventilation are recognized risk factors of *Acinetobacter* infection. Secondary colonization with *Acinetobacter* species in the ICU has been thought to be a major attribute for subsequent development of *A. baumannii* infection. Same as other multidrug-resistant nosocomial pathogens, prior use of broad-spectrum antibiotics is significantly

associated with *Acinetobacter* sepsis.

Community-acquired *Acinetobacter* infections have been reported. They include pneumonia, bacteremia, urinary tract infection and meningitis. In patients with community acquired *A. baumannii* bacteremia, malignancy was the most commonly associated disease.

A Challenge for Infection Control

Wide adaptability to the environment and the emergence of multidrug-resistant strains has led *Acinetobacter* as one of the "superbugs" in the hospital. In Hong Kong, Houang et al. noticed a high rate of infection and patient colonization by *Acinetobacter* species despite a strict practice of hand washing by the hospital staff and implementation of barrier precautions for contact isolation (2).

Outbreaks of multidrug-resistant *Acinetobacter* infection have been associated with both environmental sources such as ventilation equipment, intravascular access devices, reusable temperature and oxygen monitoring probes, curtains, mattresses and pillows, as well as the hands of hospital staff. The sources of outbreaks have been attributed to either the introduction of a new clonal strain or the emergence of a multidrug-resistant strain from the endemic pool. A study done in Taiwan showed that the increasing use of carbapenems and ciprofloxacin as well as clonal dissemination might have contributed to the wide spread of multidrug-resistant *A. baumannii* in the hospital (7). The issue of inter-institutional clonal spread of multidrug-resistant *Acinetobacter* has been discussed in recent years. In one study, the spread of an epidemic amikacin-resistant *A. baumannii* strain in 9 different hospitals was documented (8).

Treatment of *Acinetobacter* Infection

A study conducted in Hong Kong showed that *Acinetobacter* species were highly resistant to most of the beta-lactams, aminoglycosides and fluoroquinolones, with only amikacin, imipenem and meropenem reliably active against these organisms (9). Multi-drug resistance is a common characteristic of *Acinetobacter* species. Antibiotic resistance to drugs

like carbapenem and amikacin has been increasing globally. Imipenem susceptibility rates have decreased to only 50% and 64.1% in certain hospitals of New York and Jerusalem respectively. Amikacin susceptibility rates were also reported to be only 32-87% in various studies. The most worrying finding is the emergence of *Acinetobacter* species resistant to all antibiotics except polymyxin, which is a highly toxic drug for systemic use.

Sulbactam and polymyxins are drugs that may be useful to treat carbapenem-resistant *Acinetobacter*. Sulbactam (a beta-lactamase inhibitor) has an intrinsic bacteriostatic activity against *Acinetobacter* due to its binding to a penicillin binding protein of *Acinetobacter* species. In the market, sulbactam is often available in combination with ampicillin or cefoperazone. The in-vitro activity of sulbactam/ampicillin combination is virtually the antimicrobial activity exhibited by sulbactam. In a recent retrospective study, the outcome of critically ill trauma patients with *Acinetobacter* ventilator-associated pneumonia treated with either ampicillin-sulbactam or imipenem-cilastatin was similar. Other uncontrolled clinical studies have also demonstrated the efficacy of ampicillin-sulbactam in the treatment of severe multiresistant *A. baumannii* infections, including meningitis and bacteremia, and infections due to imipenem-resistant *A. calcoaceticus*. Polymyxins are regarded as the last resort of treatment for carbapenem-resistant *Acinetobacter*. They are capable of causing serious nephrotoxicity. Although their systematic use was previously abandoned due to their toxicity, the appearance of multidrug-resistant gram-negative bacteria susceptible only to polymyxins has forced their use to be reconsidered.

