ANNALS
ACADEMY OF MEDICINE, SINGAPORE
COMMITTED TO SPECIALIST EDUCATION AND TRAINING SINCE 1957

DIAMOND JUBILEE CELEBRATION 60 years 1957-2017

VOLUME 46 | NUMBER 2 | FREE PAPERS | FEBRUARY 2017 MCI(P) 022/11/2016

"Do not go where the path may lead, go instead where there is no path and leave a trail."

Ralph Waldo Emerson (1803 – 82)
American poet

Reproduced with permission from:
Dr Kong Hwai Loong

Please see inside Contents for the full list of articles.

Editorial

Child Psychiatry Without Psychiatrists: A New Model for Old Problems

Daniel SS Fung, [1-4]*MBBS (S'pore), MMed (Psy), FAMS*, Nikki SJ Lim-Ashworth, [1]*DClinPsy*

Introduction

Child psychiatry was developed around the turn of the century following an increasing recognition of childhood behavioural and emotional issues. Most child psychiatrists provide care within specialty clinics and tertiary hospitals. Treatment for mental health disorders for children and adolescents has improved considerably with more evidence-based and effective medications, and psychosocial interventions.[1] However, the practice of child psychiatry is not cost-effective in its present form. Other professionals can perform some of the functions of child psychiatrists at a fraction of the cost. In addition, there is an urgency to meet the treatment gap of childhood mental health disorders. It is not feasible to train more psychiatrists to address this increased demand due to resource constraints in terms of doctors and time.

A New Approach of Care

Existing evidence suggests that a population-based strategy is necessary, with the goal of providing balanced, step-based care, in varying intensity interventions, to young people and their families.[2] Utilising such an approach will take into consideration the increasing gap between mental health issues within the community and the limited resources available in hospitals. This mental health gap would therefore require a change in the provision of care without compromising on quality or outcomes; a move away from the traditional mental healthcare model which is largely illness-centric, stigmatising, and resource-intensive.

Response to Intervention Model

Taking reference from education which is population-based and universal, and worldwide literacy levels reaching 90%,[3] we would like to propose using an educational framework as the approach forward. Schools do not treat learning difficulties—they provide a standard of care that encourages learning, and give educational interventions as needed when the child is struggling. Ultimately, the one-to-one intervention that healthcare uses, is provided once the child is deemed needing such resource-intensive care. This model is called a Response to Intervention (RTI) model which was originally described for use in special education[4] and empirically validated.[5]

Using the RTI framework on population-based child and adolescent mental health would leverage on systematic assessment and early detection in partnership with community stakeholders (e.g. schools, primary care physicians). It identifies strengths and builds on resilience of

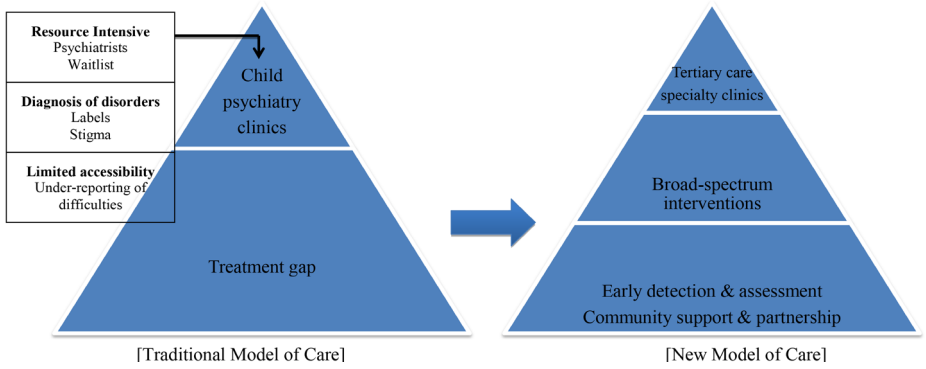

Fig. 1. A RTI framework of care for child and adolescent mental health.

[1]Department of Child and Adolescent Psychiatry, Institute of Mental Health, Singapore
[2]Duke-NUS Graduate Medical School, Singapore
[3]Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[4]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
Address for Correspondence: Adj A/Prof Daniel Fung Shuen Sheng, Department of Child and Adolescent Psychiatry, Institute of Mental Health, 10 Buangkok View, Singapore 539747.
Email: daniel_fung@imh.com.sg

the child and his surrounding systems (e.g. family, school), as well as implement broad-spectrum, community-based interventions that are transdiagnostic and non-stigmatising (Fig. 1).

Examples in the Local Context

Low intensity treatment administered within the community by teachers and counsellors can address general difficulties (e.g. academic stress, peer relationship) and milder presentation of mental health issues, with a wider outreach and a reduction of the reliance on specialty clinics. The establishment of a Singapore National Mental Health Blueprint in 2007 focused on population-based initiatives and the community mental health masterplan in 2012 reinforced the strategy. The core of the blueprint for children is a regionally deployed community team called Response, Early Assessment and Intervention in Community Mental Health (REACH). The REACH team is an early identification process for emotional and behavioural difficulties. Working with school-based professionals, the plan was to train a cadre of frontline school personnel to manage mental health issues in the early stages in school and at home. Primary care physicians and social service agencies within the school's vicinity were similarly engaged to form a network of community support for students and families. Parent support groups from schools as well as disease support groups were included to improve understanding and knowledge transfer. The REACH programme and its outcomes have been described.[6] The initial implementation has shown that unlike specialty clinics, community assessment has identified an almost equal number of behavioural and emotional disorders in schools suggesting that anxiety and depression were clearly under-diagnosed.

The traditional mental healthcare model relies on professional manpower resources within a tertiary specialist clinic setting. There is often a long wait time before children receive treatment. Evidence-based treatment is well applied only in tertiary facilities and will benefit only a portion of the population. It is now possible to adopt technology and incorporate it as part of treatment for a population-based approach to care. An array of online and application-based interventions is now widely available. Some require specialist clinical support while others are in self-help format employing either parents and/or teachers in the process. The majority of these interventions are informed by cognitive behaviour therapy principles, and have been implemented among children and adolescents with positive outcomes. Systematic reviews published to date suggest that computerised protocols for depression and anxiety are, in general, effective for young people under the age of 18.[7] In Singapore, we have started to deploy some of these strategies to assist the community teams in their work.[8]

For children and adolescents with more serious and complex needs, specialist clinics continue to provide interventions that are differentiated and empirically robust, through the expertise of a multidisciplinary team (MDT) comprising not only of psychiatrists, but clinical psychologists, social workers and other mental health professionals. This represents the final element in the stepped care approach of the population-based RTI model. The role of a specialist MDT is also to deliver suitable training and consultation for community partners to ensure seamless collaboration for accessible mental health programmes.

