

EDITORIAL

NEONATAL TETANUS IN MALAYSIA

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Introduction

Neonatal Tetanus is a severe disease with high fatality. It should no longer be present in a country with the development status of Malaysia. However, sporadic cases still occur and the disease has not been eradicated. This editorial summarizes the disease pattern, incidence and suggests reasons for the continued persistence of the condition locally.

Disease Pattern

Tetanus is an acute disease caused by a highly potent neurotoxin (tetanospasmin) produced by *Clostridium tetani*. This toxin acts at the myoneural junction of skeletal muscle and on neuronal membranes in the spinal cord blocking inhibitory pulses to motor neurons. It is characterized by muscular rigidity with superimposed agonizing contractions. The bacillus grows anaerobically at the site of wounds. Tetanus spores are present in soil and, for adults and children, may be introduced into the body during injury through puncture wounds, burns or trivial unnoticed wounds. Tetanus is not spread from person to person. The incubation period is between two days and two months, averaging ten days, and most cases occur within 14 days. Shorter incubation periods have been associated with more heavily contaminated wounds, more severe disease and a worse prognosis. Death results from respiratory failure, hypotension or cardiac arrhythmias. Case-fatality rates are high even with good intensive care.

Neonatal tetanus, due to infection of the baby's umbilical stump, is an important cause of death in many developing countries where women are not appropriately immunized against tetanus and deliveries are conducted in a non sterile manner (unsafe deliveries). Tetanus in children and adults following injuries constitutes a smaller public health problem. The case fatality rates for neonatal tetanus with good intensive care range from 10-20%. Those of us who have been

working with children for more than 25 years will still remember the agonizing state of neonates with neonatal tetanus and the frequent failure we had in salvaging them.

Tetanus Toxoid Vaccine and Immunity

There is insufficient data to answer questions about natural immunity to tetanus. There is no clear data showing a rise in natural immunity with age. It is postulated that there is no immunity induced by tetanus infection. Immunization protects by stimulating the production of antitoxin, which protects against the toxin produced by the organism. The immunogen is prepared by treating a cell free preparation of toxin with formaldehyde and thereby converting it into the innocuous tetanus toxoid. It is usually absorbed on to an adjuvant, either aluminium phosphate or aluminium hydroxide, to increase its immunogenicity. *Bordetella pertussis* vaccine also acts as an effective adjuvant. Tetanus toxoid is stable and can stand room temperature for months. However, tetanus vaccines as part of DPT should be stored at 1-8°C and should not be frozen or exposed to light. The dose is 0.5 mL given intramuscularly. As part of primary childhood immunization, tetanus vaccines should not be given as a monocomponent vaccine but in combination with diphtheria (DT) and/or pertussis (DPT). Mothers are immunized in pregnancy with tetanus toxoid as it is shown that tetanus antitoxin is transferred from the immunized mother to the foetus, thus providing transient protection to the newborn infant from tetanus. It is vital that mothers, without primary immunization in childhood (see below), are immunized as early as possible in the pregnancy to ensure an adequate interval between the second dose and delivery.

Incidence

Neonatal tetanus is a notifiable disease in Malaysia. The figure shows the number of reported cases of neonatal tetanus since 1975. Tetanus toxoid (ATT) immunization for pregnant mothers was implemented in 1976. Coverage rates in pregnancy rose until 1990 where they have remained at between 80-85%. The effect of this has been a dramatic reduction in the number and incidence of neonatal tetanus. In the ten year period from 1989-1998 there were 32 deaths out of 180 reported cases giving a case fatality rate of 17.8%. The case fatality rate has decreased in the 2000-2006 period to 2.6% (2 deaths out of 78 cases). It is important to note that the numbers have become so low that it is no longer meaningful to calculate incidence rates. In addition there has been much inter year fluctuation. An additional factor for the decline in neonatal tetanus is the primary immunization programme for children that has been in place since the 1970s – three doses of DPT at 2, 3 and 5 months followed by a DPT booster at

18 months, a DT booster at school entry and a tetanus booster at Form 3. Many of these children immunized have become child bearing adults and immunity lasts for at least 20 years after such a schedule that has 5 doses of tetanus toxoid.

Global Perspective

Neonatal tetanus was recognized as a major public health problem in the late 1980s where it was estimated that more than 750,000 neonates died of neonatal tetanus. In 1989, the 42nd World Health Assembly called for elimination of neonatal tetanus by 1995. The target date for elimination was however not met due to slow implementation and was postponed to 2000. As of 2008, there still remain 46 countries to eliminate neonatal tetanus (most in Africa). The World Health Organization estimates the international burden of newborn deaths due to neonatal tetanus at 128,000 in 2004, the latest year for which estimates are available. This accounts for 3.4% of all under 5 deaths in the world for 2004. In addition, for 2004, an estimated 40 million pregnant women were still in need of immunization against birth associated tetanus, and about 27 million children did not complete their primary tetanus immunization series.

