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EDITORIAL

ONLINE SUBMISSIONS FOR THE MEDICAL JOURNAL OF MALAYSIA (MJM)

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Times are changing. We communicate more online now through the Internet than by using the postal service both at work and privately. In the field of medical publications many medical journals have changed the process of submission of contributions from sending manuscripts in hard copies to electronic submissions. It has taken the Medical Journal of Malaysia (MJM) some time but we have come to the point of changing both our submission process as well as our review process from the old to the new.

Beginning from the first of January 2010, we want to inform all authors that manuscripts should be submitted to the MJM through a website. We are using the services of a corporation that services over a hundred scientific journals. The website for MJM is custom made and in order to submit an article, you have to log on to <http://www.editorialmanager.com/MJM>

It may be a bit intimidating for those totally unfamiliar with the Internet but it is a website like any others. It is user friendly and guides you through.

For the Authors

- The first step is to register by entering a user name and a password.
- An author can then login as an author.
- You be reminded of your user name and password by email.
- Next, you send in your manuscript by copying it on to a template where it will be put in the PDF format.
- Your submission will be acknowledged by email and;
- In due time you will then be informed of its progress.
- You can also track the progress of your paper online if you wish.

The format of submission of papers and the type of contributions we accept at the MJM remains the same. This is to be found under our 'Notice to Contributors' which will also be available at

the website. For an interim period of six months, the MJM will continue to accept manuscripts by post as hard copies but we shall then put up a notice that such submissions will be discontinued.

For the Reviewers, the process is similar

- You will be invited to register as a reviewer.
- You will then be notified by email that you have been invited to peer review an article.
- You will log on to the same website.
- You enter a user name and a password and you will then see the title of the paper that you are invited to review and be asked if you will accept it.
- You are notified of your deadline, which will be four weeks.
- You can in fact view the list of your assignments; that is if you have more than one paper pending.
- You review comments (there is an appropriate box to write text) as usual except that there is a list of multiple choice questions to answer to grade the paper.

We are sure that in the long term, this system has its advantages. For authors, there will be instant acknowledgement of your submission and a quicker review process as manuscripts can be transmitted faster. There is cost saving for authors and they have the ability to check the status of their own articles. For the MJM Secretariat, it will be easier to keep track of all the articles and a reduction of paperwork. It will eliminate the uncertainty and delay of material being sent in the mail.

We would like to ask authors and reviewers to be patient when the system begins. There will be teething problems initially. Let us have your constructive criticisms and feedback. The Editorial Office will continue to seek improvement of our effectiveness and efficiency.

EDITORIAL

SINGAPORE DECLARATION ON EQUITABLE ACCESS TO HEALTH INFORMATION IN THE WESTERN PACIFIC REGION

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PREAMBLE

As part of an initiative of the World Health Organization (WHO) to establish a virtual Global Health Library, the WHO Regional Office for the Western Pacific has developed the Western Pacific Regional Index Medicus, or WPRIM, to facilitate the sharing, exchange and management of health knowledge. It is recognized that articles in peer reviewed journals contain information that is essential for health services, health sciences, health policy and public health promotion. The need to access research publications from work done in the various countries of the region has resulted in each country's National Journal Selection Committee screening their journals using certain minimum criteria. Those selected are recommended to be part of the WPRIM.

At the second meeting on the Western Pacific Region Index Medicus, participants agreed to form a regional association of medical journal editors and to name it the Asia Pacific Association of Medical Editors (APAME). The vision of APAME is to promote health care through the dissemination of high quality knowledge and information on medicine in the Asia Pacific Region. It is a nongovernmental, non partisan and nonprofit organization that intends to support and promote medical journalism in the Asia Pacific Region by fostering networking, education, discussion and exchange of information and knowledge. It is closely affiliated with the WHO Regional Office for the Western Pacific, which hosts the WPRIM. Cooperation with the World Association of Medical Editors (WAME), EMAME, Forum for African Medical Editors (FAME) and other international associations in the field of medical journal, publishing is sought and encouraged.

Membership is open to editors, previous editors, editorial assistants of peer reviewed medical journals and those working in any branch of scientific communication in their capacity as Editor-in-Chief, Deputy, Associate, Assistant, Supplement and Managing Editors or scientists and technologists, from Member States of the WHO Western Pacific Region. Associate membership is also available. APAME is open to online membership applications and details of this and the association can be found in their website <http://www.wpro.who.int/apame>

Information on WPRIM can be found at the following site :
http://www.wpro.who.int/information_sources/library_services/wprim.htm

At the most recent joint meeting of APAME and WPRIM held in Singapore in November 2009, the Singapore Declaration on equitable access to health information was adopted and signed. It was recommended that medical journals in the region should publish the declaration. The Medical Journal of Malaysia carries this declaration in this issue.

THE DECLARATION

We, the participants in the Joint Meeting of the Asia Pacific Association of Medical Journal Editors (APAME) and the Western Pacific Region Index Medicus (WPRIM) held in Singapore from November 4 to 5, 2009 :

CONSIDERING

That quality scientific and technical health information is essential for health policy makers, healthcare providers and health researchers to develop, improve, and implement efficient and effective healthcare systems and services;

That inequitable access to quality health information could result in poor health planning and healthcare delivery which adversely affect the health conditions of the public;

That surmounting this inequity requires public-private partnerships to facilitate equitable access to both production and consumption of health information for all;

That the Western Pacific Region Index Medicus (WPRIM), the Global Health Library (GHL), and the Asia Pacific Association of Medical Journal Editors (APAME) is important collaborative initiatives which are vital instruments to ensure the global accessibility and dissemination of quality health information in the Western Pacific Region;

CONFIRM

Our commitment to free and universal dissemination and access to quality health information through the WPRIm and the GHL;

Our commitment to pursue the goals and objectives of APAME by further building networks, convening conferences, and organizing events to educate and empower editors, peer reviewers and authors in generating quality scientific and technical publications.

CALL ON

Member States of the Western Pacific Region, in collaboration with stakeholders from the private sector, to formulate and implement policies that endorse free and equitable access to quality health information;

Stakeholders from the public and private sectors, national and international organizations, to support WPRIM and the GHL in order to ensure the free and global accessibility of health research done in the Western Pacific Region;

Governments, the private sector and other editors' associations to support APAME in implementing various activities, guidelines and practices that would improve the quality of scientific writing and publications in the Asia Pacific Region;

COMMIT

Ourselves to persevere in the pursuit of the WPRIM and GHL initiatives through APAME by encouraging peer-to-peer relationships that will allow editors, editorial staff and librarians to maintain balance, work out ideas and provide mutual support;

Our organization, APAME, to building further networks, convening conferences, and organizing events to educate and empower editors, peer reviewers and authors to achieve and maintain internationally acceptable, but regionally realistic, scholarly standards.

November 6, 2009, Singapore

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(This declaration was launched at the International Forum on Academic Medical Publishing held in conjunction with the Singapore Medical Journal Golden Jubilee Conference on November 6, 2009)

REVIEW ARTICLE

MELIOIDOSIS IN MALAYSIA

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SUMMARY

Melioidosis is an important cause of sepsis in the tropics, is caused by an environmental saprophyte - *B.pseudomallei*. It affects mainly adults with underlying predisposing condition such as diabetes. The range of symptoms varies from benign and localized abscesses, to severe community-acquired pneumonia to acute fulminating septicaemia with multiple abscesses often leading to death. *B.pseudomallei* is an intracellular pathogen and some of the virulence mechanisms that govern the complex interaction between the organism and the host have been elucidated. Isolation of *B.pseudomallei* from bodily fluids of patients remains the “gold standard” in diagnosis but a sensitive and specific serological test can lend support to the diagnosis of melioidosis. Ceftazidime is the treatment of choice for severe melioidosis, but the response is slow. Maintenance or eradication therapy for a prolonged period is necessary to prevent relapse and recurrence. Monitoring IgG antibody levels may be useful as a guideline to determine the duration of eradication therapy.

Key Words: Melioidosis, *Burkholderia pseudomallei*, Malaysia

HISTORICAL BACKGROUND

Melioidosis caused by *Burkholderia pseudomallei*, a gram-negative soil saprophyte was first described by Whitmore and Krishnaswami in 1912¹ in 38 fatal cases of pneumonia amongst the destitute and morphine addicts in Rangoon, Burma. In 1913 Fletcher recognised the disease in laboratory animals at the Institute for Medical Research in Kuala Lumpur, Malaysia and in 1917 Stanton first described the infection in a human patient from Kuala Lumpur² and these authors wrote a short monograph on the disease and its sporadic occurrence in Malaya up to 1932. Since that time, cases have been reported in both man and in a variety of animals such as sheep, buffalo, deer, monkey, gibbon, orang utan, kangaroo, camel, parrot, hamster, zebra and crocodile³.

The term melioidosis was coined in 1921 by Stanton and Fletcher and is derived from the Greek words “*melis*” meaning “a distemper of asses” and “*eidos*”, resemblance. This was because the disease clinically and pathophysiologically resembled glanders, a chronic and debilitating disease of equines caused by *Pseudomonas mallei*².

Melioidosis occurred in Allied and Japanese soldiers during the Second World War in Burma, Malaysia and in Thailand. After the Second World War, sporadic reports of melioidosis appeared in the literature, with 10 cases from Malaysia being reported by Thin *et al* in 1970⁴.

The establishment of the Department of Medical Microbiology at the Faculty of Medicine, University of Malaya, saw a resurgence of interest in the disease melioidosis and several publications and reports on less known aspects of the disease in Malaysia, such as demographic details and risk factors, were published^{5,6,7}.

By the early 1990s there was sufficient interest in melioidosis in the scientific and medical world and it was thought the time was right to bring these researchers together at a forum. Thus the First International Symposium on Melioidosis convened by the Malaysian Society of Infectious Diseases and Chemotherapy, under the Chairmanship of Prof. S D Puthuchery, was held in Kuala Lumpur from April 7-8, 1994. About 100 participants from around the world attended and the papers presented were subsequently edited and published as a book⁸.