Conclusion

Mental healthcare of the future is an evolving concept that will continue to require an open mind with a compassionate heart. The population-based RTI approach is necessary because of the dual challenges of increasing demands and limited resources when working with young people and their families. It should be a model that is accessible, feasible, timely, effective, and yet affordable and safe. The paradigm shift from acute tertiary care in hospitals and specialty clinics to preventive and long-term self, family and community interventions is not easy to accept. By adopting a population-based RTI approach, we hope that this can be an evidence-based delivery system that is effective globally, regardless of resources.

REFERENCES

1. Patel V, Flisher AJ, Hetrick S, McGorry P. Mental health of young people: a global public-health challenge. Lancet 2007;369:1302-13.
2. Thornicroft G, Tansella M. Components of a modern mental health service: a pragmatic balance of community and hospital care. Br J Psychiatry 2004;185:283-90.
3. UNESCO (2015) Literacy Statistics Metadata Information Table. UNESCO Institute for Statistics. September 2015. Available at: http://en.unesco.org/gem-report/node/6. Accessed on 19 November 2015.
4. Fuchs D, Fuchs LS. Introduction to responsiveness-to intervention: what, why, and how valid is it? Reading Research Quarterly 2006:41:92-9.
5. Fox L, Carta J, Strain P, Dunlap G, Hemmeter ML. Response to Intervention and the Pyramid Model. Tampa, Florida: University of South Florida, Technical Assistance Center on Social Emotional Intervention for Young Children; 2009.
6. Cai YS, Fung DSS. Community Mental Health as a Population based Mental Health Approach. Isr J Psychiatry Relat Sci 2016;53:33-9.
7. Pennant ME, Loucas CE, Whittington C, Creswell C, Fonagy P, Fuggle P, et al. Computerised therapies for anxiety and depression in children and young people: a systematic review and meta-analysis. Behav Res Ther 2015:67:1-18.
8. Ang RP, Huan VS, Tan JL, Ooi YP, Goh DH, Boon JST, et al. A Game-Based Approach to Teaching Social Problem-Solving Skills. In: Zheng R, Gardner MK, editors. Handbook of Research on Serious Games for Educational Applications. Pennsylvania: IGI Global; 2016.

Original Article

Risk Factors for Mortality in Asian Children Admitted to the Paediatric Intensive Care Unit after Haematopoietic Stem Cell Transplantation

Haripriya Santhanam, [1]*MBBS (S'pore), MRCPCh (UK), MMed (Paeds, S'pore)*, Jacqueline SM Ong, [1]*MBBChir (Cantab), MRCPCh (UK), MMed (Paeds, S'pore)*, Liang Shen, [2]*PhD*, Poh Lin Tan,[1]*MBBS (S'pore), MMed (Paeds, S'pore)*, Pei Lin Koh, [1]*MBBS (S'pore), MRCPCh(UK), MMed (Paeds, S'pore)*

Abstract

Introduction: This study aimed to investigate the risk factors associated with mortality in haematopoietic stem cell transplant (HSCT) patients admitted to our paediatric intensive care unit (PICU) over an 8-year period. Materials and Methods: A retrospective chart review was conducted of all HSCT patients requiring PICU admission at our centre (a tertiary care university hospital in Singapore) from January 2002 to December 2010. Chief outcome measures were survival at the time of PICU discharge and survival at 6 months after initial PICU admission. Results: Ninety-eight patients underwent HSCT during this period; 18 patients (18%) required 24 PICU admissions post-HSCT. The overall survival to PICU discharge was 62.5%. Of those who survived discharge from the PICU, 33% died within 6 months of discharge. Non-survivors to PICU discharge had a higher incidence of sepsis (89% vs 33%, *P* = 0.013) and organ failure as compared to survivors (cardiovascular failure 100% vs 20%, *P* = 0.0003; respiratory failure 89% vs 20%, *P* = 0.002; and renal failure 44% vs 7%, *P* = 0.047). Mortality rates were higher in patients requiring mechanical ventilation (70% vs 14%, *P* = 0.010) and inotropic support (70% vs 14%, *P* = 0.010). Mortality in all patients with renal failure requiring haemodialysis (n = 4) was 100%. Presence of 3 or more organ failures was associated with 80% mortality (*P* = 0.003). Conclusion: Sepsis, multiple organ failure and the need for mechanical ventilation, inotropes and especially haemodialysis were associated with increased risk of mortality in our cohort of HSCT patients.

Ann Acad Med Singapore 2017;46:44-9

Key words: Bone marrow transplantation, Outcome, Prognostic factors

Introduction

Haematopoietic stem cell transplantation (HSCT) is well recognised as a definitive treatment in both malignant and certain non-malignant conditions and its use has increased significantly over time. It is, however, associated with high risks of morbidity and mortality, often necessitating admission to a paediatric intensive care unit (PICU). Once admitted to PICU, the prognosis tends to be guarded.

Several published studies seem to suggest that outcomes for paediatric HSCT patients requiring intensive care have generally shown improvement over the years.[1-5] A review by Naeem et al[1] looking at literature published between 1994 to 2004 suggests an improvement in the survival of HSCT patients requiring ICU transfer (both adult and paediatric patients) from 1998 onwards. The reported percentage of paediatric ICU patients surviving to hospital discharge or long-term survival rose from 9% to 11% prior to 1998, to 27% to 28% thereafter. Possible factors contributing to this encouraging outcome trend include use of less toxic preparative regimens, use of recombinant haematopoietic growth factors, use of mobilised blood cells rather than marrow, improved recognition of impending clinical deterioration and earlier escalation of treatment and transfer to ICU, as well as overall improved facilities in healthcare settings. Within the ICU, protective strategies for acute lung injury and early goal-directed therapy for sepsis have also likely contributed to improved survival for this patient population.

However, the question remains as to whether this reported improvement is real, or a result of better triage decisions

[1]Khoo Teck Puat-National University Children's Medical Institute, National University Health System, Singapore
[2]Biostatistics Unit, Yong Loo Lin School of Medicine, National University of Singapore, National University Health System, Singapore
Address for Correspondence: Dr Haripriya Santhanam, Department of Paediatrics, National University Health System, 1E Kent Ridge Road, Level 12, NUHS Tower Block, Singapore 119228.
Email: haripriya_santhanam@nuhs.edu.sg

regarding ICU transfer, resulting in patients with a better chance of recovery being transferred to the ICU more often and those with little chance being allowed to die in less invasive settings. Indeed, a meta-regression analysis on PICU mortality trends in children post-HSCT by van Gestel et al[6] reveals that characteristics of ICU-admitted patients have significantly changed over time, and after correcting for this, an improvement in ICU survival over time was less evident.