(Please refer to page 2 of the MJM for the graph on reported cases and deaths of neonatal tetanus with antenatal coverage of tetanus toxoid in Malaysia, 1976-2007)

Elimination of Neonatal Tetanus in Malaysia

It must be noted that, despite the existing healthcare initiatives, neonatal tetanus has not been eliminated in Malaysia and this is cause for concern. Part of the reason for this lies with the delivery of health care to immigrants. More than 90% of all cases are reported from Sabah and the majority of these from immigrants, as highlighted by a case series published in this issue of the Journal. The Ministry of Health has planned measures to eliminate neonatal tetanus. However, these need to be made effective on the ground. Neonatal tetanus can be eliminated in Malaysia if we increase the antenatal tetanus toxoid immunization rates to past 95% from its current 85%. Populations with poorest antenatal tetanus toxoid cover are immigrants, indigenous people and some pockets of rural and urban poor. Currently many illegal immigrants are not provided basic health care by our health service. They are also reluctant to come forward as they are fearful of being deported. It is important to note that treating a child with neonatal tetanus is much more expensive than providing tetanus toxoid immunization to a community. On humanitarian grounds, antenatal care must be provided regardless of

immigration status to all antenatal mothers, without fear of legal action. This is the only meaningful way to eliminate this horrific disease in neonates locally.

ORIGINAL ARTICLES

COMPARING EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY AND URETEROSCOPY FOR TREATMENT OF PROXIMAL URETERIC CALCULI : A COST EFFECTIVENESS STUDY

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Summary

Extracorporeal shockwave lithotripsy (ESWL) and ureteroscopy (URS) are two main methods of treating proximal ureteric stones. Success rates and cost effectiveness of the two methods were compared. A total of 67 patients who underwent treatment between January 2007 and July 2007 at a state general hospital were included in the study. The success rate for ESWL group was 81.8% and for URS group was 84.6%. ESWL technique produced a significant higher overall cost per patient than URS (RM930.02 versus RM621.95 respectively). There was no significant difference in quality of patient's life. Cost effectiveness ratio was lower for URS. The analysis suggested that URS was more cost effective than ESWL.

Key Words : Cost Effectiveness Analysis, Shock Wave Lithotripsy, Ureteroscopy, Ureteric Calculi

IS THE FEMORAL NECK GEOMETRY ADEQUATE FOR PLACEMENT OF THE PROXIMAL FEMORAL NAIL IN THE MALAYSIAN POPULATION? A REVIEW OF 100 CASES

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Summary

Issues that had been encountered during proximal femoral fracture fixation using proximal femoral nail include i) the adequacy of the femoral neck width in the local population and ii) the potential difficulty encountered during fixation in certain prefixed angles as determined by the implant. This was a retrospective, descriptive study evaluating the anterior posterior pelvic radiographs of 100 consecutive patients, from January to August 2007, managed at University Malaya Medical Centre, Kuala Lumpur. The femoral neck width in the population studied were not a factor influencing the placement of femoral neck lag screws and anti rotation pin.

Key Words : Femur Neck, Intramedullary Nailing, Hip Fractures, Intertrochanteric, Fractures, Subtrochanteric Fractures

PAHANG MELIOIDOSIS REGISTRY

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Summary

Melioidosis has a high annual incidence and mortality rate in Pahang, Malaysia. We initiated the first melioidosis registry in the country on 1 July 2005 to improve the management of melioidosis in the state. Continuous medical education on melioidosis was carried out in all hospitals in the state to highlight the magnitude of the disease and to educate the doctors on the treatment of the disease. All culture confirmed cases were registered and analysed. During the one year study period from 1st July 2005 till 30th June 2006, a total of 63 patients had positive culture for *Burkholderia pseudomallei*. The calculated annual incidence of melioidosis in Pahang state was 4.3 per 100,000 population per year (Adult, 6.0 per 100,000 population per year and paediatric, 1.6 per 100,000 population per year). There were 55 Malays (87.3%), three Chinese (4.8%), four aborigines (6.3%) and one Indonesian. Nine (14.3%) were less than 18 years old. The median age was 49 years (range : 1-68 years). Only one patient (1.6%) had a previous history of confirmed melioidosis. With this programme, we had observed a decline in adult mortality from 54% to 44%, although this was not statistically significant. However, culture confirmed relapses had dropped from 19% to nil. Several measures need to be taken to decrease mortality from melioidosis in endemic countries.

Key Words : Melioidosis, Burkholderia Pseudomallei, Registry, Mortality

A REVIEW OF PAROTID TUMOURS AND THEIR MANAGEMENT : A TEN YEAR EXPERIENCE

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Summary

To review the demographics, management and outcome of patients undergoing parotidectomy at a tertiary center. A total of 76 patients who underwent parotidectomies from January 1996 to December 2005 at the ORL Department of our center were reviewed. All clinical, operative, post operative, histological data were gathered and reviewed. Fine needle aspiration cytology (FNAC) was diagnostic in 90% of patients with a sensitivity of 76% and specificity of 96%. Twenty one patients had malignant tumours and the rest had benign or inflammatory lesions. There were a total of 48 superficial and 28 total parotidectomies performed. Facial nerve palsy occurred in 30 (39%) patients with 4% permanent palsy and 35% temporary palsy. The recurrence rate of pleomorphic adenoma was 2.6%. FNAC and CT scan were performed prior to the surgery were useful guidance in planning the operation but clinical judgment is more important. The most common surgery performed was superficial parotidectomy and the most common cause was due to pleomorphic adenoma. The incidence of complications and recurrence of tumour are comparable to other international studies. Prior knowledge of anatomy and careful planning is needed to decrease the incidence of facial nerve palsy.