Antibiotic Resistance to Aminoglycosides and Carbapenems

Acinetobacter species have a variety of resistance mechanisms to aminoglycosides. The most common mechanism is enzymatic modification of the aminoglycosides. The differences in the antibacterial activity among the aminoglycosides are determined by their relative susceptibility to these enzymes. Previous studies showed that the genes encoding these enzymes were present on plasmids, transposons, or within integron-type structures. These structures may be important in the dissemination of aminoglycoside resistance among *Acinetobacter*

species. Plasmids, transposons and integron-type structures are all mobile elements. *Acinetobacter* species can potentially act as a reservoir of aminoglycoside resistance genes for other bacterial species and genera.

Resistance of *Acinetobacter* species to carbapenems was increasingly recognized. Possible mechanisms include the production of carbapenemase and decreased permeability due to a change in the bacterial outer membrane porin. Carbapenemases belonging to Ambler molecular classes A, B and D are emerging in *Acinetobacter* species. The genes encoding these enzymes are found in plasmid, chromosome or integron. Among them, the class B enzymes are most clinically significant. Class B enzymes are metalloenzymes of the IMP or VIM series. They have been reported in Hong Kong and other countries such as Japan, Korea, Italy and Portugal (10). International results have shown that carriage of a carbapenemase gene does not always result in the expression of phenotypic carbapenem resistance. Horizontal transfer of carbapenemase gene *bla*_{IMP-1} between several aerobic and aerobic/anaerobic Gram-negative species have been implicated in previous studies (10). This underlined the spread of these carbapenemase genes across several Gram-negative species as a consequence of their plasmid/integron locations.

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Management of chronic HBV infection in children
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Patients with HBsAg detected in blood on 2 separate occasions 6 months apart are chronic carriers. Currently, there is no well-established guidelines and protocol for the management of chronic HBV infection in children. The consensus paper published in Journal of Pediatric Gastroenterology and Nutrition (1) was prepared by questionnaire survey. Children were included in the Practical Guidelines prepared by Dr. A. Lok for the American Association for the Study of Liver Disease (AASLD) based on the studies of adult series (2). The questions and answers between Dr. Y. F. Liaw and Dr. A. Lok on the Guidelines were interesting and informative (3).

Children patients are usually asymptomatic. Sometimes, they are referred for high alanine transaminase (ALT) levels. Pre-core mutants of the virus are seldom checked, but the test is available locally. According to the literature, about 2% of paediatric patients would have cirrhosis at presentation. Hepatocellular carcinoma (HCC) is rare. Occasionally, there are co-infections with hepatitis C virus, hepatitis D virus and human immunodeficiency virus. More often, we have chronic patients on immunosuppressive therapy for other conditions. The currently available treatments are interferons (IFN) and lamivudine (nucleoside analogue). Other treatments for consideration include thymosin, therapeutic vaccines, Chinese herbs, and adoptive immunity transfer. They are mainly immuno- modulatory therapies. It is a general belief that, after sustained e-sero-conversion (clearance of HBeAg and presence of anti- HBe) and clearance of HBV DNA in the blood, there will be resolution of necro-inflammatory activity in the liver, which would reduce the risk of cirrhosis and HCC. Virologic response (serologic clearance of HBeAg and HBV DNA) is the usual definition of response in most clinical studies. Cost-benefit analysis in children was calculated (4) based on the following assumptions: 2% paediatric patients with cirrhosis, 5% annual risk of decompensation, 17% annual death rate without transplantation, 50% cirrhotic patients receiving transplantation, 2% annual incidence of HCC in cirrhosis, 40% annual mortality rate on HCC and IFN preventing cirrhosis and HCC despite a low response rate.

After a series of calculations, IFN treatment to children was recommended. But IFN treatment was found to be helpful in pre-existing cirrhosis only. The European Study Group on Viral Hepatitis found that there was insufficient data to establish a presumed beneficial effect of IFN on the disease progression and survival (5). The adjusted relative risk of HCC for untreated Vs IFN-treated HBV infected was 0.98 (95 % CI: 0.32-2.92), as reported by the International IPN-a HCC Study Group (6). Certainly, there were supports for the IFN treatment (7).