Several studies have looked at the risk factors influencing outcomes for this group of patients, in order to aid prognostication and parental counselling. Well known factors associated with increased mortality during PICU stay include allogeneic HSCT, respiratory, cardiovascular and neurologic failure, hepatotoxicity, multi-organ system failure, gross haemorrhage, graft-versus-host disease, the need for mechanical ventilation, need for renal replacement therapy (haemodialysis, ultrafiltration, or a combination), higher APACHE and oncological Pediatric Risk of Mortality (O-PRISM) scores at PICU transfer and higher Pediatric Risk of Mortality (PRISM) scores on the day of intubation.[7-20]

However, almost all of these studies have been conducted in the Western population, and a search of existing literature revealed only 1 paper by Cheuk DK et al[21] in which the study population was Asian. The objective of our study was to investigate the risk factors associated with mortality in our local Asian population of paediatric HSCT patients requiring admission to the PICU, with the aim of achieving a descriptive analysis of these risk factors in our local context.

Materials and Methods

A retrospective 8-year chart review was conducted of all HSCT patients admitted to our PICU located within a tertiary university hospital in Singapore from 2002 to 2010. Paediatric patients who had undergone HSCT for any reason, including non-malignant disease, were identified from a pre-existing HSCT database. Those admitted to the PICU had their medical records reviewed to collect data on their demographics, characteristics, medical complications, details of therapy, interventions, PICU acuity scores (O-PRISM[13] and PRISM-III[16] scores) and outcomes.

Patients admitted to the PICU for routine postoperative monitoring, and those HSCT patients who were admitted more than a year after their transplant, were excluded. The primary outcome variables were survival at the time of PICU discharge and survival at 6 months after initial PICU admission.

Sepsis and organ system failures were defined based on the 'International Pediatric Sepsis Consensus Conference: Definitions for Sepsis and Organ Dysfunction in Pediatrics' as described by Goldstein et al.[22]

The relationship between mortality and specific morbidity variables was analysed using SPSS software. Fisher's exact t-test was used to examine the significance of the association between categorical variables, with the Mann-Whitney U test used to compare median mortality risk scores between groups. This study was approved by our hospital institutional review board, with waiver of the need for informed consent.

Results

Ninety-eight patients underwent HSCT during this period, with 18 patients (18%) requiring 24 PICU admissions, as 6 patients were readmitted a second time. Fourteen out of 18 (78%) patients survived their first PICU admission. Of the 14 survivors, 6 were readmitted to PICU within the next 6 months. Of this group, only 1 (17%) survived the readmission to PICU. The overall survival to PICU discharge was 62.5% (15 out of 24 admissions). The overall survival rate of this population within 6 months of PICU admission was 50% (9 out of 18). Patient characteristics are summarised in Table 1.

Bone marrow transplant (BMT) was the most common type of transplant performed (40% of all transplants). Only 1 patient received autologous stem cell rescue (ASCR) for neuroblastoma. One patient had an underlying diagnosis of beta-thalassaemia major and received both cord blood and peripheral blood stem cell transplant from her younger brother in the same sitting, while the other patient with acute myeloid leukaemia (AML) with secondary juvenile myelomonocytic leukaemia (JMML) received first a peripheral blood stem cell transplant (PBSCT) from his mother, but as there was only 20% engraftment of his mother's cells, he went on to receive a BMT from a matched unrelated donor. No statistically significant differences in survival outcome could be found with regard to type of transplant or conditioning regimes used.

The frequency of occurrence of sepsis was higher among non-survivors than survivors (89% vs 33%, $P = 0.013$) (Table 1). Sepsis included bacterial, fungal and viral sepsis, and in a number of patients, more than 1 organism was isolated. The most frequently isolated organism was *Pseudomonas aeruginosa*. Other bacteria isolated were *Klebsiella pneumoniae*, *Acinetobacter baumanii*, and *Stenotrophomonas maltophila*. Fungal agents isolated were *Candida tropicalis*, *Aspergillus* and *Pneumocystis jiroveci*. Virus isolates included *Cytomegalovirus*, *Herpes simplex* virus, *Varicella-zoster* virus and *Parainfluenza Type 3*. Organisms isolated from those who died versus those who survived were similar.

The type of organ system failures occurring among non-survivors versus survivors to PICU discharge is shown in Table 1. Non-survivors had a higher incidence of

Table 1. Characteristics of Children Admitted to Paediatric Intensive Care Unit (PICU) after Haematopoietic Stem Cell Transplant and PICU Mortality

Demographics	Total	Non-Survivors	Survivors	*P* Value
Number of patients	18	9	9	-
Number of admissions	24	9	15	-
Gender				
Male	10	3	7	0.153
Female	8	6	2	0.153
Ethnicity				
Chinese	13	7	6	1.000
Malay	3	1	2	1.000
Vietnamese	2	1	1	1.000
Median age at PICU admission	9	5	8.5	0.138
Range	(1 – 16)	(1.5 – 16)	(1 – 16)	
Median day post-transplant of PICU admission	47	44	60	0.411
Range	(6 – 267)	(22 – 180)	(6 – 267)	
Median Pediatric Risk of Mortality III (PRISM-III) score at 24 h from PICU admission	18 (0 – 51)	20.5	17	0.150
Median Oncological-Pediatric Risk of Mortality (O-PRISM) score at 24 h from PICU admission	21 (2 – 49)	27.5 (17 – 49)	13 (2 – 29)	0.002
Primary diagnosis				
Acute myeloid leukaemia	6	3	3	1.000
Acute lymphoblastic leukaemia	5	2	3	1.000
Aplastic anaemia	2	1	1	1.000
Beta thalassaemia major	2	1	1	1.000
Leucocyte adhesion defect	1	1	-	1.000
CD40 ligand deficiency	1	-	1	1.000
Neuroblastoma	1	1	-	1.000
Type of transplant				
Bone marrow transplant	8	3	5	0.637
Umbilical cord blood transplant	6	4	2	0.620
Peripheral blood stem cell transplant	5	3	2	1.000
Autologous stem cell rescue	1	1	-	1.000
Conditioning regimes				
Myeloablative	15	7	8	1.000
Non-myeloablative/reduced intensity conditioning	3	2	1	1.000
Total body irradiation	4	1	3	0.577
Grade 4 graft vs host disease	2	2	0	0.471
Failure of engraftment	5	3	2	1.000
Occurrence of sepsis	13	8	5	0.013
Type of organ system failures				
Cardiovascular	12	9	3	0.0003
Respiratory	11	8	3	0.002
Neurological	8	4	4	0.412
Haematological	18	7	11	1.000
Renal	5	4	1	0.047
Hepatic	3	2	1	0.533
Therapeutic interventions used				
Mechanical ventilation	10	7	3	0.010
Inotropes	10	7	3	0.010
Haemodialysis	4	4	0	0.012
None	12	2	10	0.089