Burkholderia Pseudomallei

This bacterium was known by many names over the past 100 years, generally well known as *Pseudomonas pseudomallei* but in 1992 Yabuuchi and co-workers incorporated it into the new genus *Burkholderia*⁹. This organism is a soil saprophyte and can be readily recovered from water and wet soils in endemic areas.

Burkholderia pseudomallei are motile aerobic, non-spore forming gram negative bacilli. The genome is relatively large, 7.24 Mb, and is divided unequally between two chromosomes (4.07 Mb and 3.17 Mb), with a G+C content of 68%¹⁰.

In the laboratory, *B.pseudomallei* grows aerobically on most agar media, and produces clearly visible colonies within 24-48 hours at 37°C. Ashdown's medium or modifications of it are commonly used and the organism demonstrates differing colonial morphology, with mostly smooth colonies initially and dry or wrinkled colonies on further incubation. Large and small colony variants have also been isolated from blood cultures of patients with previous antibiotic therapy¹¹. Gram stain shows gram negative rods described as having bipolar staining. The organism is oxidase positive, uses glucose by an oxidative pathway, and can be identified reliably from its biochemical profile with kit-based systems. *B.pseudomallei* exhibits resistance to diverse groups of antibiotics, including third generation cephalosporins, penicillins, rifamycins and aminoglycosides. In addition, its relative resistance to quinolones and macrolides limits therapeutic options for the treatment of melioidosis. In Malaysia, Puthuchery *et al* in 1987, were the first to publish the antimicrobial susceptibilities on a large collection of 57 isolates of *B.pseudomallei* using 15 chemotherapeutic agents. Significant results were: 86% sensitivity to trimethoprim-sulphamethoxazole, 84% to chloramphenicol, 58% to tetracycline and 100% to ceftazidime¹². Almost 20 years later and from the same institution, 80 clinical isolates of *B.pseudomallei*, collected between 1978 and 2003, were tested for *in vitro* susceptibility using the E-test. 100% of the isolates were sensitive to imipenem and meropenem and 97.5% were sensitive to trimethoprim-sulphamethoxazole¹³.

The largest collection of 146 clinical isolates of *B.pseudomallei* from Malaysia, when tested for MIC by the E- test gave a sensitivity of 100% for ceftazidime, imipenem and meropenem; 99.3% for amoxicillin-clavulanate; 97.9% for chloramphenicol; 88.4% for trimethoprim-sulphamethoxazole and 82% for ciprofloxacin (unpublished data, See KH Masters thesis). Although it is reassuring that the drugs of choice had no problems with resistance, nevertheless we have reported that a single infectious clonal population of *B.pseudomallei* from a patient, did contain subpopulations with differing ceftazidime and amoxicillin-clavulanate susceptibilities and that these were associated with a single nucleotide substitution in the *penA* gene ¹⁴.

Ecology and Distribution

Burkholderia pseudomallei is an environmental saprophyte and melioidosis is endemic in southeast-Asia and tropical Australia but the global distribution boundaries of melioidosis continue to expand well beyond these traditionally recognised endemic regions. In Malaysia the organism has been isolated from soil and water from all states in West Malaysia by Strauss and co-workers in 1969 ¹⁵. Samples were taken from primary and secondary forests, wet rice fields and recently cleared areas. The isolation rates were lower from the forested areas compared to the cleared areas of wet rice fields and newly planted oil palm plantations. Soil moisture was an important criterion in the isolation of the organism and the incidence of melioidosis peaks during the months of heavy rainfall in Thailand and Australia: this is because the water table rises to the surface carrying with it the bacteria that normally reside below the surface. In Malaysia, although the percentage of water and soil specimens positive for *B.pseudomallei* was higher during increased rainfall ¹⁵, there appeared to be only a slight increase in the number of cases during the wet monsoon period. Our findings of correlation of rainfall and the occurrence of 125 patients with culture proven melioidosis, over a 30 year period, support the hypothesised general association between melioidosis and rainfall. But the correlation appeared less strong than those reported in other centres, which may be due to other factors, including the different local patterns of rainfall intensity ¹⁶, as well as increased exposure to the organism during ploughing and planting of the rice paddies in endemic areas ¹⁷.

Soil and surface waters are highly complex ecosystems in which a vast range of physical, chemical and biological factors interact. But the organism is found to persist in some tropical regions better than others, such as hyper endemic foci or “hot spots” such as north-eastern Thailand and East Malaysia where more cases are reported than from the rest of the country¹⁷ but the exact reasons for this are far from clear. The tenacity of this soil saprophyte to survive in a hostile environment should not be underestimated. There is a homeostatic balance in nature between man, organism and the environment and any disturbance of this by logging, clearing of large tracts of vegetation will upset this equilibrium with drastic consequences for man, animals and the environment¹⁷.

Epidemiology

In a comprehensive review of 98 septicaemic and 43 non-septicaemic cases studied over a period of 35 years in our institution, we found a bimodal distribution of age in both groups of patients (Fig.1). Age of patients ranged from 17 days to 79 years. The increase in the 10-30 year group possibly reflects the greater environmental exposure during play or outdoor recreational activities. The peak age-specific incidence occurred from 41 – 59 years for both males and females in Malaysia but in Thailand the peak age-specific incidence was 50-59 years for women and 60-69 years for men¹⁸, whilst in Singapore the risk of melioidosis increased steadily with age, being maximal in those over 65 years¹⁹. In every published case series on melioidosis, males have outnumbered females but the proportions varied considerably (ratio of male: female from 5:1 to 1.4:1). This likely reflects involvement in activities which lead to exposure to contaminated soil and water. In Malaysia the M: F ratio was found to be 3.2:1¹¹.

Ethnic differences in susceptibility to melioidosis were suggested by studies in Singapore where morbidity rates were highest in Indians, lowest in Chinese and intermediate in Malays in both the general population and the military. In Malaysia, the morbidity rate was highest amongst the Indians, lowest in Malays and intermediate in the Chinese¹¹. However, it is possible that the groups differed in their frequency of activities resulting in occupational and environmental exposure to soil and water and so no firm conclusions can be drawn.

Modes of Acquisition

Three modes of acquisition, i.e., inhalation, ingestion and inoculation are recognised for *B.pseudomallei*, but the relative contribution of each are yet to be determined. As with other infectious diseases, it is likely that these factors as well as the size of the inoculums are responsible for the pattern and severity of disease. Inhalation was initially thought to be the primary mode of acquisition, based on studies of U.S. soldiers in Vietnam, where it was noted that helicopter crews seemed to have a high incidence of the disease. This and the long incubation period resulted in melioidosis acquiring the sobriquet “the Vietnamese time bomb”²⁰, but it seems logical to assume that melioidosis is acquired mainly by contact with contaminated soil and water through penetrating wounds or existing skin abrasions, ulcers, burns or by inhalation of dust particles, by aspiration of contaminated water during near-drowning episodes²¹ iatrogenic inoculation and by laboratory accidents²².

Predisposing or risk factors

It has been recognised that *B. pseudomallei* behaves as an opportunistic pathogen. Exposure to the organism is widespread and yet disease is not that common, occurring predominantly in those with underlying predisposing conditions suggesting that the susceptibility of the host is an important factor. The majority of patients with clinically apparent melioidosis are recognised as having underlying diseases: 76% in Malaysia⁷, 88% in Australia²³ and 53% in Thailand¹⁸. The difference in the percentages between the studies is probably accounted for by the definition of underlying diseases and the extent to which they were sought. In Malaysia, northeast Thailand and Singapore, diabetes mellitus was the most frequently reported predisposing condition with up to 60% of patients having pre-existing or newly diagnosed type 2 diabetes¹⁸. Studies in Thailand clearly showed that the prevalence of diabetes mellitus in patients with culture proven melioidosis was significantly higher than in patients with septicaemia due to other bacteria. Renal failure, renal calculi, retroviral infections, malignancy, steroid therapy, alcoholism, occupational exposure, trauma and parenteral drug abuse were also confirmed as important predisposing factors both in Malaysia and Thailand^{7,24}.

The precise nature of the predisposing immune dysfunction is poorly understood. The underlying conditions described above lead to a wide range of immune deficits including phagocytic defects, diminished humoral and cellular responses and diminished cytokine production. It has also been postulated that insulin deficiency may contribute directly to the association of melioidosis with diabetes mellitus²⁵. Underlying disease was seldom reported in cases from the Singapore Armed Forces, and in children and young adults from East Malaysia, suggesting that a substantial exposure to *B. pseudomallei* will cause infection even in healthy individuals.

Clinical Manifestations

The infection is a collection of disease states and the clinical entity of melioidosis is virtually impossible to define as the spectrum of signs and symptoms can range from benign skin and soft tissue infections to a rapidly fulminant and fatal septicaemia. Due to this wide array of clinical signs and symptoms, the causative bacterium *Burkholderia pseudomallei* has been called “the great mimicker.”

The incubation period of melioidosis has not been accurately defined in melioidosis. Estimates are possible of the time taken for wound sepsis to appear following trauma or motor vehicle accidents. After a laboratory accident an incubation period of 2 days was recorded. Currie et al²⁶ give an incubation period of one to 21 days (mean 9 days) in 25 cases where a clear incubation period could be determined between the inoculating injury and the onset of symptoms.