Key Words : Parotidectomy, Parotid Gland, Complications, Outcome

ACUTE STROKE PATIENTS WITH HIGH BMI ARE LESS LIKELY TO HAVE SEVERE DISABILITY AT INITIAL PRESENTATION

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Summary

This is a prospective study to determine the severity of disability and prognosis of acute stroke patients related to their Body Mass Index (BMI). A total of 79 consecutive CT scan proven acute stroke patients who were admitted to Hospital Tuanku Ja'afar, Seremban between November 2006 and April 2007 were recruited (male:female 49:30; mean age 62.7 years; ischemic stroke 70, intracerebral bleed 9). The patients were divided according to BMI less than 25 (Group A) and equal or greater than 25 (Group B). Severity of disability was measured between 24-48 hours by modified Rankin's score. Patients were followed up after one month. Thirty seven patients had severe disability (Rankin Score 5). Twenty nine patients had adverse outcomes including 11 deaths and 18 rehospitalization or prolonged hospital/nursing home stay. 34.3% of Group B had severe disability compared to 31.8% of Group A (χ^2 P = 0.046). Conversely 42.9% of Group B had adverse events at one month compared to 56.8% of Group A (χ^2 P = 0.312). There were no statistical differences between high and low BMI groups for gender ratio, smoking, hypertension, diabetes, prior cardiovascular disease, mean age, mean lipid profile and blood pressure. When comparing patients with Rankin Score 1-4 versus 5, age and BMI were statistically significant between the two groups. By multivariate analysis only age is independent predictor for severe disability (P < 0.05). The results of this pilot study should be confirmed in larger prospective multicentre trial.

Key Words : Stroke, Body Mass Index (BMI), Rankin's Score, Disability, Adverse Outcomes

ISOLATION OF MEASLES VIRUS FROM CLINICAL SPECIMENS USING B95a AND VERO/Hslam CELL-LINES

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Summary

The clinical presentation of acute measles is normally quite typical, especially in the presence of Koplik's spots, that laboratory test is seldom required to confirm the diagnosis. However, with wide measles vaccination coverage and the extensive use of immunosuppressive chemotherapy, the diagnosis of atypical manifestations of acute measles may require laboratory confirmation. When compared with B95a cell-line, this study shows that the Vero/hSLAM cell-line is sensitive and is recommended for use in the primary isolation of wild-type measles virus from clinical specimens. Throat swab and urine specimens are the clinical specimens of choice and both are recommended for optimal isolation of measles virus from patients suspected of acute measles virus infection.

Key Words : Measles Virus, B95a Cell-Line, Vero/hSLAM Cell-Line

AWARENESS AND KNOWLEDGE ON EYE DONATION AMONG UNIVERSITY STUDENTS

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Summary

Four hundred (400) students studying first year Medicine, Dentistry, Laboratory Technology, Pharmacy, Biomedicine and Bioengineering degree courses in the University of Malaya were assessed on their awareness and knowledge on eye donation using an open ended questionnaire. The majority of the students (344, 86%) in this study were aware about eye donation; the awareness was higher in biomedical (77.1%) and medical students (76.7%) compared to the others (55.9% - 70.7%). One hundred and eight students (27%) were willing to donate their eyes. Most of the students (376, 94%) did not know about any eye bank in Malaysia. One hundred and sixty (40%) students were aware that whole eye can be removed from the donor and 101 (25.25%) were aware that the cornea can be removed separately. However, only 121 (30.25%) knew that donated eyes were used for corneal grafting. More than half of the students (231, 57.7%) did not know that the donor eye could be stored before transplantation. The results of this study indicate that there is a need to educate the young adults in our society about corneal transplantation so that they can in turn motivate other members of society and their own family members to become eye donors, thus facilitating the availability of donor corneas for corneal transplantation in Malaysia.

Key Words : Eye Donation, Awareness, Knowledge, Corneal Transplantation

HOW SHOULD MALAYSIA RESPOND TO ITS AGEING SOCIETY?

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Summary

As Malaysia ages, its health and social care systems will have to adapt to a changing pattern of disease and dependency. Improved public health measures extend life expectancy at the relative expense of increased prevalence of currently incurable conditions such as dementia and Parkinson's disease. In this article, we discuss how these demographic changes will impact and suggest possible means of coping with the altered epidemiology of disease and disability. Malaysia will need to swiftly develop sufficient expertise in acute Geriatric Medicine, rehabilitation of older people; the management of long term conditions in older people with multiple complex problems within Primary Care; as well as an infrastructure for home and institutional care.

Key Words : Older People, Elderly, Malaysia, Ageing, Geriatric Medicine, Primary Care

TRAINING FUTURE DOCTORS TO BE PATIENT CENTRED : EFFICACY OF A COMMUNICATION SKILLS TRAINING (CST) PROGRAMME IN A MALAYSIAN MEDICAL INSTITUTION

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Summary

This study evaluates the efficacy of the preclinical communication skills training (CST) programme at the International Medical University in Malaysia. Efficacy indicators include students' 1) perceived competency 2) attitude 3) conceptual knowledge and 4) performance with regard to patient centred communication. A longitudinal study with a before after design tracked a preclinical cohort's progress on the aforementioned indicators as they advance through the training. Results indicate that following the CST, students perceived themselves to be more competent in interpersonal communication, had more positive attitude towards patient centred communication, and developed a better conceptual knowledge of doctor patient communication. In addition, those with good conceptual knowledge tend to demonstrate better communication skills performance at the Objective Structure Clinical Examination 12 months following the initial CST.