PICU: Paediatric intensive care unit

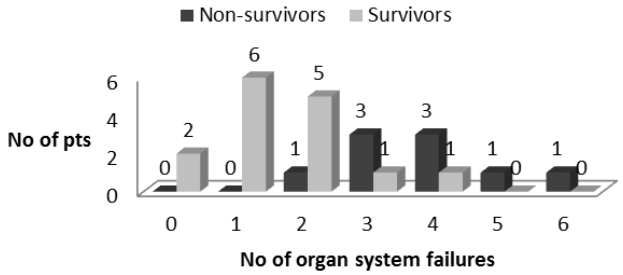

Fig. 1.Chart showing the comparison of the number of organ system failures among non-survivors versus survivors to PICU discharge. Data presented as number of patients in each group.

cardiovascular, respiratory and renal failure as compared with survivors. Pulmonary disease (in particular acute respiratory distress syndrome [ARDS]) was a frequent cause of mortality, featuring in at least 5 out of 9 (56%) mortalities. The number of organ system failures occurring among non-survivors versus survivors to PICU discharge is shown in Figure 1. An increased risk of mortality was associated with increasing number of organ system failures, with 3 or more organ failures associated with 80% mortality ($P = 0.003$).

The types of therapeutic interventions required by both non-survivors and survivors to PICU discharge are shown in Table 1. Mortality rates were significantly higher in patients requiring mechanical ventilation (70% vs 14%, $P = 0.010$) and inotropic support (70% vs 14%, $P = 0.010$) compared to those who did not require these interventions. Mortality in all patients with renal failure requiring haemodialysis was 100%. All 4 non-survivors who required haemodialysis also required both mechanical ventilation and inotropic support.

Of the 10 admissions for which mechanical ventilation was necessary, only 1 was on bilevel positive airway pressure (BiPAP) before being converted to conventional ventilation, followed by high frequency oscillation ventilation (HFOV). Eight had acute respiratory distress syndrome (ARDS), of which 2 had mild ARDS, 4 had moderate ARDS, and 2 had severe ARDS. ARDS was defined as per the 'Berlin Definition' published in 2012.[23] The 4 key diagnostic criteria as per this definition are that of acute onset, meaning onset over 1 week or less, presence of bilateral opacities consistent with pulmonary oedema and detected on computed tomography or chest radiograph, PaO_2/FIO_2 ratio (ratio of arterial oxygen partial pressure to fractional inspired oxygen) <300mmHg with a minimum of 5 cm H_20 positive end-expiratory pressure (or continuous positive airway pressure), and "must not be fully explained by cardiac failure or fluid overload" in the physician's best estimation using available information (an "objective assessment", meaning an echocardiogram in most cases, should be performed if there is no clear risk factor present like trauma or sepsis). ARDS is further classified as mild, moderate or severe based on the degree of hypoxemia (mild: 200 mmHg $<PaO_2/FIO_2 \leq 300$ mmHg, moderate: 100 mmHg $<PaO_2/FIO_2 \leq 200$ mmHg, and severe: $PaO_2/FIO_2 \leq 100$ mmHg). The remaining 2 patients requiring mechanical ventilation did not have underlying lung parenchymal lung disease—1 was intubated for airway protection for status epilepticus, and the other for airway obstruction. The median duration of mechanical ventilation was 10.5 days (range, 12 hours to 37 days) among non-survivors, and 7 days (range, 4.5 days to 11 days) among survivors ($P = 1.000$).

The median length of PICU stay was 10.5 days (range, 0.5 days to 37 days) among non-survivors compared to 2.5 days (range, 1 day to 12 days) among survivors ($P = 0.318$). The median duration post-transplant for non-survivors at the time of death was day +63 (range, +23 to +181).

The primary reason for PICU admission among non-survivors and survivors to PICU discharge is shown in Table 2. Respiratory distress featured as the main reason for PICU admission among both survivors and non-survivors.

Discussion

In our centre, 18% of the transplanted population required PICU admission with an overall survival to PICU discharge of 62.5%, and a 6-month survival rate of 50%. This data

Table 2. Primary Reason for PICU Admission among Non-Survivors and Survivors to PICU Discharge

Primary Reason for PICU Admission	Non-Survivors n = 9 (37.5%)	Survivors n = 15 (62.5%)	*P* Value
Respiratory distress	4 (17%)	7 (29%)	1.000
Pneumonia	2	2	0.615
Pulmonary haemorrhage	2	1	0.533
Upper airway obstruction	-	2	0.511
Diaphragmatic splinting	-	2	0.511
Neurologic changes	2 (8%)	3 (12.5%)	1.000
Altered mental state	2	-	0.130
Recurrent seizures	-	1	1.000
Status epilepticus	-	2	0.511
Haemodynamic compromise	2 (8%)	3 (12.5%)	1.000
Cardiogenic shock	-	-	1.000
Septic shock	1	2	1.000
Haemorrhagic shock	1	1	1.000
Others	1 (4%)	2 (8%)	1.000

PICU: Paediatric intensive care unit

suggests improved survival rates compared to previously published studies.[1,4,7,12,24,25] This might be due to the fact that many of these studies looked at data from the 1990s, whereas our study period was more recent (from 2002 to 2010), by which time significant advances in ICU care have occurred; additionally, lower thresholds for ICU transfer in our institution may have contributed to earlier supportive care and better outcomes.

Objective assessments of severity of illness assist with prognostication in the PICU; as such, several scoring systems and probability models predicting mortality risks in the PICU have been developed over the years. These include the Pediatric Risk of Mortality-III (PRISM-III) score by Pollack MM et al[16] as well as the newer O-PRISM score by Schneider et al.[13,14]

In our study, the O-PRISM score served as a more accurate predictor of outcome than the PRISM-III score, when computed at 24 hrs from the time of admission. A 24-hour O-PRISM score of ≥30 was strongly associated with mortality in our study population. This is higher than what has been reported in previous studies in paediatric cohorts post-HSCT, which showed increased mortality in patients with O-PRISM scores ≥10 points.[14,15] In our study, all non-survivors had O-PRISM scores >10 points, however, a fairly large proportion of survivors (73%) also had O-PRISM scores >10 points. This potentially suggests better survival rates in our institution for the same severity of illness as quantified by the O-PRISM score; however, interpretation of this data is limited by our small sample size and possibly different patient characteristics as compared to other institutions. Threshold scores for predicting mortality may need to be individualised to each institution, due to factors such as variations in practice involving triage and time to intervention.