In all series, the lung was the most commonly affected organ, either presenting with cough and fever resulting from a primary lung abscess or pneumonia, or secondary to septicaemic spread (blood-borne pneumonia). Sputum is often purulent but seldom blood-stained. Large or peripheral lung abscesses may rupture into the pleural space to cause empyema²⁷. Thus, melioidosis is usually perceived as an acute pulmonary illness characterized by prostration and marked toxicity that is often out of proportion to objective physical findings or chest radiographic findings. However, melioidosis has been recognized to give rise to inapparent infections, transient bacteraemia, asymptomatic pulmonary infiltration, acute localised suppurative lesion, acute pulmonary infection, disseminated septicaemic infection, non-disseminated septicaemic infection or chronic suppurative infection. Since melioidosis is a multi-system disease and the signs and symptoms are non-specific, the clinical classification of melioidosis has been controversial. The subdivision into acute, subacute and chronic melioidosis is unsatisfactory as

there exists a clinical continuum as the less acute or localised forms may rapidly progress to the septicaemic form especially if there is concomitant debilitating illness. The same is true of a classification by organ involvement as more than one organ may be involved⁷. Melioidosis has a high mortality rate of 30-70%. Both this and the severity of the acute manifestations of the disease appear to depend on whether the patient is septicaemic or not. Therefore a more functional and useful clinical classification for melioidosis would be into septicaemic and non-septicaemic melioidosis¹¹. The overall mortality of non-septicaemic melioidosis is 5-20%, which is very much lower than that of septicaemic melioidosis.

Septicaemic melioidosis may present in many forms, from a simple bacteraemia with no obvious focus of infection to the most severe form of disseminated bacteraemia with fulminant shock and multi-organ involvement. It is almost always community-acquired and patients often present simply with a history of fever (median duration 6 days with a range of several days to several months) and often with no evidence of a focus of infection. In one of the largest series of 1000 culture proven cases seen at the Sappasithiprasong Hospital in northeast Thailand, 15% of the patients did not have an obvious primary site of infection²⁷. This may be true at the time of admission to hospital, nevertheless a thorough septic screen must be implemented including a chest X-ray and an ultrasound of the abdomen.

Septicaemia of abrupt onset may rapidly progress with dissemination of the primary focus of infection, frequently evidenced clinically by the subsequent development of multiple subcutaneous abscesses, multiple nodular lesions visible on chest X-ray, joint swelling and myositis. Patients with the septicaemic form usually have a rapidly progressive course particularly if there is concomitant debilitating illness, such as uncontrolled diabetes mellitus, haematological malignancies and disorders, solid tumours, collagen vascular disease, renal disease, retroviral infections and alcoholism. Up to 25% of these patients may be hypotensive with signs of organ dysfunction on admission²⁸ and multi-organ involvement was seen in 25-30% of cases. In the series mentioned earlier, the lungs were the commonest site (50%) when only a single organ was involved, other sites being CNS (brain abscess), joints, prostate or testes, liver and/or spleen²⁷. Renal involvement such as pyelonephritis, perinephric abscess, skin and soft tissue sepsis, cellulitis accompanied by regional lymphangitis and multiple superficial abscesses were also recorded in septicaemic patients. Unlike other pyogenic infections, haematologic dissemination to the viscera involved the spleen more frequently than kidney or liver in the form of multiple abscesses²⁹. Other uncommon conditions seen were

pericardial effusion, meningitis, empyema of the gall bladder, abscess of the parotid gland, abscess of tail of pancreas, and mycotic aneurysms^{30,31}. Paranasal sinus infections such as acute ethmoiditis and frontal sinus empyema have also been described³². Melioidosis of the central nervous system is uncommon, but macroscopic brain abscess³³ and a case of epidural abscess of the spine in Malaysia³⁴ have been reported from our institution.

Localised melioidosis may occur in the form of acute suppurative lesions, superficial and deep abscess such as in the psoas muscle and the parotid glands, cellulitis, chronic otitis media and sepsis following burns, trauma or motor vehicle accidents¹¹. Parotid abscesses and cervical lymphadenopathy are seen commonly in children³⁵. Localised osteomyelitis has been described in 10 patients from Thailand whose ages ranged from 28 to 62 years with 7 of them having underlying predisposing conditions. The vertebrae were involved in 4, the proximal humerus in 4 and the proximal femur and tibia in 2 patients respectively. Osteomyelitis of the skull although very rare, has been observed (SD Puthucheary, unpublished observations). It must be emphasised that *B.pseudomallei* has the potential to cause pyogenic or granulomatous inflammation at virtually at any site in the body. Two manifestations of melioidosis that are occasionally very dramatic are the rapid progression of respiratory failure, and profound weight loss. Our report on the clinical and pathological study of 6 cases of respiratory failure in melioidosis suggested that a combination of acute necrotising pneumonia and the acute respiratory distress syndrome appeared to be responsible³⁶.

Nearly all clinical studies have come from Thailand, Malaysia, Singapore and northern Australia and the overall mortality in adults ranged from 40-65%^{7, 18}. In northern Australia the mortality in severe melioidosis has been falling in recent years with earlier recognition and intensive care treatment¹⁰ and is expected to also decrease in other endemic areas.

Radiographic findings

We found approximately 50% of all septicaemic cases to have lung involvement. In a series of 50 septicaemic cases from Malaysia, 46% had pneumonia⁷. In the 1,000-case series seen in northeast Thailand, 66% of the cases had radiological abnormalities. Unilateral pulmonary shadowing (56%) was more common with predominant involvement of the right lung. More than one lobe was affected in one out of 5 patients. The right upper and lower lobes were the common sites of involvement²⁷. Bilateral pulmonary shadowing was seen in 44% of the cases

in northern Australia. A cavitating lesion was present in 14% of the cases. These cavities in melioidosis, unless very large, usually do not have an air-fluid level³⁷.

Fibro-nodular infiltrates with or without cavitation in the upper-lobe (i.e. single lobe) can be quite similar to that of pulmonary tuberculosis and in chronic pulmonary melioidosis the appearance may closely simulate that of tuberculosis, but the tendency for the apices to be uninvolved makes the possibility of melioidosis more likely, especially in cases with minimal or no signs of fibrosis. The nodular lesions in melioidosis are neither discrete nor as uniformly distributed as in disseminated tuberculosis or fungal infections^{38, 39}.

In severe septicaemic cases of melioidosis there is a rapid appearance of diffuse, fluffy alveolar infiltrates in both lungs within one to two days, leading to the acute respiratory distress syndrome and inevitable death usually due to primary respiratory failure³⁶. Visceral abscesses are common in melioidosis⁴⁰ and an ultrasound of the abdomen should be performed in all culture proven cases. Hepatic abscesses are usually multifocal, unlike the large solitary abscess found in other pyogenic infections. The presence of miliary or micro abscesses in the liver and spleen seen at autopsy⁴¹ may not be easily evident on ultrasound examination and a CT scan is indicated, as the presence of micro abscesses will have important implications for both management and prognosis.

Relapse and recurrence

Relapse and recurrent infections are not uncommon in melioidosis, especially in hosts who are immunocompromised, and occur in spite of appropriate and prolonged antimicrobial therapy. Relapse is the reappearance of signs and symptoms after initial clinical response while still on antimicrobial therapy. A recurrent infection or recrudescence is a new episode of melioidosis caused by the same organism after convalescence and full clinical recovery. Relapse and recurrence are potential problems in patients who survive acute melioidosis. Such infections are assumed to be due to failure by the host to eliminate the organism during the initial infection. In northeast Thailand, the overall relapse rate was from 15-30% per year of survivors of severe melioidosis despite treatment for at least 2 months (and longer in patients with persisting abscesses or osteomyelitis). The same organ was involved in 44% of the relapsed cases⁴².

In Malaysia, the rate of relapse or recurrence was found to be approximately 13% over a period of 5 years, an underestimate due to cases being lost to follow-up. Numerous episodes of infections after initial recovery occurred in several patients followed-up over many years, the longest period of follow-up being 5 years (SD Puthucheary, unpublished observations). Chaowagul *et al*⁴² during their study period were not aware of any cases of relapse in children, which is similar to our experience in Malaysia. This suggests that relapse is less common in children and is consistent with the observation that the acute prognosis is better in the younger age group.

This infection has the potential for prolonged latency and recurrence into a fulminating form which can present acutely. Factors thought to contribute to this include the survival of *B. pseudomallei* in protected sites such as within phagocytic cells⁴³ and in sealed abscesses where the organisms can evade the host immune response. Other reasons for recurrence are the ability of *B. pseudomallei* to form glycocalyx, biofilms and microcolonies in infected tissues where antimicrobials are unable to penetrate⁴⁴. Factors that influence the likelihood of relapse and recurrence include clinical severity at original presentation and the type and length of parenteral and oral antimicrobial treatment. Patients with severe infections have an overall higher risk of relapse than those with localised infections.

But the most important factor for relapse is non-compliance of maintenance (eradication) oral antimicrobial therapy. Therefore any patient with a previous history of melioidosis presenting with fever or symptoms of sepsis, should be suspected of having a relapse or recurrence and empirical antibiotic therapy effective against *B. pseudomallei* should be instituted without delay. With improvements in the management and treatment of severe melioidosis, a greater proportion of patients now survive and return to the community. Therefore relapse of melioidosis will become more significant. The adage, “once a melioidosis, always a melioidosis” seems to hold true for many infected patients²⁹.

In the majority of cases, relapse or recurrence is due to reactivation of the original infecting strain, and we³³ demonstrated this with isolates recovered from 4 patients over a period of 3 months to 5 years, using pulsed-field gel electrophoresis (PFGE). Isolates from each patient were identical but PFGE patterns from different patients were distinctly different⁴⁵. These findings also imply *in vivo* genomic stability of *B. pseudomallei* in the presence of selective pressures of antimicrobial therapy and host defence mechanisms Ribotyping and PFGE

provided further differentiation between isolates from 5 patients with clearly distinguishable episodes of melioidosis suggesting that repeated episodes of infections in melioidosis are due to the original infecting strain, although reinfection with strains of similar types from the environment cannot be ruled out. We concluded that some patients with melioidosis may be infected by more than one strain of *B. pseudomallei* and that infection with one strain does not prevent concurrent infection with another strain. Only one of the 13 patients in this report harboured 2 strains of different ribotypes⁴⁶.