Key Words : Attitude, Communication Skills Training, Efficacy, Knowledge, Medical Students, Preclinical

DIZZINESS, A REVIEW OF WALK IN PATIENTS AT A SPECIALISED NEUROLOGY CLINIC

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Summary

A retrospective review of 100 walk in patients at a specialized neurology clinic in dizziness at a tertiary referral centre is presented. The most common cause of dizziness was BPPV, forming 31% of the cases. Other causes in order of frequency include recurrent vestibulopathy, idiopathic causes, Meniere's disease and central causes.

Key Words : Vertigo, Dizziness, Benign Paroxysmal Positional Vertigo (BPPV)

ROUTINE HISTOLOGICAL EXAMINATION FOR NASAL POLYP SPECIMENS : IS IT NECESSARY?

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Summary

Nasal polyp is one of the common causes of nasal obstruction. The diagnosis is usually made on clinical ground and rarely needs histological examination. However, when a candidate is selected for the surgical option of polyp removal, there is tendency to send all specimens for routine histological examination. The objective of this study was to assess the necessity of routinely performed histological examination in all nasal polyp specimens. A retrospective review of all nasal polyp histological reports was done from patients who underwent polypectomy or functional endoscopic sinus surgery in Universiti Sains Malaysia Hospital between January 2000 to July 2006. It consisted of 95 patients. Majority of the reports came back as benign nasal mass (5.3%). However, one specimen was noted to be malignant (1.1%). In conclusion, all nasal polyp specimens should be sent for histological examination in order to confirm the diagnosis.

Key Words : Histopathology, Nasal Polyp Specimens, Unilateral, Bilateral

CANDIDAEMIA AND ANTIFUNGAL SUSCEPTIBILITY TESTING IN A TEACHING HOSPITAL

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Summary

We reviewed cases of candidaemia at Universiti Kebangsaan Malaysia Medical Centre from 1 January 2005 to 30 June 2006. All blood cultures positive for *Candida* species or its teleomorphs within the study period were identified and antifungal susceptibility testing was performed. Out of 50 blood isolates, 20 (40%) were identified as *Candida albicans*, 16 (32%), *C tropicalis*, five (10%), *C parapsilosis*, three (6%), *C famata*, two (4%), *C glabrata*, two (4%), *Pichia ohmeri*, one (2%), *C krusei* and one (2%) *P etchell/carsonii*. Susceptibility to amphotericin B was 100%, fluconazole 90%, itraconazole 40%, ketoconazole 88%, 5-flucytosine 98% and voriconazole 98%.

Key Words : Antifungal Susceptibility, Candida, Candidaemia, Fungaemia

COMPLIANCE TOWARDS METHADONE MAINTENANCE THERAPY AND ITS ASSOCIATED FACTORS IN SELANGOR PRIMARY CARE CENTERS AND KUALA LUMPUR HOSPITAL

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Summary

This Paper seeks to determine the client's compliance level towards Methadone Maintenance Therapy (MMT) and identify its associated factors. A cross sectional study was conducted from June to September 2007 where 288 samples were interviewed. The outcomes were divided into good compliance and partial compliance categories. Overall client's compliance level is good at 86.1%. There are significant difference between mean age of groups ($t = -2.041$, $p = 0.04$); and significant associations of job's status ($\chi_2 = 9.54$, $p = 0.008$); client's confident score ($t = -2.308$, $p = 0.002$) and client's social function score ($t = -2.308$, $p = 0.002$) and client's social function level ($\chi_2 = 5.43$, $p = 0.02$) with compliance toward program. With multivariate analysis, only client's age, client's confidence score and client's job status were related to compliance status. It was concluded that there is high compliance rate among clients who received the program. Younger clients, low scores on clients' confident and social function, and clients with unsteady jobs are at risk not to comply with treatment.

Key Words : Compliance Level, MMT Program, Impact of MMT Therapy

COMPARISON OF MORPHINE WITH FENTANYL ADDED TO INTRATHECAL 0.5% HYPERBARIC BUPIVACAINE FOR ANALGESIA AFTER CAESAREAN SECTION

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Summary

This was a prospective randomized, controlled, single blind study done to determine the effect of intrathecal morphine 0.1 mg as compared with intrathecal fentanyl 25 μ in terms of analgesia and duration of postoperative pain relief after Caesaerean section. Sixty ASA I or II parturients were randomized into two groups. Group 1 (n=33) received 1.8ml of 0.5% hyperbaric bupivacaine combined with 0.1mg morphine while Group 2 (n=27) received 1.8ml of 0.5% hyperbaric bupivacaine combined with 25 μ g fentanyl for spinal anaesthesia. Postoperatively, all patients were provided with patient controlled analgesia (PCA) morphine. Pain was assessed using visual analogue score (VAS) at 6, 12, 18 and 24 hours. Time to first demand of PCA morphine, cumulative PCA morphine requirement and opioid side effects were documented. The VAS for pain and the cumulative PCA morphine requirement were both significantly lower in Group 1 ($p < 0.05$) during the 24 hours study period. The time to first demand was also significantly longer in Group 1 ($p < 0.05$). Overall, there were no significant difference between the two groups in side effects, except for a high incidence of nausea and vomiting requiring treatment in Group B in the first six hours. In conclusion the addition of 0.1mg morphine for spinal anaesthesia provided superior and longer postoperative analgesia after Caesarean section.