The reasons for admission to our PICU were similar to those described in other studies, most notably respiratory compromise.[24] The risk factors associated with mortality in our study population also mirror several previous studies on this topic conducted in Western populations. These include the presence of sepsis,[8,19] cardiovascular failure,[7,8] respiratory failure,[7,8,12,19,21,24,26] renal failure,[10-13,15,19,21,24] multi-organ failure involving ≥3 organs,[7,8,21] the need for mechanical ventilation,[4,7,8,12,15,20,21,24] inotropic support,[8,27] and haemodialysis.[10,11,19] That an increased number of organ system failures is associated with a proportionally increased risk of mortality is not surprising, as multi-organ system failure is well recognised to correlate with severity of complications and attendant poor outcome.

In our study, all 4 patients requiring haemodialysis died, and all 4 of these patients also required both mechanical ventilation and inotropic support. Most studies have found the need for mechanical ventilation and/or haemodialysis in paediatric stem cell transplant patients to be a poor prognostic factor for survival. In a study by Rajasekaran S et al,[10] only 1 out of 29 allogeneic haematopoietic stem cell transplantation patients who underwent haemodialysis survived beyond 6 months. Survival rates in stem cell transplant patients requiring both mechanical ventilation and haemodialysis have been dismal. Rossi et al[12] reported only 1 of 8 patients surviving after receiving both haemodialysis and mechanical ventilation. Both Jacobe et al[20] and Keenan et al[28] reported no survivors in patients receiving both therapies.

High grade graft versus host disease (GvHD),[7,9] allogeneic transplant[7,9] and neurologic deterioration[8,12] were associated with increased mortality in other studies. In our cohort of patients, while 2 out of 9 non-survivors had grade IV GvHD, none of the survivors did, though the difference was not statistically significant. Our small sample size with small numbers of patients in each subgroup likely precluded detection of any statistically significant differences in outcomes with regard to these risk factors.

The main limitation of our study is the small sample size, hence data such as mortality rates obtained from our cohort of patients may not be comparable to mortality rates in much larger patient cohorts abroad, with potentially very different patient characteristics. Nonetheless, our study serves to characterise this patient population in our local context and we hope to be able to prospectively assess mortality predictors to aid prognostication in our local patient population in future studies.

Conclusion

Sepsis, multiple organ failure (particularly ≥3 organ system failures) and the need for mechanical ventilation, inotropes and haemodialysis were associated with increased risk of mortality in our cohort of HSCT patients. Awareness of these risks will assist in appropriate prognostication and counselling for this group of critically ill patients and their families.

REFERENCES

1. Naeem N, Reed MD, Creger RJ, Youngner SJ, Lazarus HM. Transfer of the hematopoietic stem cell transplant patient to the intensive care unit: does it really matter? Bone Marrow Transplant 2006;37:119-33.
2. Chima RS, Daniels RC, Kim MO, Li D, Wheeler DS, Davies SM, et al. Improved outcomes for stem cell transplant recipients requiring pediatric intensive care. Pediatr Crit Care Med 2012;13:e336-42.
3. Tamburro RF, Barfield RC, Shaffer ML, Rajasekaran S, Woodard P, Morrison RR, et al. Changes in outcomes (1996-2004) for pediatric oncology and hematopoietic stem cell transplant patients requiring invasive mechanical ventilation. Pediatr Crit Care Med 2008;9:270-7.

4. Kache S, Weiss IK, Moore TB. Changing outcomes for children requiring intensive care following hematopoietic stem cell transplantation. Pediatr Transplant 2006;10:299-303.
5. Zinter MS, Dvorak CC, Spicer A, Cowan MJ, Sapru A. New insights into multicenter PICU mortality among pediatric hematopoietic stem cell transplant patients. Crit Care Med 2015;43:1986-94.
6. van Gestel JP, Bollen CW, van der Tweel I, Boelens JJ, van Vught AJ. Intensive care unit mortality trends in children after hematopoietic stem cell transplantation: a meta-regression analysis. Crit Care Med 2008;36:2898-904.
7. Lamas A, Otheo E, Ros P, Vázquez JL, Maldonado MS, Muñoz A. Prognosis of child recipients of hematopoietic stem cell transplantation requiring intensive care. Intensive Care Med 2003;29:91-6.
8. Abraham RB, Toren A, Ono N, Weinbroum AA, Vardi A, Barzilay Z, et al. Predictors of outcome in the pediatric intensive care units of children with malignancies. J Pediatr Hematol Oncol 2002;24:23-6.
9. Fernández-García M, Gonzalez-Vicent M, Mastro-Martinez I, Serrano A, Diaz MA. Intensive care unit admissions among children after hematopoietic stem cell transplantation: incidence, outcome, and prognostic factors. J Pediatr Hematol Oncol 2015;37:529-35.
10. Rajasekaran S, Jones DP, Avent Y, Shaffer ML, Elbahlawan L, Henderson N, et al. Outcomes of hematopoietic stem cell transplant patients who received continuous renal replacement therapy in a pediatric oncology intensive care unit. Pediatr Crit Care Med 2010;11:699-706.
11. Flores FX, Brophy PD, Symons JM, Fortenberry JD, Chua AN, Alexander SR, et al. Continuous renal replacement therapy (CRRT) after stem cell transplantation. A report from the prospective pediatric CRRT Registry Group. Pediatr Nephrol 2008;23:625-30.
12. Rossi R, Shemie SD, Calderwood S. Prognosis of pediatric bone marrow transplant recipients requiring mechanical ventilation. Crit Care Med 1999;27:1181-6.
13. Schneider DT, Lemburg P, Sprock I, Heying R, Göbel U, Nürnberger W. Introduction of the oncological pediatric risk of mortality score (O-PRISM) for ICU support following stem cell transplantation in children. Bone Marrow Transplant 2000;25:1079-86.
14. Schneider DT, Cho J, Laws HJ, Dilloo D, Göbel U, Nürnberger W. Serial evaluation of the oncological pediatric risk of mortality (O-PRISM) score following allogeneic bone marrow transplantation in children. Bone Marrow Transplant 2002;29:383-9.
15. Tomaske M, Bosk A, Eyrich M, Bader P, Niethammer D. Risks of mortality in children admitted to the paediatric intensive care unit after haematopoietic stem cell transplantation. Br J Haematol 2003;121:886-91.
16. Pollack MM, Patel KM, Ruttimann UE. PRISM III: an updated Pediatric Risk of Mortality score. Crit Care Med 1996;24:743-52.
17. Gonzalez-Vicent M, Marin C, Madero L, Sevilla J, Díaz MA. Risk score for pediatric intensive care unit admission in children undergoing hematopoietic stem cell transplantation and analysis of predictive factors for survival. J Pediatr Hematol Oncol 2005;27:526-31.
18. Hagen SA, Craig DM, Martin PL, Plumer DD, Gentile MA, Schulman SR, et al. Mechanically ventilated pediatric stem cell transplant recipients: effect of cord blood transplant and organ dysfunction on outcome. Pediatr Crit Care Med 2003;4:206-13.
19. Hassan NE, Mageed AS, Sanfilippo DJ, Reischman D, Duffner UA, Rajasekaran S. Risk factors associated with pediatric intensive care unit admission and mortality after pediatric stem cell transplant: possible role of renal involvement. World J Pediatr 2013;9:140-5.
20. Jacobe SJ, Hassan A, Veys P, Mok Q. Outcome of children requiring admission to an intensive care unit after bone marrow transplantation. Crit Care Med 2003;31:1299-305.
21. Cheuk DK, Ha SY, Lee SL, Chan GC, Tsoi NS, Lau YL. Prognostic factors in children requiring admission to an intensive care unit after hematopoietic stem cell transplant. Hematol Oncol 2004;22:1-9.
22. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6:2-8.
23. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;20;307:2526-33.
24. Hayes C, Lush RJ, Cornish JM, Foot AM, Henderson J, Jenkins I, et al. The outcome of children requiring admission to an intensive care unit following bone marrow transplantation. Br J Haematol 1998;102:666-70.
25. Díaz de Heredia C, Moreno A, Olivé T, Iglesias J, Ortega JJ. Role of the intensive care unit in children undergoing bone marrow transplantation with life-threatening complications. Bone Marrow Transplant 1999;24:163-8.
26. Eikenberry M, Bartakova H, Defor T, Haddad IY, Ramsay NK, Blazar BR, et al. Natural history of pulmonary complications in children after bone marrow transplantation. Biol Blood Marrow Transplant 2005;11:56-64.
27. Duncan CN, Lehmann LE, Cheifetz IM, Greathouse K, Haight AE, Hall MW, et al. Clinical outcomes of children receiving intensive cardiopulmonary support during hematopoietic stem cell transplant. Pediatr Crit Care Med 2013;14:261-7.
28. Keenan HT, Bratton SL, Martin LD, Crawford SW, Weiss NS. Outcome of children who require mechanical ventilatory support after bone marrow transplantation. Crit Care Med 2000;28:830-5.