Diagnosis of Melioidosis

In endemic areas, a high index of suspicion and a good travel history in patients from non-endemic regions are important factors involved in establishing a diagnosis. Melioidosis should be considered in the differential diagnosis of any febrile illness if the presenting features are those of fulminant respiratory failure, if multiple pustular or necrotic or subcutaneous lesions develop, or if there is a radiological pattern of tuberculosis from which tubercle bacilli cannot be demonstrated, especially in a patient who is immunocompromised, has diabetes mellitus, and either resides or has travelled to endemic areas¹¹. The diagnosis of melioidosis can be missed or dismissed when such histories are not adequately acquired or the time between possible exposure and presentation is considered too great⁴⁸. History of occupational and recreational exposure should be sought and abrasions and trauma, however minor, must be elucidated as these may be considered too trivial for medical attention¹⁷. Asymptomatic carrier state is not known and so recovery of the organism from specimens such as throat swabs and urines indicates active disease⁴⁸.

Isolation of *B.pseudomallei* from bodily fluids of patients remains the “gold standard” in diagnosis and requires the use of selective media for non-sterile specimens. The organism is not fastidious and will grow on almost all routine media, but with non-sterile specimens *B.pseudomallei* can be overgrown by contaminating flora due to paucity of the organisms especially from deep-seated abscesses and infected tissues. Therefore incubation of the culture aerobically at 37⁰C for 3-5 days may be necessary. Recognition and identification of *B. pseudomallei* depends very much on awareness and familiarity with the cultural characteristics of the organism. The colonial morphology can vary with the medium used and source of the strain¹¹. Many tests based on molecular detection of *B.pseudomallei* have been described, but few have been field tested.

Serology

In situations where patients are critically ill with fulminating sepsis or when infections are deep seated and no specimens are available, serology may be sufficiently rapid to facilitate aggressive and appropriate treatment and management of patients. But serological diagnosis of melioidosis has been hampered by factors such as raised antibody levels in the population of endemic regions, the presence of subclinical and asymptomatic infections, poorly standardised antigens and probable cross reactions with other organisms. We developed an indirect immunofluorescent test using whole cells of *B.pseudomallei* as the antigen⁴⁹, and evaluated its diagnostic and prognostic value in the detection of total antibodies (IgG and IgM) to *B.pseudomallei*. This test was found to be rapid and useful as it required only a day to complete. A cutoff value of 1:80 was used to differentiate between true infections from background titres due to basal antibody levels in endemic areas. This study also demonstrated the need to include melioidosis as one of the differential diagnosis in patients with PUO in endemic regions, and in military personnel, eco-tourists and others returning home from endemic areas⁵⁰.

Pathogenesis and Virulence

B.pseudomallei like many soil bacteria is a difficult organism to kill. It can survive in triple distilled water for years⁵¹ and yet it has the ability to transcend the environmental saprophytic state to become a pathogen of humans and animals. Melioidosis is a fascinating infection in terms of pathogenesis. The outcome of the host pathogen interaction ranges from asymptomatic seroconversion to rapidly fatal and fulminant sepsis. Between these extremes the infection may run a chronic or relapsing course, or remain latent for many years before reactivation into an active infection. This outcome will depend on the interplay of several factors such as the size of the inoculum, the virulence of the infecting strain and the susceptibility of the host as well as possible as yet unknown genetic factors¹¹.

We set about studying aspects that contribute to the suspected virulence of the organism:

- i) The mucoid colonial morphology suggests the presence of slime or extracellular polysaccharide layer. Ruthenium-red stained preparations of bacterial cultures viewed by electron microscopy revealed 3 morphologically distinct variants; one with a very marked and another with a less electron-dense layer surrounding the cell wall, and a third layer devoid of such a structure⁵². Subsequently it has been shown that *B.pseudomallei* produces a highly hydrated glycocalyx polysaccharide capsule, an

- important virulence determinant that helps to form slime. This capsule facilitates formation of microcolonies in which the organism is both protected from antibiotic penetration and phenotypically altered ²⁶.
- ii) Intracellular penetration and survival of *B.pseudomallei*. We demonstrated by transmission electron microscopy, the internalisation of *B.pseudomallei* by human macrophages via conventional phagocytosis enclosed within membrane-bound phagosomes ⁵³.
 - iii) We further showed by a quantitative approach, that phagolysosome fusion occurred slowly and inefficiently in monocytes of patients with melioidosis, leading to an increased number of intracellular organisms compared with monocytes obtained from healthy donors ⁵⁴. Our observations in this study suggest that a small number of *B.pseudomallei* are able to overcome the microbicidal armamentarium of the human host cell, to persist and multiply or remain latent in a dormant state, giving rise to relapse and recurrence at a later date.
 - iv) Nitric oxide, a major microbicidal mechanism in phagocytic cells, together with other reactive nitrogen intermediates produced during the respiratory burst is cytotoxic and inhibits replication of many intracellular pathogens. The activation state of macrophages can be determined by measuring the generation of 8-iso-PGF2 α , a bioactive product of free radical induced lipid peroxidation. We demonstrated that macrophages obtained from melioidosis patients generated significantly lower levels of nitric oxide and 8-iso-PGF2 α compared to macrophages obtained from normal subjects ⁵⁶.

Burkholderia pseudomallei isolates produce a number of factors that may contribute to the progression of disease such as secretory virulence determinants: protease, catalases, peroxidases, superoxide dismutase, lipase, phospholipase C (lecithinase) and hemolysins as well as at least one siderophore. Cell-associated virulence determinants, quorum sensing, type III secretion systems and flagella have also been implicated. Resistance to complement-mediated bacteriolysis is also a key virulence determinant as described by Ismail *et al* ⁵⁶.

The immune response

Burkholderia pseudomallei produce a humoral antibody response during all stages of the disease including asymptomatic seroconversion. We used 2 types of antigen preparation, a culture filtrate antigen and a whole cell antigen, and two different tests, an ELISA and an immunofluorescent antibody test (IFAT) to detect antibody levels in the sera of various groups of subjects and patients ^{50,57,58,59}.

Collectively, these studies demonstrated:

- i) Serology was useful and rapid in the presumptive diagnosis of both septicaemic and non-septicaemic melioidosis
- ii) The need to include melioidosis as one of the differential diagnosis in patients with fevers in endemic regions
- iii) Strong IgG, IgA and IgM responses were produced by melioidosis patients to the culture filtrate antigen throughout the infection.
- iv) Analysis of IgG isotypes demonstrated that IgG1 followed by IgG2 were the predominant subclasses involved in the humoral response
- v) *In vivo* killing / clearing of the pathogen was not evident despite elevated Th1 response as demonstrated by the presence of IgG1 antibody response.
- vi) Septicaemic patients, mainly adults, maintained high levels of antibody for many years, suggesting the continuous sequestration of the organism or bacterial products.
- vii) The non-septicaemic patients were mainly children where initial high levels of antibodies were found to taper down and eradication antimicrobials were stopped when titres dropped to below diagnostic levels. They remained symptom free on follow up for up to 2 years.
- viii) These studies provide evidence that monitoring either IgG or IgG+IgM antibody levels in patients under maintenance /eradication therapy may be useful as a guideline to determine the duration of this therapy.

It has been recognised that serodiagnosis is problematic in areas of endemicity due to background seropositivity. We demonstrated that if a suitable cut-off titre is used to exclude background antibody levels, then a sensitive and specific serological test can lend support to the diagnosis of melioidosis ^{50, 59}.

Histopathology

Histopathology was used to study human tissues infected with *B.pseudomallei*. The lesions which varied from acute to chronic granulomatous inflammation were not tissue specific. In 5 autopsy cases, the inflammations were usually focal or diffuse acute necrotising inflammation with varying numbers of neutrophils, macrophages lymphocytes and “giant cells”. Numerous gram negative, non-acid fast, intra- and extracellular bacilli were also present. Intracellular bacteria within macrophages and “giant cells” were so numerous as to resemble “globi.” In 14 surgical cases, biopsies showed acute inflammatory lesions, no different from acute inflammation due to other causes. However, the inflammation was either an acute-on-chronic inflammation with a focal granulomatous component, or was purely granulomatous in character. Bacilli were difficult to demonstrate in surgical biopsies even with the gram stain ⁶⁰.

Apart from pathological changes of the inflammatory lesions caused as a result of *B.pseudomallei* infection, there may also be other associated pathological changes especially in the lungs of patients with acute respiratory failure. The lungs, in few of these cases where autopsy was performed, exhibited changes typical of acute respiratory distress syndrome (ARDS) with inflammation and fibrinoid hyaline membranes in the alveolar spaces ³⁶.

Treatment and Management

Severe septicaemic melioidosis or patients with a provisional diagnosis of septicaemic melioidosis should be treated with parenteral antimicrobial therapy. The conventional drug regimen was a combination of high dose chloramphenicol, doxycycline and trimethoprim-sulphamethoxazole respectively. Present day treatment consists of high dose intravenous ceftazidime (100-120 mg/kg/day) in 3 divided doses alone ⁶¹ or in combination with co-trimoxazole (8-12 and 40-60mg/kg/day). This combination has been shown to be far more effective in lowering the mortality rates than the conventional regimen or ceftazidime monotherapy for septicaemic melioidosis ⁶². Monotherapy with ceftazidime may be indicated in cases of simple bacteraemia with no obvious focus of infection but the clinical condition of the patient should dictate this decision.