Key Words : Intrathecal Morphine, Intrathecal Fentanyl, Caesarean Section, Postoperative Analgesia

CONTINUING MEDICAL EDUCATION

THE A-B-C OF HAEMATOPOIETIC STEM CELL TRANSPLANTATION

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Introduction

Haematopoietic stem cell transplantation (HSCT) refers to any procedure where haematopoietic stem cells (HSC) of any donor type and any source are infused to a recipient with the intention of repopulating or replacing partly or totally the recipient's haematopoietic system. Dr Ed Thomas pioneered this field whereby his team performed the first allogeneic SCT in a patient with end stage leukaemia. Since then, HSCT has progressed in leaps and bounds in various aspects including source of stem cells, types of donors and conditioning regimens. In fact, its indications are no longer in haematological malignancies only, but have expanded to some of the incurable congenital and acquired diseases of the haematopoietic system and other non haematological disorders (Table I). This advancement has also extended to the third world countries, for example Malaysia, with its first allogeneic bone marrow transplantation performed in University of Malaya in a child in 1987 and in an adult in 1993. Up to December 2008, a total of 468 autologous, 982 allogeneic and 9 syngeneic adult and paediatrics HSCTs were performed in all transplant centres in Malaysia.

HSC have unique biological properties, including their capacity to proliferate and self generate in the lymphohaematopoietic system, their ability to migrate to the bone marrow spaces following intravenous infusion and their ability to maintain viability following cryopreservation, prolonged freezing and thawing process prior to re-infusion.

HSCT can be classified according to the :

- Donor type ["autologous" (auto)-patient's own cells, "syngeneic" – from an identical twin, "allogeneic" (allo) – from a non identical donor]
- Relationship between donor and recipient ("related" or "unrelated")

- Degree of HLA-matching between donor and recipient [“matched” or “mismatched”]; haplo identical HSCT may now be performed, often from a parent donor to a child recipient)
- Anatomical source of the stem cells (“bone marrow”, “peripheral blood” or “cord blood”)
- Type of conditioning regimen [“myeloablative” (standard) or “non myeloablative” (reduced intensity)]
- Type of graft manipulation (if any) (e.g. “T-cell depleted”, “tumour cell purged”)

Table I : HSCT Indications in Adult Patients

Disease	Status	Allogeneic (Sibling)	Allogeneic (Unrelated)	Autologous
AML	CR1 low risk	CO	NR	CO
	CR1 intermediate risk	S	CO	CO
	CR1 high risk			
	CR2	S	CO	CON
	Refractory	S	S	NR
	CR1 molecular +ve	CO	CO	NR
APML	CR2 molecular –ve	S	CO	NR
	CR1 low risk	S	CO	S
ALL	CR1 high risk	CO	NR	NR
	CR2	S	S	NR
	Refractory	S	S	NR
	CP1	CO	CO	NR
CML	AP OR CP2	S#	CO	NR
	BP	S	S	NR
	IPSS low	NR	NR	NR
MDS	IPSS intermediate	CO	NR	NR
	IPSS high	S	CO	CO
	CR1 high IPI	S	CO	NR
CLL	CR2	NR	NR	CO
	CR1 high IPI	CO	NR	S
	CR2	NR	NR	CO

DLBCL	Refractory	CO	NR	S
	CR1	CO	CO	NR
	CR2	NR	NR	CO
Follicular lymphoma	Refractory	CO	CO	S
	CR1	CO	CO	CO
	CR2	NR	NR	CO
Hodgkin lymphoma	Refractory	CO	NR	S
		CO	CO	CO
	Metastatic	CO	CO	S
Myeloma		D	NR	NR
Renal cell carcinoma				
Ovarian carcinoma				
Small cell lung carcinoma		NR	NR	D
Severe aplastic anaemia		S	CO	NR
SLE & immune cytopaenias		D	NR	CO

(Adapted with modification from ref.)

S – indicated and considered as standard of care in the suitable candidate with access to facilities

CO - clinical option, discussion between the attending physician, patient and an independent physician* with careful consideration of the benefits versus risks is recommended

NR - not recommended

D - developmental, shall be conducted in well designed clinical trials with ethics review and approval

* clinician with experience in the related clinical condition

In general, HSCT is indicated in adult patients with chronic phase CML in whom treatment with tyrosine kinase inhibitors has failed.

AML-acute myeloid leukaemia; APL-acute promyelocytic leukaemia; ALL-acute lymphoblastic leukaemia; CML-chronic myeloid leukaemia; MDS-CR-complete remission; CP-chronic phase; AP-accelerated phase; BP-blast transformation phase; IPSS-international Prognostication Scoring System; IPI-International Prognostic Index

Sources of Haematopoietic Stem Cells (HSC)

Stem cells can be harvested from bone marrow (BM), peripheral blood (PB) and cord blood (CB). According to latest data in National Transplant Registry of Malaysia, a total of 511 bone marrow alone, 823 peripheral blood alone, 53 cord blood alone, 10 combined bone marrow and cord blood, and 61 combined bone marrow and peripheral blood stem cell transplantations were performed up to December 2008. When HSCT was first developed, BM was the only available source of stem cells. A CD34⁺ cell dose of $3 \times 10^6/\text{kg}$ or more (which may require up to of 0.5-1.5 litres of BM) has been associated with successful engraftment, decreased transplant related mortality, and improved overall survival in HLA-identical sibling BM transplantation. The procedure is tedious as multiple marrow aspirations need to be performed and donors are subjected to general anaesthesia. There is a possibility that the BM cells are contaminated by the tumour cells in autologous collection, which is a source of relapse.