Original Article

Surveys of Stroke Patients and Their Next of Kin on Their Opinions towards Decision-Making and Consent for Stroke Thrombolysis

Nithia Angamuthu, [1]*MBBS, MRCP (UK)*, Kian Kheng Queck, [1]*MD (UKM), MRCP (UK)*, Sumytra Menon, [2]*LLB, LLM*, Shu Swen Ho, [1]*BSc (Hons)*, Elaine Ang, [1]*BSc (Hons)*, Deidre Anne De Silva, [1]*MBBS, MRCP (UK)*

Abstract

Introduction: Early initiation of stroke thrombolysis is associated with improved outcomes. Procurement of consent is a key factor in prolonging the door-to-needle duration. This study aimed to determine the attitudes and preferences of stroke patients and their next of kin (NOK) towards decision-making for stroke thrombolysis in Singapore. Materials and Methods: We surveyed acute ischaemic stroke patients (n = 171) who presented beyond the 4.5-hour therapeutic window and their NOK (n = 140) using a questionnaire with scenarios on obtaining consent for intravenous thrombolysis. Results: In the patient survey, 83% were agreeable for their NOK to decide on their behalf if mentally incapacitated and 74% were agreeable for the doctor to decide if the NOK was absent. In the NOK survey, the majority (81%) wanted to be consulted before mentally capacitated patients made their decision; 72% and 74%, meanwhile, were willing to decide on behalf of a mentally capacitated and mentally incapacitated patient, respectively. In the scenario where a doctor recommended a mentally incapacitated stroke patient to undergo thrombolysis but the family declined, there was a near equal split in preference to follow the family's or doctor's decision in both the patient and NOK surveys. Conclusion: The survey found that in the decision-making process for stroke thrombolysis, there was no clear consensus on the preference for the decision maker of the mentally incapacitated patient. In Singapore, there is a strong influence of the NOK in decision-making for thrombolysis.

Ann Acad Med Singapore 2017;46:50-63

Key words: Door-to-needle time, Reperfusion, Therapeutic window

Introduction

Intravenous thrombolysis for acute treatment of ischaemic stroke is proven to reduce disability and increase the likelihood of functional independence. However, it is also associated with increased bleeding risk including devastating symptomatic intracerebral haemorrhage.[1,2] Earlier initiation of thrombolysis is associated with greater potential benefit.[3] There is a narrow 4.5-hour therapeutic window for acute thrombolysis and the American Stroke Association recommends a door-to-needle duration of less than 60 minutes.[1] The urgency to initiate stroke thrombolytic treatment adds a time pressure to the decision-making process. Procurement of consent is a rate-limiting step in achieving the target door-to-needle time.[4]

Stroke often impairs cognition, language and consciousness, thus, limiting the patient's ability to give consent.[5,6] The Singapore Mental Capacity Act (MCA) states that for emergency life-sustaining treatment for a patient lacking mental capacity, the treating physician is given the responsibility to make the decision according to the patient's best interest.[7] The MCA also states that the physician should, where practicable, consult anyone engaged in caring for the patient or named by the patient as someone to be consulted. Prior to this study, the common practice in Singapore was to obtain written consent for intravenous thrombolysis administration directly from the next of kin (NOK) of mentally incapacitated stroke patients.[8] Previous studies on the attitudes towards consent

[1]Department of Neurology, National Neuroscience Institute, Singapore General Hospital, Singapore
[2]Lien Centre for Palliative Care, Duke-NUS Medical School, Singapore
Address for Correspondence: A/Prof Deidre Anne De Silva, Singapore General Hospital, Academia Building, 20 College Rd, Singapore 169856.
Email: deidre.desilva@singhealth.com.sg

for stroke thrombolysis had surveyed non-stroke patients.[9] In this study, we surveyed the attitudes and preferences of stroke patients and their NOK towards consent and decision-making issues for intravenous stroke thrombolysis and investigated factors associated with their responses.

Materials and Methods

We conducted 2 surveys at the Singapore General Hospital, a large tertiary public hospital in Singapore—one was among consecutive patients admitted for ischaemic stroke and were not eligible for intravenous thrombolysis while the other was among the NOK of these stroke patients. We only included patients who were assessed to be mentally competent by the clinical team. The NOK was the person identified by the patients as the person who would make decisions on their behalf if needed. Basic demographic data of the participants including age, gender, ethnicity, marital status, number of surviving adult relatives and relationship between patient and NOK were collated. A questionnaire containing 5 scenarios was given to the patient participants (Table 1) (Appendix 1). A separate questionnaire with 5 different scenarios was given to the NOK participants (Table 2) (Appendix 2).