Carbapenems kill *B.pseudomallei* more rapidly than do cephalosporins, and imipenem proved equivalent to ceftazidime in a large randomised trial; imipenem (50-60 mg/kg/day) is a safe and effective treatment for acute severe melioidosis and maybe considered an alternative to ceftazidime ⁶³. Even with appropriate antimicrobial therapy, the mean time to resolution of fever

was approximately 9 days, but patients with large abscesses or empyema often have fluctuating fevers for more than one month and therefore parenteral antimicrobial therapy should be given for at least 10-14 days and continued until there is clear evidence of symptomatic improvement⁶⁴. This may take several weeks, particularly when visceral abscesses are present; fever persisting for more than one week is common and does not necessarily imply treatment failure. We have successfully treated an adult patient with acute and severe melioidosis with 12 weeks of imipenem and trimethoprim–sulphamethoxazole (SD Puthuchery, unpublished observations). Physicians who are not experienced in the management of melioidosis often switch antibiotic treatment prematurely, fearing the emergence of drug resistance, but resistance to ceftazidime is rare. Enlargement of an abscess or appearance of new abscesses, especially in skeletal muscle, or seeding to a joint, is not uncommon in the first week of treatment, and is not necessarily a sign of failure¹⁰. Localised infections do not always need parenteral antimicrobials.

Oral therapy with the conventional antimicrobial agents, ampicillin-sulbactam or amoxicillin-clavulanic acid can be used from the beginning. But an initial short course of parenteral antibiotics followed by oral drugs may sometimes be indicated especially in the older aged patients with underlying predisposing or immunocompromised states. Children with simple and uncomplicated wounds following trauma usually do well with oral therapy for 6-8 weeks¹¹.

Adjunctive or supportive therapy

The objective of this therapy is to reduce the in-hospital mortality of patients with severe and septicemic melioidosis, which is usually seen in the older-aged patients. Supportive and symptomatic treatment of shock to maintain good tissue perfusion and oxygenation are of paramount importance. If possible surgical drainage of abscess should be carried out. Complications such as septic shock, acute renal failure and acute respiratory distress syndrome (ARDS) are commonly seen in severe melioidosis³⁶. Therefore, these patients should be nursed in a high dependency location or in intensive care units. Patients with uncontrolled diabetes mellitus should be given continuous infusion of insulin. Partial splenectomy should be considered rather than total splenectomy, when indicated, for large solitary or a perforated abscess. Surgical curettage and debridement of affected muscle and bone is essential in musculoskeletal melioidosis in addition to antimicrobials.

Maintenance or eradication therapy

Patients who have recovered from melioidosis require long term oral maintenance therapy and follow-up because of the high risk of relapse, latency and recurrence which may lead to an acute, often fulminating, fatal infection. Long courses of oral maintenance therapy have been recommended in order to eradicate melioidosis in an approach similar to antituberculous therapy. The combination of oral chloramphenicol, doxycycline and co-trimoxazole is the most widely used maintenance therapy for melioidosis⁴² but carries a significant risk of serious chloramphenicol or sulphonamide toxicity and cannot be used in children or pregnant women. Amoxicillin-clavulanic acid is a good alternative as it has good activity against *B. pseudomallei*. In a comparative trial co-amoxyclav was found to be safer and better tolerated but may be less effective than the oral “conventional” regimen⁶⁵.

There are no well-established guidelines for the duration of maintenance antibiotic therapy although 3 to 6 months has been mentioned in many reports⁶⁶. Treatment courses of less than 8 weeks for maintenance therapy in survivors of severe disease are clearly insufficient as the relapse rate was 23%⁴². With an increase to 20 weeks of oral therapy the relapse rate was reduced significantly to 10%⁶⁵.

In our experience, relapse or recurrence of signs and symptoms have occurred while patients were on maintenance therapy and also after completing 6 months of antibiotics, with signs and symptoms appearing between 2 and 6 years later. In this group the antibody levels, measured (using an IFAT) at intervals of one to two months from initial presentation, remained high⁵⁰. These were mainly adult patients with diabetes mellitus and other immunocompromised states. Adults with localised non-septicaemic infections showed a reduction in antibody titres over a period of 20-28 months. This decrease in titre on follow-up suggests that the infection was either being resolved or arrested. In contrast, among patients who had developed septicaemia, the titres remained at a high level over a period of one to 3 years, suggesting the continuous sequestration of antigen or organisms in an intracellular or cryptic site in the host. In children with melioidosis, the initial high antibody levels were found to taper down during maintenance therapy and antibiotics were stopped when the titres decreased to below diagnostic levels. The children were followed up for an average of 2 years and remained symptom free. Thus we believe that serological follow-up may be useful as a guideline to determine the optimal duration of maintenance antibiotic therapy for this persistent and potentially lethal infection. Life-long

follow-up and counselling, particularly regarding compliance, should be a requirement in the prevention of relapse and recurrence ⁵⁹.

Empirical therapy

As *B.pseudomallei* is intrinsically resistant to most beta-lactams and aminoglycosides, it is often untreated by empirical broad-spectrum antibiotic therapy (such as ampicillin and gentamicin) for patients admitted with suspected septicaemia. In our series of 50 septicemic melioidosis cases, 76% of the patients did not receive appropriate empirical antibiotic therapy effective against *B. pseudomallei*. Another situation is when unconfirmed cases of pulmonary melioidosis may be empirically treated with anti-tuberculous drugs ⁷. In most Southeast Asian countries both diseases are usually endemic and therefore awareness is essential. Amoxicillin-clavulanic acid is appropriate as empirical broad-spectrum antibiotic in areas where *B. pseudomallei* is a recognised pathogen, but once the diagnosis has been confirmed, ceftazidime remains the treatment of choice in acute presentations ⁶⁴.

Prevention and Prophylaxis

There is no effective vaccine available that protects against *B.pseudomallei* infection and the prospect of one in the immediate horizon seems remote! In the endemic regions of southeast Asia, the sites most likely to yield *B.pseudomallei* are cleared, cultivated and irrigated agricultural lands, but exposure to this organism is very difficult to prevent in rural rice growing areas. It would be ideal for persons engaged in occupational or recreational activities to take simple precautionary measures such as covering all open wounds with waterproof dressings and wearing boots and gloves during outdoor activities. In endemic areas where *B.pseudomallei* is an ubiquitous environmental saprophyte, it is expected that clinical diagnostic laboratories would process samples at a BSL-2 level facility, and safe laboratory practice will serve to minimise the risk of exposure. Accidental exposure in the laboratory to *B.pseudomallei* must be reported to the laboratory safety officer and post exposure management should be offered ⁶⁷.

CONCLUSION

In Malaysia the true incidence and epidemiology is still unknown and thus there is a compelling need for it to be made a notifiable disease⁶⁸. This disease remains greatly under-diagnosed in the tropics and hence there is a need for greater awareness and improved diagnostic microbiology services, which will enable early and rapid diagnosis and treatment to overcome the high mortality rates. This environmental saprophyte of tropical and subtropical countries is not going to disappear. Therefore more work need to be carried out on the distribution and incidence of melioidosis in Malaysia. There has been increased interest in melioidosis since *B.pseudomallei* has been designated as a potential agent for biological warfare and terrorism by the CDC (www.cdc.gov/od/sap) and hopefully there will be growing research interest in all aspects of melioidosis.

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ORIGINAL ARTICLES

PREDICTED EQUATIONS FOR VENTILATORY FUNCTION AMONG KUCHING (SARAWAK, MALAYSIA) POPULATION

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Summary

Spirometry data of 869 individuals (males and females) between the ages of 10 to 60 years were analyzed. The analysis yielded the following conclusions :

1. The pattern of Forced Vital Capacity (FVC) and Forced Expiratory Volume in One Second (FEV_1) for the selected subgroups seems to be gender dependant; in males, the highest values were seen in the Chinese, followed by the Malay, and then the Dayak; in females, the highest values were seen in the Chinese, followed by the Dayak, and then the Malay.
2. Smoking that did not produce respiratory symptom was not associated with a decline in lung function, in fact we noted higher values in smokers as compared to non smokers.
3. Prediction formulae (54 in total) are worked out for FVC & FEV_1 for the respective gender and each of the selected subgroups.

Key Words : Spirometry, Malays, Chinese, Dayaks, Predicted Equations

SEVERE TRAUMATIC BRAIN INJURY : OUTCOME IN PATIENTS WITH DIFFUSE AXONAL INJURY MANAGED CONSERVATIVELY IN HOSPITAL SULTANAH AMINAH, JOHOR BAHRU – AN OBSERVATIONAL STUDY

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Summary

Patients with isolated severe head injury with diffuse axonal injury and without any surgical lesion may be treated safely without cerebral resuscitation and intracranial pressure (ICP) monitoring. Seventy two patients were divided into three groups of patients receiving treatment based on ICP-CPP-targeted, or conservative methods either with or without ventilation support. The characteristics of these three groups were compared based on age, gender, Glasgow Coma Scale (GCS), pupillary reaction to light, computerized tomography scanning according to the Marshall classification, duration of intensive care unit (ICU) stays, Glasgow Outcome Score (GOS) and possible complications. There were higher risk of mortality ($p < 0.001$) worse GCS improvement upon discharge ($p < 0.001$) and longer ICU stays ($p = 0.016$) in ICP group compared to Intubation group. There were no significant statistical differences of GOS at 3rd and 6th months between all three groups.

Key Words : Severe Traumatic Brain Injury, Diffuse Axonal Injury, Intracranial Pressure Monitoring, Outcome

PROFILE OF LOW VISION CHILDREN IN THE SPECIAL EDUCATION SCHOOLS IN MALAYSIA

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Summary

This study looked at the causes of vision loss, levels of distance, near vision and the use of low vision devices (LVDs) in children studying at special schools in Malaysia. A total of 139 children from two special education schools took part. Visual acuity was measured with and without LVDs. Those who required further assessment were referred to Low Vision Clinic. Near visual acuity in 71 children ranged from N4 to N64. Sixty eight children could not read the N64 chart or they were totally blind. Only eight students were using LVDs before intervention. Seventy one children were referred to low vision assessment and 48 were found to benefit from the LVDs prescribed. The major cause of visual impairment was cataract (17%). Hand held magnifier was the most preferred LVD. Majority of the children attending the blind schools had residual vision but did not have LVDs. LVDs are able to significantly improve near visual acuity and hence there is a need to prescribe and train the children to use the LVDs.