If we are going to treat our patients, is it better to treat at stage 2 (immune clearance phase) of the disease? Prof. C. L. Lai reported that the virologic response to IFN in the HK Chinese childhood HBV carriers was very poor. His data were re-analysed later and the response in those with high pre-treatment ALT levels was as good as that in adults. But there was no difference in long-term outcome between IFN-treated and untreated children. IFN simply accelerated a spontaneous event and loss of HBeAg was not influenced by steroid pre-treatment in children. Two-third of children with ALT > 100 IU/I would clear HBeAg in blood spontaneously within the next year (8). Even worse, cirrhosis and HCC were reported in children in Italy, Taiwan and Japan years after early e-sero-conversion. IFN can be used in childhood HBV carriers: at 5-10 MU/m², IM or SC, 3 times a week for 3-6 months. It should not be given to children < 2 years old because IFN causes growth problem, and occasionally paraplegia in young children. Liver biopsy is recommended before the treatment. Dosages have to be adjusted for cirrhosis or ALT levels > 5 X upper limits of normal. From the Cochrane's Library Database, steroid is not recommended. Patients with pre-core mutants will respond poorly to IFN, and usually relapse after cessation of treatment. There were scanty data on dual infections. IFN may flare up HBV in HCV treatment. It is not effective in HDV positive patients.

Lamivudine is another treatment for HBV chronic carrier. It inhibits active viral replication, reduces viral load, and improves serum ALT levels and liver histology. It does not kill the virus, nor the infected cells. It is given orally, rapidly absorbed with the drug concentration-time-curve not being altered by food but by trimethoprim, diffusing freely across placenta, secreted into breast milk, and mainly excreted in urine

unchanged. After 4 weeks of treatment, serum HBV DNA levels is reduced by more than 99.5 %. Viral cccDNA is resistant to both nucleoside analogues and IFN treatment. Extra-hepatic (lymphoid) tissues and extra-hepatocytes (e.g., bile duct cells) are also reservoirs of the virus. Prolonged treatment is required. There was only one paper in children from the International Pediatric Lamivudine Investigator Group (9). The virologic response rate was 23 % after 52 weeks treatment. 19 % of treated group had YMDD mutants after treatment and 1/31 of them achieved e-seroconversion. The dose was 3 mg/kg/day, up to 100 mg daily, Again, liver biopsy was recommended before treatment. Lamivudine can be stopped 2-6 mth after e-seroconversion. There may be HBV DNA rebound after cessation of drug. Patients should be closely monitored. YMDD mutant is resistant to lamivudine, but replication is less efficient. Some patients may have flares. There is no specific treatment to the YMDD mutant and its flare. One patient died from multiple drug resistant strains in Hong Kong. The drug can be used in pre-core mutants, IFN resistance, cirrhosis, liver transplantation, and as prophylaxis for immuno-suppressive therapy. There is no data on treatment for dual infections, long-term survival, and progression to cirrhosis and HCC. Combined IFN and lamivudine was not helpful in children (10). Famciclovir (penciclovir) has synergistic effect with lamivudine. But mutations (cross resistance) to both lamivudine and famciclovir were reported. Adefovir dipivoxil, now registered in Hong Kong, is active against lamivudine and famciclovir resistance. But there is dose-dependent nephrotoxicity. There are a great number of anti-HBV agents available over-the-counter. Many are not thoroughly studied. There are problems of inappropriate use and resistance. In general, drugs causing massive simultaneous death of infected hepatocytes can lead to acute necrosis and liver failure. There is no well-documented protocol for children. Early sero-converted subjects may still go into reactivation, cirrhosis and even HCC. Serology and imaging studies are not sensitive for the detection of cirrhosis development. Alpha-fetal protein screening for early HCC detection is recommended for adults after mid-30s. There are still no answers for children.

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