Participants either completed the questionnaire independently or with the aid of a research coordinator. Participants were instructed to read the enclosed Patient Information Sheet (PIS) (Appendix 3) prior to completing the questionnaire. Trained research coordinators checked that they had understood the PIS and answered any queries they may have had. Participation was voluntary and informed consent was obtained from participants. The study was approved by the hospital's Institutional Review Board. We used SPSS version 18 for statistical analyses with chi-square test to assess for associations with the following variables: age, gender, ethnicity, education level, marital status, education level and having a living adult child.

Table 1. Patient Questionnaire

Scenario*	Questions
Patient Scenario 1	If you were eligible for thrombolysis and your doctors advised it, how agreeable would you be to receive it?
Patient Scenario 2	How agreeable are you for your NOK to give consent on your behalf?
Patient Scenario 3	Your NOK is not available. How agreeable are you with the doctor's decision to proceed with thrombolysis treatment in your best interests?
Patient Scenario 4	Who would you prefer to make treatment decisions on your behalf?
Patient Scenario 5	If the doctor recommends thrombolysis but your NOK disagrees, would you prefer that treatment is given in accordance with the doctor's advice or the decision of the NOK is accepted and treatment not given?

NOK: Next of kin

*For Scenarios 2 to 5, participants were asked to assume lack of mental capacity.

Results

Patient

We surveyed 171 patients (mean age 64 ± 11 years; 66% male; ethnic distribution: 76% Chinese, 13% Malay, 7% Indian and 4% of other ethnicities, consistent with the Singapore population; marital status: 75% married, 11% single, 9% widowed, 4% divorced, 1% separated; educational level: 40% primary, 38% secondary, 22% tertiary; and 74% had a living child aged above 21 years).

In Scenario 1, 58% of patients were willing to receive thrombolysis if recommended by the doctor, with 17% undecided and 25% being unwilling (Table 3). In Scenario 2, in which the patient was mentally incapacitated, 83% were agreeable for their NOK to decide on thrombolysis on their behalf. In Scenario 3, where the patient was mentally incapacitated and the NOK was not present, 74%

Table 2. NOK Questionnaire

Scenario*†	Questions
NOK Scenario 1	As a family member would you like the doctor to ask for your opinion before your relative makes the treatment decision?
NOK Scenario 2	Your relative is undecided and asks you to make a decision. How willing are you to make the treatment decision on their behalf?
NOK Scenario 3	How comfortable are you in letting the doctors make the decision on behalf of your relative?
NOK Scenario 4	How willing are you to make this treatment decision on your relative's behalf?
NOK Scenario 5a	If you personally suffered an ischaemic stroke and your ability to make decisions is affected, would you prefer that treatment is given in accordance with your doctor's advice or the decision of your NOK is accepted even if they decline consent for the treatment?
NOK Scenario 5b	If you personally suffered an ischaemic stroke and you have the mental capacity to make decisions, who do you think should make the treatment decision?

NOK: Next of kin

*For Scenarios 3 to 4, NOK participants were asked to assume the patient has no mental capacity.

†For Scenarios 5a and 5b, NOK participants were asked on their opinions if they were to personally suffer a stroke.

Table 3. Responses for Patient Scenarios 1 to 3

Scenario	Patient's Response	Strongly Agree n (%)	Agree n (%)	Undecided n (%)	Disagree n (%)	Strongly Disagree n (%)
Patient Scenario 1	If you were eligible for thrombolysis and your doctors advised it, how agreeable would you be to receive it?	26 (15%)	73 (43%)	29 (17%)	38 (22%)	5 (3%)
Patient Scenario 2	If mentally incapacitated, how agreeable are you for your NOK to give consent on your behalf?	41 (24%)	100 (59%)	5 (3%)	20 (12%)	4 (2%)
Patient Scenario 3	Your NOK is not available. How agreeable are you with the doctor's decision to proceed with thrombolysis in your best interests?	28 (17%)	98 (57%)	16 (9%)	24 (14%)	5 (3%)

NOK: Next of kin

would be agreeable for the doctor to decide. There were no associations of age, gender, ethnicity, education level, marital status, education level and having a living child with any of the responses for patient Scenarios 1 to 3, except a lower proportion of Malays (62%) compared to non-Malays (86%) were agreeable for their NOK to decide regarding thrombolysis if they themselves were mentally incapacitated ($P = 0.012$).

If the patient was mentally incapacitated and given a choice as illustrated in Scenario 4, 58% preferred to follow their NOK's decision and 42% the doctor's. A higher proportion of female patients (71%) as compared to males (53%) would prefer the NOK to make the decision instead of the doctor ($P = 0.026$). If the doctor recommended thrombolysis but the NOK disagreed (Scenario 5), 52% would prefer to follow the NOK's decision while 48% would prefer the doctor's. None of the other responses for patient Scenarios 4 and 5 were associated with age, gender, ethnicity, marital status, education level and having a living child.

NOK

We surveyed 140 NOK of stroke patients (mean age 47 ± 14 years; 39% male; ethnic distribution: 78% Chinese, 11% Malay, 8% Indian and 3% of other ethnicities, consistent with the Singapore population; educational level: 15% primary, 32% secondary and 53% tertiary).

In Scenario 1, 81% of the NOK would like to have their opinion sought before the mentally capacitated patient made any decision on stroke thrombolysis. In Scenario 2, if requested, 72% of NOK were willing to decide on behalf of a mentally competent patient (Table 4). A higher proportion of male NOK (86%) compared to female NOK (64%) were willing to decide on thrombolysis for a mentally capacitated stroke patient ($P = 0.006$). There were no other associations with responses to NOK Scenarios 1 and 2 with age, ethnicity, education level and relationship to patient.

When the patient was mentally incapacitated, 61% of the NOK were comfortable to let doctors decide on stroke thrombolysis (Scenario 3), and 74% were willing to decide

Table 4. Responses for NOK Scenarios 2 to 4

Scenario	NOK Response	Very Willing n (%)	Willing n (%)	Undecided n (%)	Unwilling n (%)	Very Unwilling n (%)
NOK Scenario 2	Your relative is undecided and asks you to make a decision. How willing are you to make the treatment decision on their behalf?	30 (21%)	71 (51%)	26 (19%)	12 (8%)	1 (1%)
NOK Scenario 3	How comfortable are you in letting the doctors make the decision on behalf of your relative if your relative had no mental capacity?	8 (6%)	77 (55%)	16 (11%)	27 (19%)	12 (9%)
NOK Scenario 4	If your relative was mentally incapacitated, how willing are you to make this treatment decision on your relative's behalf?	25 (18%)	78 (56%)	19 (13%)	17 (12%)	1 (1%)

NOK: Next of kin

on behalf of the patient (Scenario 4). These responses to NOK Scenarios 3 and 4 were not associated with age, gender, education level and relationship to patient, except a lower proportion of Malay (50%) compared to non-Malay (77%) NOK were willing to decide on behalf of the patient ($P = 0.034$).