Key Words : Low Vision Devices, Visually Impaired Students, Low Vision Assessment

SURGICAL MANAGEMENT OF LARGE ACOUSTIC NEUROMAS : A REVIEW

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Summary

Acoustic neuromas operated at UMMC from 2001 to 2006 were retrospectively reviewed. There were a total of 27 cases. All tumors were large, measuring more than 2 cm. Hearing loss was the most common presenting symptom (63%), followed by headache (52%), disequilibrium (30%), facial numbness (30%), tinnitus (26%) and gait disturbances (15%). Eleven (41%) of patients had hydrocephalus at the time of presentation, for which a shunt procedure was required. The translabyrinthine (TL) approach was used for 12 patients and the retrosigmoid (RS) with or without complications included one mortality and three cerebrovascular accidents (CVA's). The one year facial nerve outcome was good to acceptable in 62% (House-Brackmann Grade I – IV) of patients. A literature review of current management of acoustic neuromas is presented.

Key Words : Acoustic Neuroma, Vestibular Schwannoma, Translabyrinthine Approach, Retrosigmoid Approach

PLACENTA ACCRETA : CLINICAL RISK FACTORS, ACCURACY OF ANTENATAL DIAGNOSIS AND EFFECT ON PREGNANCY OUTCOME

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Summary

The aim of this study is to evaluate the clinical risk factors, accuracy of antenatal ultrasound for diagnosis, and the effect of these on pregnancy outcome. It is a retrospective study looking at cases which had hysterectomy following vaginal or caesarean section deliveries from 1993 to 2005. Data regarding the maternal demographic characteristics, number of previous CS, number of previous termination/curettage, antenatal scan findings (state features) and the gestation at which accreta was first suspected/diagnosed, MRI scan findings, pregnancy outcome (need for hysterectomy, amount of blood loss, amount of transfusion, length of ICU and hospital stay, other maternal complications, and neonatal outcome) were collected and evaluated. There were a total of 40 cases diagnosed to have abnormal placental attachment and majority of these were actually diagnosed antenatally by sonography. Visualization of an absence or thinning of hypoechoic myometrial zone had the highest sensitivity to detect placenta accreta followed by intraplacental lacunae, focal mass tissue elevation and disruption of uterine serosal bladder wall.

Key Words : Accreta, Increta, Placenta, Adherent Placenta

PRETERM BIRTH : MODE OF DELIVERY AND NEONATAL OUTCOME

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Summary

To evaluate the perinatal outcome of premature babies according to the mode of delivery. A total of 113 pregnant women and 124 neonates who delivered from 30 to 35 weeks of gestation were enrolled and outcomes of 70 neonates born vaginally were compared to 54 neonates born by caesarean. Neonatal mortality rate was 20 percent for infants in caesarean group as compared to 10 percent for vaginal group. There was no significant difference in the neonatal morbidity among both the groups. Caesarean delivery cannot be routinely recommended, unless there are obstetric indications.

Key Words : Preterm Vaginal Delivery, Preterm Caesarean Delivery, Premature Baby, Neonatal Complications, Perinatal Mortality

RETROSPECTIVE REVIEW OF SURGICAL MANAGEMENT OF FOREIGN BODY INGESTION

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Summary

Endoscopic examination and removal of foreign body under general anaesthesia are recommended for persistent symptomatic patient with or without significant findings on radiological examination. This report evaluates the management outcome of surgical removal of foreign body ingestion in upper gastrointestinal tract. A total of 70 cases with full documentation were reviewed retrospectively from June 1998 until December 2007. There were 32 males and 38 females with age range from 6 months to 87 years old (mean : 36.9 years). Sixty five patients (93%) were adults and 15 (7%) were below 13 years. Fish bones were the most common foreign body found (44.3%). Radiologically, foreign bodies were highly suspicious in 51 cases (76.1%). Intraoperatively, thirty six cases (70.6%) were positive. From 16 cases (23.9%) with normal radiograph, 10 cases (62.5%) were found to have foreign bodies. Therefore the plain radiograph is helpful, but clinical presentation is more reliable to determine surgical removal under general anaesthesia.

Key Words : Foreign Body, Fish Bone, Plain Radiograph, Endoscopic Examination

THE PREVALENCE AND CHARACTERISTICS ASSOCIATED WITH MOTHER-INFANT BED-SHARING IN KLANG DISTRICT, MALAYSIA

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Summary

This was a cross-sectional study to determine the prevalence and characteristics of mother-infant bed-sharing practice in Klang district, Malaysia. Data was collected by face-to-face interview using a structured questionnaire for a four month period in 2006. A total of 682 mother-infant pairs attending government health clinics were included in the study. Data regarding socio-demographic characteristics of the mothers, information on the infants, bed-sharing and breastfeeding practices were collected. The mean maternal age was 28.4 ± 5.1 years while the mean infant gestational age was 38.8 ± 1.8 weeks. The study showed the prevalence of bed-sharing was 73.5% (95% CI : 70.0, 76.7). In multivariate analysis; area of interview, maternal occupation, family income, breastfeeding and infant birth weight were associated with bed-sharing after adjusted for maternal ethnicity, age, marital status, educational level, parity, infant gender and infant gestational age. In conclusion, bed-sharing is a common practice in Klang district, Malaysia, not specific to ethnicity, but strongly associated with low family income and breastfeeding.

Key Words : Bed-Sharing, Maternal Factors, Infant Factors, Breastfeeding, Malaysia

RISK FACTORS ASSOCIATED WITH DEVELOPMENT OF DENGUE HAEMORRHAGIC FEVER OR DENGUE SHOCK SYNDROME IN ADULTS IN HOSPITAL TENGGU AMPUAN AFZAN, KUANTAN

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Summary

A retrospective study was conducted to investigate 183 serologically-confirmed cases of dengue fever (DF) admitted from October 2004 to March 2005 in a large hospital in Pahang. Clinical and laboratory features, progress and outcome of these patients were analyzed in order to identify risk factors associated with development of dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS). Individually, we found that older patients, secondary dengue infection, high baseline haematocrit levels, low platelet levels and prolonged activated partial thromboplastin time (APTT) ratio were significant associations with bleeding tendencies. Of these risk factors, haematocrit and APTT ratio were two independent significant risk factors on multivariate analysis. Older patients with primary infection and younger patients with secondary infection had significant bleeding tendencies. We also verified the validity of the haematocrit levels suggested as cut off levels for plasma leakage for the Malaysian population by Malaysian Clinical Practice Guidelines for Dengue Infection in Adults (2003).

Key Words : *Dengue Haemorrhagic Fever, Dengue Shock Syndrome, Risk Factors, Predictor, Haematocrit*

CONTINUING MEDICAL EDUCATION

FUNDAMENTALS OF THE MANAGEMENT OF NON-HODGKIN LYMPHOMA

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INTRODUCTION

Non-Hodgkin Lymphomas (NHL) is a heterogeneous group of lymphoproliferative disorders originating in B-lymphocytes, T-lymphocytes or natural killer (NK) lymphocytes. B-cell lymphomas accounts for 80-90% of the cases with 15-20% being T-cell lymphomas. NK lymphomas are very rare.

NHL is the fifth leading type of new cancer cases among men and women, accounting for 4-5% of new cancer cases and 3% of cancer-deaths among men and the sixth among women in the United States. In Malaysia, NHL is the third commonest cancer (7.4%) in male and tenth (2%) in female aged 15-49 years, and tenth (2-4%) in males and 14th (1-2%) females aged above 50.

The pattern and frequency of NHL vary in different populations and geographical regions. Compared to the West, follicular NHL is less common and T- and NK-cell NHL are more common in Asia. Additionally, the incidence of primary extranodal lymphoma is high among Asian population, with the commonest site being the gastrointestinal tract, nasal cavity and tonsils. Extranodal lymphoma is distinct from nodal NHL in many ways ranging from treatment strategies to prognosis.

Many patients with DLBCL and FL will have widespread disease at presentation and can be rapidly fatal if left untreated. Expedited and holistic care should be provided by a team of health care professionals who are experienced in treating NHL. This team may include medical oncologist, radiation oncologist, haematologist, surgeon, pathologist, oncology nurse, radiologist, and social worker.

In addition, adequate psychological and family support is vital to ensure effective delivery of treatment and to facilitate recovery from therapy. Shared decision making is recommended in all instances.

The outcome of patients with lymphoma is highly variable, and the histology of the lymphoma is the major determinant of treatment outcome and prognosis. Some patients with indolent lymphoma may remain well for many years with minimal or no therapy, whereas patients with aggressive lymphoma may succumb rapidly unless aggressive treatment is initiated promptly.

Owing to the clinical heterogeneity of NHL, individualized treatment approach is the cornerstone of ensuring successful treatment outcome. For this, several prognostic models have been used to design therapeutic trials for patients with aggressive and indolent NHL, and in the selection of appropriate treatment approaches for individual patients.

Currently, multiple novel agents are being developed for the treatment of NHL. Despite these major therapeutic advances, a significant proportion of patients will relapse or remain refractory to initial treatment.

On the other hand, as more patients will be cured with availability of novel therapeutic strategy, late effects of cytotoxic chemotherapy and radiotherapy among long term lymphoma survivors remain a major concern. Hence, there is an increasing emphasis on attaining long term survival with the least acute and late toxicity from chemotherapy and RT.

This review explores the fundamental elements involved in the management of patients with NHL with particular reference to the common and pertinent queries from patients and their caregivers. The information presented herein may be used as guidelines in counseling patients to understand their disease and the treatment.

What causes NHL?