Due to these limitations, researchers tried to find alternative source of stem cells. HSC constitute a very small amount in the peripheral blood of a healthy donor (less than 0.1% of all nucleated cells). These HSC are identified by their immunophenotypic and thus can be measured as CD34⁺ cells. In the steady-state situation, BM and PB stem cells in equilibrium with each other. Therefore, this allows the stem cells to migrate from extravascular marrow sites to PB and *vice versa*. CD34⁺ stem cells concentration in PB is approximately $3.8 \pm 0.8 \times 10^6/\text{L}$ which is too low to be harvested. However, these HSC can be mobilized from the BM into the PB by systemic administration of granulocyte-colony stimulating factor (G-CSF) with or without chemotherapy and are subsequently collected via leukocytapheresis. Apart from increasing the number of cells, G-CSF causes the release of proteases that degrade the proteins that anchor the stem cells to the marrow stroma, causing their release into the PB. Following G-CSF administration, there is 16- to 23-fold increase in PB CD34⁺ stem cells over the baseline. A minimum threshold of 2×10^6 CD34⁺ cells/kg in the PBSC collection has been associated with prompt leukapheresis. Following collection, PBSCs are then processed and can be cryopreserved for months to years. The main advantage of PBSCT as compared with BMT is faster engraftment of the haematopoietic cells in the bone marrow, probably because of

the higher content of committed haematopoietic precursor cells. This will result in shorter hospitalization time and lower overall cost of the procedure. Nevertheless, there is an increased risk of chronic graft-versus-host disease (GvHD) in allogeneic PBSCT.

At birth, the human umbilical cord blood (UCB) contains rates of CD34⁺ cells similar to those observed in normal BM for HSCT. There is no risk to the donor as the collection of UCB takes place after the delivery of the newborn and placenta and the cord is appropriately clamped. The first successful CB transplantation was performed by Dr E Gluckman in 1988 in a boy with Fanconi's anaemia using umbilical cord blood collected at the birth of his sibling. Since then, the use of CB has rapidly increased due to several favourable factors (Table II). However, the major limitation of CB stem cells is that the amount that can be collected is small and transplantation in an adult might need multiple cord blood donors. One of the advantages of UCB is easy procurement. There is a low risk of viral transmission of cytomegalovirus (CMV), hepatitis and human immunodeficiency virus (HIV). A higher degree of mismatch is also acceptable with a lower risk of acute and chronic GvHD as CB is relatively deficient in mature T-cells.

Table II : Cellular and Clinical Characteristics for Various Sources of Stem Cells

Characteristics	Bone Marrow	Peripheral Blood	Cord Blood
1. Stem-cell content	Adequate	Good	Low
2. Progenitor-cell content	Adequate	High	Low
3. T-cell content	Low	High	Low, less mature T-cells
4. Risk of tumour contamination	High	Low	Not applicable
5. HLA matching	Requires close matching	Requires close matching	Less restrictive
6. Engraftment*	Faster than CB but slower than PB	Fastest	Slowest
	Same as PB	Same as BM	Slowest
7. Risk of acute GvHD	Lower than PB	Highest	Slowest
8. Risk of chronic GvHD			

(Adapted with modifications from ref.)

*Engraftment for adults and children is defined as the point at which a patient can maintain a sustained absolute neutrophil count (ANC) of more than $0.5 \times 10^9/L$ and sustained platelet count of more than $20 \times 10^9/L$, lasting for more than 3 consecutive days without transfusions.

Types of HSCT

a) Autologous

Autologous transplantation is used as a method of infusing patient's own stem cells which was harvested earlier as a rescue therapy after high dose myeloablative therapy. The aim of administration of high dose chemotherapy is to eradicate the remaining tumor cells. This is followed by subsequent rescue of the host's bone marrow with previously collected autologous HSC (*Please refer to Figure 1 – Process of Peripheral Blood Stem Cell Transplantation [PBSCT]*). As there is no risk of graft rejection or GvHD, immunosuppressive agents are not required.

b) Allogeneic

In allogeneic HSCT, stem cells harvested from another person are infused into the patient following high dose chemotherapy, whereby donor and recipient are not immunogenically identical (*Please refer to Figure 1 – Process of Peripheral Blood Stem Cell Transplantation [PBSCT]*). The preferred donors are human leukocyte antigens (HLA)- matched sibling donors. In the pre-transplant work up, class I and class II HLA antigen comparability is tested via serological or molecular techniques and compared between the patient and the siblings. Class I includes HLA-A, HLA-B and HLA-C while Class II includes HLA-DR, HLA-DP and HLA-DQ. Fully HLA-matched matched sibling has all HLA loci identical to the recipient and this will reduce the possibility of GvHD and graft failure. However, an HLA-matched sibling donor is only available in 30-40% of patients. In the absence of matched sibling donors, several alternatives of allogeneic transplantation are nowadays available which include matched unrelated donors (MUD), unrelated umbilical cord blood (UCB) or haploidentical donors (3 out of 6 HLA alleles mismatched).

Other factors to be taken into consideration in choosing a donor are donor age (younger is better), sex (female stem cells given to a male is less favorable), cytomegalovirus (CMV) serology (CMV-negative has better outcome), pregnancy and transfusion history (preferably lower parity and no history of miscarriage), donor-recipient blood group compatibility and body weight. Immunosuppression is very crucial and needs to be monitored closely. This is to prevent GvHD and graft rejection without risking the stem cells engraftment. Two most common immunosuppressive drugs are methotrexate and cyclosporine which can be used alone in combination.

