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EDITORIAL

ONLINE SUBMISSIONS FOR THE MEDICAL JOURNAL OF MALAYSIA (MJM)

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Editor, Medical Journal of Malaysia

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

www.wpro.who.int/apame

apame@wpro.who.int

(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)

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, Translabrynthine 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.