In most cases, the causes of NHL are unknown. However, it has been associated with chronic inflammatory or autoimmune diseases such as Sjogren syndrome, Hashimoto's thyroiditis and rheumatoid arthritis. Chronic infection also is associated with lymphoma pathogenesis as shown by the association between mucosa-associated lymphoid tissue (MALT) lymphomas and *Helicobacter pylori* infection.

Immune suppression also has been associated with an increased risk of NHL. In patients who undergo solid organ transplantation, the risk of lymphoma has been associated specifically with the duration of immunosuppression and with the drugs used. Furthermore, *human immunodeficiency virus* (HIV) infection has been associated with a substantially elevated risk of NHL.

What are the Types of NHL?

Because there are so many types of NHL, several different systems have been developed to classify the disease. The International Working Formulation (IWF) classifies NHL into indolent/low grade, aggressive/intermediate grade or highly aggressive/high grade according to their morphology and natural histories.

In many centers, the histological report should give the diagnosis according to the currently internationally accepted revised REAL/WHO system. This system sorts NHL into B cell, T-cell and NK-cell neoplasm based on their morphology, immunophenotype and genetic features. These features have aided in defining active treatment for specific subtypes or lymphoma.

The two most common histological disease entities are diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL).

What are the Clinical Manifestations of NHL?

Patients with indolent lymphomas, such as follicular, marginal zone and lymphoplasmacytic lymphoma, commonly present with slowly progressive and usually painless peripheral lymphadenopathy. Spontaneous regression of enlarged lymph nodes can occur. Primary extranodal involvement or systemic symptoms are less common at presentation but are seen more commonly as the disease advances or transforms to aggressive NHL. Bone marrow involvement in indolent lymphomas is frequent and sometimes is associated with cytopenias. Splenomegaly is seen in approximately 30% to 40% of patients, but the spleen is rarely the only site of disease involvement at presentation.

The clinical presentation of aggressive lymphomas, such as DLBCL, is more variable. Most patients present with lymphadenopathy; however, many present with extranodal involvement. The most common extranodal sites are the gastrointestinal (GI) tract, skin, bone marrow, sinuses, thyroid, or central nervous system (CNS). Molecular studies have indicated substantial

differences between nodal and extranodal DLBCL, suggesting that both have distinct genetic origins and could arguably be regarded as different entities. B-symptoms are more, occurring in approximately one third of patients. Patients with lymphoblastic lymphoma often present with an anterior mediastinal mass that is sometimes associated with superior vena cava obstruction. Burkitt lymphoma typically disseminates to the bone marrow and meninges and involves extranodal sites.

How is NHL Diagnosed?

No effective method is available for screening patients for lymphoma, and identifying populations at high risk of lymphoma is challenging. Currently, patients are identified only after they develop lymphadenopathy or other symptoms associated with their disease.

Histology remains compulsory to establishing the diagnosis in all cases and a definitive diagnosis can be made only after biopsy specimens are reviewed by an expert haematopathologist.

Diagnosis should be made on the basis excisional lymph node or extranodal tissue biopsy providing enough material for formalin-fixed samples. Core biopsies should only be performed in patients without easily accessible lymph nodes (e.g. retroperitoneal bulk) or in patients requiring emergency treatment. Fine needle aspiration alone (FNA) is not acceptable as reliable for initial diagnosis of NHL. For patients with intra-abdominal and retroperitoneal mass as the only sites of disease, laparoscopy has a role in establishing the diagnosis.

Immunohistochemical study is essential for differentiating the various subtypes of NHL and also to determine prognosis as these will influence the choice of therapy. It can be performed by flow cytometry and/or immunohistochemistry utilizing a minimal antibody panel (CD45, CD20 and CD3) to identify B, T or NK subtypes. The typical immunophenotype for DLBCL is CD20+, CD45+ and CD3- and FL CD20+, CD10+, bcl-2+, CD43- and CD5-. Other additional markers aid identification of subtypes, e.g. cyclin D1 for mantle cell lymphoma. Ki-67 a marker of proliferation index (PI) which is used in the histological grading of NHL, is valuable in predicting survival. Overall survival (OS) was significantly reduced in patients with high Ki-67 (high PI) compared to those lower PI.

Molecular cytogenetic analysis to identify the specific chromosomal translocations that are more commonly seen in particular NHL subtypes may be necessary in cases of diagnostic difficulties. Most cases (80%) of Burkitt lymphoma have a translocation of c-myc from chromosome 8 to the immunoglobulin (Ig) heavy chain region on chromosome 14 [t (8;140)].

What Investigations are required once a Patient is Diagnosed with NHL?

Since treatment depends substantially on the stage of the disease and medical status of the patient, a thorough initial work up designed to identify all sites of known disease and baseline organ functions.

Initial work up should include complete blood count, serum lactate dehydrogenase (LDH), renal/liver function tests, uric acid, computed tomography (CT) scan of the chest and abdomen as well as a screening test for human immunodeficiency virus and hepatitis B and C viruses. Cardiac function should be tested before treatment because most chemotherapy regime includes an anthracycline drug that can damage the heart. Patients amenable to curative therapy should have a bone marrow aspirate and biopsy. Bone marrow involvement is associated with significantly shorter survivals in patients with intermediate or high grade lymphomas.

A diagnostic spinal tap directly combined with a first prophylactic instillation of cytarabine and/or methotrexate is indicated in high risk patients according to international prognostic index (IPI), especially with involvement of CNS, orbital, bone marrow, testis, spine, or base of the skull. It is also indicated in the case of HIV-associated lymphoma and highly aggressive NHL.

Based on the Ann Arbor staging system (Box 1), patients are categorized into limited (Stage I, II) and advanced (Stage III, IV) disease. This system is designed based on the distribution and number of involved sites, presence or absence of extranodal involvement and constitutional symptoms.

Box 1

Cotswolds Modification of Ann Arbor Staging System **Stage Area of Involvement**

I	Single lymph node group
II	Multiple lymph node groups on same side of diaphragm
III	Multiple lymph node groups on both sides of diaphragm
IV	Multiple extranodal sites or lymph nodes and extranodal sites
X	Bulk > 10 cm
E	Extranodal extension or single isolated site of extranodal disease
A/B	B symptoms : weight loss > 10%, fever, drenching night sweats

Adapted from reference no. 18

The next step is to identify specific group of patients who are more or less likely to be cured with standard therapy. On the basis of age, tumor stage, LDH serum level, performance status, and number of sites of extranodal disease, the International Prognostic Index (IPI) distinguishes four different risk groups. The four groups had a predicted 5 years survival of : 73% (low risk group), 51% (low intermediate risk group), 43% (high intermediate risk group) and 26% (high risk group). Because younger and older patients may have different outcomes and younger patients may be considered for more aggressive therapy, an age adjusted IPI (Box 2) for patients aged 60 years or younger also has been developed. This model identifies four risk groups with a predicted 5 year survival of : 83% (no adverse factors), 69% (one adverse factor), 46% (two adverse factors), and 32% (three adverse risk factors).

Box 2

INTERNATIONAL PROGNOSTIC INDEX

ALL PATIENTS :

Age > 60 years
Serum LDH > 1 x normal
Performance status 2-4
Stage III or IV
Extranodal involvement > 1 site

INTERNATIONAL INDEX, ALL PATIENTS :

Low	0 or 1
Low intermediate	2
High intermediate	3
High	4 or 5

AGE ADJUSTED INTERNATIONAL PROGNOSTIC INDEX

PATIENTS ≤ 60 YEARS :

Stage III or IV
Serum LDH > 1 x normal
Performance status 2-4

INTERNATIONAL INDEX, PATIENTS ≤ 60 YEARS :

Low	0
Low/intermediate	1
High/intermediate	2
High	3

Adapted from reference no. 4

The IPI was designed for aggressive lymphoma and may not clearly identify patients with indolent lymphoma who are at high risk; thus, a new prognostic factor model has been devised for FL. The Follicular Lymphoma International Prognostic Index (FLIPI) uses the patient's age (> 60 vs ≤ 60 years), Ann Arbor stage (III or IV vs I or II), haemoglobin level (< 12 g/dL vs ≥ 12 g/dL), number of nodal areas (> 4 vs ≤ 4) and serum LDH level. The FLIPI is predictive of overall survival hence may be used to identify patients that may benefit from more aggressive therapy.

Learning Points

1. Core needle biopsy is discouraged unless the clinical situation dictates that this is the only safe means of obtaining diagnostic tissue.
2. Fine needle aspiration alone is inappropriate for an initial diagnosis of NHL, though it may be sufficient to establish relapse.
3. The diagnosis of NHL should be made based on adequate sample by an experienced pathologist.
4. Studies of immunophenotype and molecular genetics are essential to refine the diagnosis.
5. Key elements in determining the optimal therapeutic strategies of NHL are the tumor histology and stage and patient's prognostic index.
6. PET scan is useful in evaluating residual masses following chemotherapy for DLBCL.
7. Rituximab-CHOP is considered the standard of care for DLBCL.
8. Autologous HSCT is an established treatment in relapse lymphoma.

What are the Treatment Options and Outcome of Treatment in Patients with Newly Diagnosed NHL?

Not all patients with lymphoma require immediate treatment upon diagnosis. The decision to initiate therapy depends primarily on the histology NHL. Since the natural course of indolent NHL is characterized by spontaneous regressions in 15-20% of cases, chemotherapy should be initiated only upon the occurrence of symptoms including B symptoms, haematopoietic impairment, bulky disease or rapid lymphoma progression. In contrast, treatment should not be delayed in patients diagnosed with aggressive or advanced stage lymphoma.

Apart from the histology, the overall treatment strategies should be tailored according to tumour stage and patient's baseline prognostic index and preference.

The patient should be involved in the decision process from the start, which has to balance the chance of cure against the risks of treatment related mortality. When cure is the aim, it is desirable to treat patients with the least toxic therapy that will achieve a durable complete remission. These include limiting the number of chemotherapy cycles and restricting radiotherapy to those most likely to benefit from it.