In the post-transplantation period, donor-recipient chimaerism studies need to be performed. This can be done via fluorescent-in-situ hybridisation (FISH) studies of sex chromosomes (for donor and recipient with different gender), short tandem repeats (STR) analysis or variable number of tandem repeats (VNTR) analysis.

Conditioning Regimens

In general, conditioning therapy must be given prior to stem cell infusion. Conditioning regimens can be myeloablative (standard) or nonmyeloablative (reduced intensity). The aim of myeloablative conditioning is eliminate the malignant cells and make space in the bone marrow for the infused stem cells to regrow and expand. Common myeloablative regimens used in ALL and AML patients are cyclophosphamide-total body irradiation (CyTBI) and busulfan-cyclophosphamide (BuCy), respectively.

In nonmyeloablative conditioning regimen, the aim is to induce immunosuppression in the recipient's system so that donor cell engraftment can take place and exert graft-versus-tumour effect. This less toxic approach enables HSCT in elderly patients and patients with organ dysfunction who cannot tolerate full myeloablative conditioning. One of the most commonly used protocols is fludarabine-busulfan-anti-T-cell immunoglobulin (FluBuATG) as suggested by Slavin *et al.* The advantages and disadvantages of both autologous and allogeneic HSCT are described in Table III.

Table III : Advantages and Disadvantages of Autologous and Allogeneic HSCT

	Autologous	Allogeneic
Advantages	<ul style="list-style-type: none"> • Safer than allogeneic HSCT • Less transplant related mortality • Does not require immunosuppression • No risk of GvHD or graft rejection • Less infection, especially post engraftment period • No graft-versus-tumour effect, hence higher risk of disease relapse/progression than allogeneic HSCT 	<ul style="list-style-type: none"> • Lower risk of disease relapse or progression • No risk of graft contamination by tumour cells
Disadvantages	<ul style="list-style-type: none"> • Impaired ability to collect HSC if patient is heavily treated with prior chemotherapy • Graft may be contaminated with tumour cells 	<ul style="list-style-type: none"> • Limited to younger and patients with good performance status • Requires match donor • Requires immunosuppressive agents and strict monitoring • Higher transplant related mortality rate • Longer time to recover immune function, higher risk of infection • Risk of GvHD

Complications of HSCT

Complications of HSCT can be generally divided into conditioning-related or immune-related. Both myeloablative and nonmyeloablative conditioning regimes may cause early (within 30 days) complications such as nausea, vomiting, mucositis, alopecia and interstitial pneumonitis. Cyclophosphamide may cause haemorrhagic cystitis which may manifest as dysuria and haematuria. Late conditioning related complications include endocrine problems such as infertility, premature ovarian failure and osteoporosis, and risk of secondary malignancies such as AML and solid organ tumours.

A potentially fatal early complication is veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome. The incidence has been reported to be as high as 70% with a mortality rate up to 70%. It is caused by damage to the sinusoidal endothelium, resulting in sinusoidal obstruction, necrosis of hepatocytes in zone 3 of liver acinus and narrowing and fibrosis of central veins. Predisposing factors include conditioning with total body irradiation or busulfan, preexisting liver disease, hepatotoxic drugs and certain genetic mutations. Patients present with tender hepatomegaly, weight gain, ascites and predominantly direct hyperbilirubinaemia within the first 30-60 days. Diagnosis is based on clinical suspicion as there is no specific non invasive tool available at the moment. There is no standard effective therapy at present. Defibrotide may be effective treatment for severe VOD but prospective randomized studies are required.

Immune related complications may develop within months to years after HSCT due to suppressed host immunity. Infection remains a leading cause of morbidity among autologous HSCT. The preventive measures include conducive physical environment, isolation procedures, neutropaenic diet, care of central venous lines, antimicrobial prophylaxis and vaccination. The type, timing and duration of antibacterial, antifungal and antiviral prophylaxis used depend on the type of transplantation and the degree of immunosuppression.

Allogeneic transplant recipients may develop characteristic infections during the three different phases post HSCT (*Please refer to Figure 2 – Phases of Opportunistic Infection among HSCT Recipients*). During the first phase, the aplastic period, the risk of infection is mediated mainly through neutropaenia and damage to the mucocutaneous barriers as a result of conditioning regimen and frequent vascular access requirements. Hence, oral, gastrointestinal and skin flora are the source of infection which is commonly bacterial in origin. During the second phase

which is the phase of acute GvHD, impaired T-cell function predominates causing delayed immunologic recovery and prolonged immunodeficiency. Therefore, HSCT recipients are more vulnerable to opportunistic viral and fungal infections. Meanwhile, the third phase is characterized by B-cell dysfunction in combination with T-cell dysfunction in patients with chronic GvHD. Hence they are at greater risk for serious bacterial infections such as the encapsulated organisms in addition to the similar opportunistic viral and fungal infections.

In autologous HSCT recipients, the aplastic phase is similar to the allogeneic recipients. However, the most important difference is the better T-cell function in autologous SCT. After engraftment, most patients will be at lower risk of infection.

Despite new advancement of antimicrobial therapy, bacterial infections still pose a major problem in HSCT patients especially in the febrile neutropaenia phase. Prevalences of Gram-negative bacilli such as *Pseudomonas aeruginosa*, *Escherichia coli* extended spectrum β -lactamase (ESBL) and *Stenotrophomonas maltophilia* as well as Gram-positive cocci such as methicillin-resistant *Staphylococcus aureus* have increased at many institutions. Inappropriate use of antibiotics is known to cause the emergence of these bacteria. Since HSCT patients are immunocompromised, broad spectrum antibiotics such as carbapenems, third to fourth generation cephalosporin such as cefepime with or without vancomycin are indicated as empirical therapy. Cultures must be taken from possible sites of infection as soon as possible prior to administration of antibiotics.

The timing of invasive fungal infections (IFI) is bimodal distribution, with peak that is correlated with prolonged neutropaenia (pre-engraftment) and GvHD (late recovery period). Patients who have undergone cord blood HSCT and T-cell depleted HSCT are especially at high risk of developing IFI. Identification of glucan and galactomannan, the antigens from the fungal cell walls, coupled with high resolution computed tomography (HRCT) has enabled early diagnosis and treatment of IFI leading to significant drop in mortality rates.

Viral infections caused by *Herpes simplex* occur early in the course of transplantation while cytomegalovirus (CMV) infection usually occurs after engraftment. The prevention of CMV disease is essential since the results of therapy for proven CMV pneumonia are still poor. Involvement by CMV in the gastrointestinal tract (GIT) may be confused with the development of GvHD and warrants upper and/or lower endoscopic examination and biopsy.

Vaccination

To prevent late infections as a result of suppressed recipient immunity that can persist for months to years after HSCT, a guideline for revaccination has been developed. The most important vaccines are tetanus, diphtheria, poliovirus and *Haemophilus influenzae*. Most killed vaccines are safe but, vaccination with live-attenuated vaccines is generally contraindicated until about 18 months post HSCT and should be avoided in patients with chronic GvHD and those receiving immunosuppressive therapy. Revaccination is recommended at approximately 12 to 18 months post HSCT, but this needs to be individualized. Vaccination earlier than this timeline may not result in an appropriate immune response.

GvHD

GvHD occurs when transplanted donor T-lymphocytes react to foreign host cells and it causes a wide variety of host tissue injuries. It can occur despite aggressive immunosuppressive prophylaxis even when the donor is a perfectly matched (HLA-identical) sibling. The classification of GvHD is now based upon the clinical manifestations that will determine whether the clinical syndrome of GvHD is acute or chronic, rather than the time to symptomatic onset after HSCT.

Acute GvHD comprises classic acute GvHD (arising less than day 100 post HSCT), and persistent, recurrent and late-onset acute GvHD (after day 100). Incidence of grades II to IV acute GvHD is approximately 10-64% in allogeneic PBSCT patients. HLA mismatch between donor and recipient is one of the major risk factors for acute GvHD. Other risk factors include gender mismatch, older age of the recipient, high dose conditioning regimens, seropositivity to several herpes viruses in the recipient and donor and the graft type. The main target organs involved in acute GvHD are the skin, liver and gut. Preventive and therapeutic measures include immunosuppression with cyclosporine, corticosteroids, tacrolimus, methotrexate and mycophenolate mofetil. Many centres treat mild GvHD of the skin (grade I) with topical steroids alone, but for more severe disease and any degree of visceral GvHD involvement high dose systemic steroids are usually initiated. The outcome of acute GvHD depends on the grade and the response to treatment. The mortality rate of severe (grade III/IV) or steroid refractory acute GvHD exceeds 60-70%.

The incidence of chronic GvHD varies according to studies and can be as high as 85%. The most important risk factor is previous acute GvHD. It can be divided into classic chronic GvHD and overlap syndrome. Skin is usually involved in the form that resembles systemic autoimmune disease such as sclerodermatous and lichenoid skin changes. Xerostoma, keratoconjunctivitis sicca and bronchiolitis obliterans may also develop. The pathophysiology of chronic GvHD remains poorly understood and the disease is treated with various immunosuppressive agents. Supportive care is vital and this includes antimicrobial prophylaxis, artificial tears and anti-osteoporosis agents for patients receiving long term steroids.

Relapse Post HSCT

Relapse of the initial disease is the commonest cause of treatment failure after HSCT. Relapse rates are reported between 2-34% depending on the primary diseases. The risks depend on the disease stage at the time of transplant (complete remission is better) and the type of HSCT and conditioning regimen (autologous HSCT and nonmyeloablative conditioning regimen have higher risk of relapse) and the presence of GvHD (GvHD is associated with a lower risk of tumour relapse). The prognosis of relapse haematological malignancies after HSCT is generally poor. Treatment of tumour relapse include withdrawal of immunosuppressive agents, salvage chemotherapy, radiotherapy, donor lymphocyte infusion and second HSCT. No single method has been proven effective in all patients.

Conclusion

HSCT currently offers the only potential cure for a large number of malignant and non malignant haematological disorders. Future research will focus on ways to decrease the transplant related mortality and increase relapse free survival. As the numbers of patients receiving HSCT increases, there is a need for a better understanding of this procedure among the general physicians who may encounter recipients and donors of HSCT in their clinical practice. This is to ensure that HSCT recipients will be referred early to the transplant physicians or centers if they developed complications even long after the procedure.

References & MCQs on The A-B-C of Haematopoietic Stem Cell Transplantation : Kindly refer to the March 2009 issue of the Medical Journal of Malaysia, Volume 64, Issue No. 1