B-cell NHL

Treatment strategies for patients with DLBCL differ between patients with limited or advanced disease and the presence or absence of risk factors. Patients of all ages with stage I-II DLBCL and no adverse prognostic factors (non-bulky disease and IPI prognostic index equal to 0) should receive abbreviated (three-four cycles) chemotherapy with an anthracycline-containing regimen plus involved field RT (35-40 Gy) or a full course (six-eight cycles) of chemotherapy alone. Patients with stage I-II disease and at least one adverse prognostic factor (bulky disease, elevated LDH, performance status ECOG > 1) should be treated according to the recommendations for stage III-IV disease. These patients should receive six to eight cycles of chemotherapy.

Standard first-line chemotherapy for all patients with CD20+ DLBCL is cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) combined with rituximab (R) given every 21 days. This results in complete remission (CR) rate of 75%-80% and a 3-5-year progression-free survival (PFS) of 50%-80%. The addition of rituximab to CHOP (R-CHOP) has been the most significant advance in treatment of DLBCL with an improvement in PFS and OS by 15%-20% over CHOP chemotherapy alone.

Patients with symptomatic stage I-II FL can be treated with radiotherapy alone while patients with stage III-IV or grade 3 histology should be treated with chemotherapy as for DLBCL. Highly aggressive NHL such as Burkitt's lymphoma and lymphoblastic lymphoma has generally been treated with acute lymphoblastic leukaemia (ALL)-like regimens that include intrathecal chemotherapy due to the propensity for CNS relapse.

T-cell NHL

The management of peripheral T-cell lymphomas (PTCL) has not been well defined, but therapy should be based on the stage of disease and the specific immunopathologic disease entity. However, the complete response rate, with the exception of ALK+ anaplastic large cell lymphoma, is lower than in B-cell lymphomas treated with the same chemotherapy combination. Because of a paucity of comparative trials, there is little evidence that any particular combination chemotherapy is superior to the others. Therefore, clinical trials are the preferred treatment option for all patients with PTCL.

HIV-Associated Lymphoma

Optimal management of HIV-associated lymphoma (HAL) is not established. CHOP given with concomitant HAART or EPOCH regimen (etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) without HAART have proven to be effective and tolerable in patients with HAL. The NCCN guidelines recommend full dose chemotherapy with growth factor support and prophylactic therapy with intrathecal chemotherapy. Rituximab appears to increase the risk of neutropenia and infection and there is no net benefit in patients with HAL. The omission of rituximab is strongly suggested for DLBCL patients with CD4 counts of less than 50 due to the higher risk of infectious toxicities.

Ancillary Therapy and Care

Other than tumor specific therapies, good supportive care is essential in ensuring successful treatment outcome. In cases with high tumor load, special precautions (e.g. corticosteroid pre-phase and alkaline diuresis) are required to avoid tumor lysis syndrome. Anti-emetics and anti-infective measures should be initiated prior to commencement of chemotherapy. Antiviral prophylaxis is beneficial in preventing hepatitis B virus reactivation. History of febrile neutropenia following chemotherapy justifies prophylactic use of haematopoietic growth factors in patients treated with curative intent. Because treatment may affect fertility, this issue including sperm banking needs to be addressed if the patient wants to have a family.

Following chemotherapy, the patients should be monitored closely for the development of infection and bleeding associated with myelosuppression. Empiric antibiotic therapy and growth factors are important measures in the treatment of febrile neutropenia.

How would Response be Determined?

Abnormal radiological tests at baseline should be repeated after mid-cycle and last cycle of treatment. Bone marrow aspirate/biopsy should be repeated only at the end of treatment if initially involved. CT is the most commonly used imaging modality for response assessment but CT has limitations in differentiating between viable tumor, necrosis and fibrosis in residual masses. By contrast PET scan is useful in determining the etiology of post-therapy residual masses in aggressive NHL.

PET scans are particularly informative for response evaluation after treatment because they can distinguish residual fibrotic masses from masses containing viable tumor. Early interim PET correlates with progression-free survival and overall survival. For these reasons, PET/CT is rapidly replacing CT scan for treatment response assessment and has now been incorporated into the response criteria.

Response to treatment is categorized as CR, partial remission (PR), stable disease (SD) and relapsed disease or progressive disease (PD) based on the reduction in the size of the enlarged lymph node and the extent of bone marrow involvement. Patients with insufficient or lack of response to initial therapy should be evaluated for early salvage regimens.

How should Patients who Achieved Complete Remission be Monitored?

Clinical evaluation should be performed every 3 months for 1 year, every 6 months for 2 more years and then once a year with special attention to development of secondary cancers including leukaemia, and thyroid and breast carcinomas.

After having received chest irradiation at premenopausal age, especially at an age < 25 years, women should be screened for secondary breast cancers clinically and, after the age of 40 years, by mammography. Evaluation of thyroid function (thyroid-stimulating hormone) in patients with irradiation to the neck at 1, 2 and 5 years.

Full blood counts and serum LDH at 3, 6, 12 and 24 months, then as required for evaluation of suspicious clinical findings suggestive of disease recurrence. Minimal adequate radiological examinations at 6, 12 and 24 months after end of treatment by CT scan are indicated.

Will the Cancer Recur (Relapse) and what should be done if the Cancer Recurs?

Despite recent therapeutic advances, up to 50% of patients relapse after initial chemoimmunotherapy. A repeat biopsy is strongly recommended, and is mandatory in relapses > 12 months after the initial diagnosis, in order to rule out a secondary transformation into aggressive lymphoma from low grade NHL and also to ensure CD20 positivity.

Patients still amenable to curative therapy should have the same work up as at the first presentation. The cumulative dose of anthracyclines used in first line therapy has to be specified. If further anthracyclines are to be used, echocardiography for quantification of the ejection fraction should be done.

What are the Treatment Options in Patients with Relapsed NHL?

To date, the standard of care in the management of relapsed/refractory DLBCL is salvage chemotherapy followed by an autologous haematopoietic stem cell transplantation (HSCT) for those with chemotherapy-sensitive disease. Event-free survival (EFS) and OS at 5 years in the transplant arm were 46% and 53%, respectively, compared with 12% and 32% in the chemotherapy alone arm.

Currently, there is no standard salvage chemotherapy regimen. The choice of salvage treatment depends on efficacy of prior regimens. In early relapses (< 12 months), a non cross resistant scheme should be preferred. Combining rituximab with salvage therapy clearly suggest superior response and disease-free survival over chemotherapy alone [II, A] in relapse DLBCL. Any of the published salvage regimens such as R-DHAP, R-ICE, etc may be adequate until results of comparative trials are known. The most frequently used high dose regimen locally is BEAM (carmustine, etoposide, cytosine-arabioside and melphalan). Patients not suitable for high dose therapy may be treated with the same or other salvage regimens (e.g. R-IMVP16, R-GEMOX, etc) and may be combined with involved-field radiotherapy. Radioimmunotherapy (RIT) with [¹³¹I]-tositumumab and ⁹⁰Y-ibritumomab tiuxetan is an alternate treatment option for relapsed, refractory or histologically transformed FL.

What is the Role of Haematopoietic Stem Cell Transplantation (HSCT)?

HSCT is recommended in patients with relapsed NHL. HSCT currently does not have a well defined role in the primary therapy for aggressive lymphomas but may be considered for high risk patients who achieve a CR to initial conventional chemotherapy. However, the late effects of transplantation need to be considered because the risk of myelodysplastic syndrome and acute myeloid leukaemia is significant. Because of the poor response rates and outcome reported to date, autologous HSCT is not recommended in primary refractory or relapsed aggressive NHL not responding to salvage chemotherapy. Alternative treatment strategies are required in these cases, and wherever possible, patients should be enrolled in clinical trials assessing new treatment regimens and novel therapeutic agents.

Allogeneic HSCT is potentially curative due to its graft versus lymphoma effect, hence should be considered in younger patients with relapsed disease or highly aggressive lymphomas. However, the benefits of lower relapse rates are abrogated by higher treatment-related mortality. The use of non-myeloablative or reduced-intensity allogeneic transplants has significantly decreased the early treatment related mortality and can increase the number of patients eligible for allogeneic HSCT.

Recent efforts to improve the outcome of HSCT in NHL by reducing relapse include the addition of radioimmunoconjugates to conditioning regimens and the use of rituximab for “in vivo purging” around the time of stem cell harvesting and also as adjuvant therapy after SCT.

What is the Role of Radiotherapy?

Radiation therapy is now used infrequently as the sole curative therapy in NHL except in limited stage follicular FL. Consolidative radiotherapy is often used to initial bulky sites and in residual disease after completion of systemic chemotherapy. Radiotherapy may be used as palliation of symptoms in patients not suitable for systemic therapy.

What is the Role of Surgery?

Surgery is useful only in selected situations, most commonly to establish a diagnosis by obtaining a biopsy specimen. Because lymphoma is a systemic illness, resection of the sites of disease is used only in selected situations. Surgery may be particularly useful in primary GI lymphomas when the disease is localized or when there is a risk of perforation. Orchiectomy is commonly the initial treatment for patients with testicular lymphoma.

CONCLUSION

The accurate documentation of the pathologic diagnosis, the anatomic extent of tumor, patient's individual prognostic index and the response to therapy are of paramount importance in the management of lymphoma. A personalized and holistic approach provided by a highly experienced team of health care professionals is the cornerstone of ensuring successful treatment outcome.

Recent therapeutic advances including the use of monoclonal-antibody based therapy and the more widespread use of HSCT have increased cure rates of patients with NHL. Enhancements in the understanding of the pathogenesis and biology of lymphoma have led to a continual development of targeted therapies for this disease. Molecular profiling of tumors has allowed the prognosis to be determined more accurately and has potentially identified new targets for treatment. New monoclonal antibodies against a wide range of T-cell and B-cell surface markers are in clinical development.