In Scenario 5a, where the NOK hypothetically suffered a stroke, was mentally incapacitated and the doctor recommended intravenous (IV) thrombolysis treatment but their family declined, 46% preferred to follow the doctor's advice to be treated with IV thrombolysis and 54% preferred to follow their family's decision to not be treated. In Scenario 5b, where the NOK hypothetically suffered a stroke and was mentally capacitated, 61% chose the option of making their own decision and 19% each would leave the decision-making to their family and doctor, respectively. None of the responses for NOK Scenarios 5a and 5b were associated with age, gender, ethnicity, relationship to the patient and educational level.

Discussion

This is the first study to investigate the preferences and attitudes of patients and their NOK towards the decision-making process for stroke thrombolysis. The key finding was that there was no consensus for preference with a near equal split for the doctor or the NOK to be the decision maker for a mentally incapacitated stroke patient. This was reflected in both the stroke patient and NOK surveys, even when posed with the situation that the doctor and NOK had differing opinions. The inference is that if a doctor follows the NOK's decision to withhold stroke thrombolysis for a mentally incapacitated stroke patient despite the doctor advising the treatment, the doctor would be not acting according to the patient's wishes about half of the time. More importantly, there is no legal basis within the Singapore MCA for a NOK (regardless of whether the NOK is the patient's donee of a lasting power of attorney with healthcare decision-making authority) to make decisions for a mentally incapacitated patient for emergency treatment.

Our group has shown previously that the majority of Singapore neurologists are willing to make decisions on stroke thrombolysis for mentally incapacitated stroke patients.[8] A published study found that the inability to give consent did not reduce a person's desire for stroke thrombolysis.[10] Following this study, our institution has revised our protocol for stroke thrombolysis from taking consent from the NOK for a mentally incapacitated stroke patient to the current practice of the doctors making the decision in the best interest of such patients. In addition to being consistent with the MCA, this new protocol will hasten the decision-making process and in turn, reduce the door-to-needle duration for thrombolysis.

There are important issues to bear in mind with regard to surrogate consent. When faced with the hypothetical situation of being a stroke patient, 61% of the NOK participants wanted to make their own decision regarding stroke thrombolysis if mentally capacitated, although 81% of these individuals, in their real-life role as a NOK, wanted to be consulted on the mentally capacitated stroke patient's decision for thrombolysis. This shows the difference between decision-making as a NOK or surrogate. It has been shown previously that a higher proportion of relatives acting as proxy decision makers (rather than the stroke patients themselves) were uncertain about the thrombolysis decision.[11]

Both the patient and NOK surveys reported in this study indicated the strong influence of the NOK in Singapore in the decision-making for thrombolysis. About half of the stroke patients surveyed would rather follow the NOK's decision and have the treatment withheld even if the doctor had recommended it. The NOK were also very keen to be consulted for their opinions during the decision-making process and majority of the NOK surveyed were comfortable and willing to make the decision on behalf of a mentally incapacitated patient. Doctors in Singapore should bear this in mind and include the NOK in discussions regarding thrombolysis for stroke patients, even though the final decision should be made by the patient if mentally capacitated and by the doctor in the patient's best interest if the patient is mentally incapacitated.

For most of the scenarios, there were no associations between patient demographics with responses; thus, it would not be possible to anticipate preferences for any particular patient subgroup. Ethnicity and gender were factors influencing the attitudes towards consent processes for stroke thrombolysis in 2 scenarios each. Malays, as a patient, were less likely to be agreeable to accept a decision made by the NOK; as a NOK, they were less likely to be willing to make decisions for the mentally incapacitated patient. In the scenario as a mentally incapacitated patient, a higher proportion of females than males would prefer their NOK to decide the treatment for them instead of the doctor; as a NOK, a lower proportion of females were willing to decide for a mentally capacitated stroke patient. The reasons for these associations were not investigated in this study and should be explored in future research.

The main strength of this study is that the participants were acute stroke patients themselves and had experienced stroke symptoms. Thus, they would closely represent the preferences and attitudes of patients having to make decisions about stroke thrombolysis. Furthermore, we obtained opinions from both stroke patients and their NOK.

However, there were some limitations. In this study, we studied stroke patients who were not eligible for thrombolysis and respondents were not approached during the hyperacute period, thus they were not under the same time pressure as in real-life thrombolysis decision-making situations. Respondents, though, were given information on thrombolysis and were told that the decision-making for this treatment was time-sensitive. The completion of the questionnaire by the patient and NOK was not always done concurrently. The NOK surveyed was the person identified by the patient as the surrogate decision maker, although this may vary in real-life situations depending on availability. We did not explore differences between responses from a spouse, sibling or parent nor the influence of stroke severity on opinions provided. The information conveyed regarding thrombolysis included a standardised patient information leaflet but there were no visual aids. The study involved ethnic Asian participants in Singapore, a small city-nation in Southeast Asia, and the preference and attitudes found may differ in other ethnic groups and countries.

Conclusion

This study of stroke patients and their NOK found that in the decision-making process for stroke thrombolysis, there is no clear consensus on the preference for the decision maker for the mentally incapacitated patient. In Singapore, there is a strong influence of the NOK in decision-making for thrombolysis.

REFERENCES

1. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, et al. Guidelines for the early management of patients with acute ischaemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:870-947.
2. Wardlaw JM, Murray V, Berge E, Del Zoppo GJ. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev 2009;4:CD000213.
3. Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS and EPITHET trials. Lancet 2010;375:1695-703.
4. Kwan J, Hand P, Sandercock P. A systematic review of barriers to delivery of thrombolysis for acute stroke. Age Ageing 2004;33:116-21.
5. Rose DZ, Kasner SE. Informed consent: the rate-limiting step in acute stroke trials. Front Neurol 2011;2:65.
6. Eissa A, Krass I, Bajorek BV. Barriers to the utilisation of thrombolysis for acute ischaemic stroke. J Clin Pharm Ther 2012;37:399-409.
7. Singapore Statutes Online. Mental Capacity Act (Chapter 177A). Available at: http://statutes.agc.gov.sg/aol/search/display/view.w3p;ident=3fb55a4c-06dc-4a94-bc7a-b07a59ab0540;query=DocId%3A7f933c47-8a34-47d1-8d0a-0a457d6fa1c2%20%20Status%3Ainforce%20Depth%3A0;rec=0#legis. Accessed on 10 March 2015.
8. Talabucon LP, Menon S, Toh AJ, Oh DC, De Silva DA. Attitudes and practices on the consent process and decision-making for intravenous stroke thrombolysis: physicians' perspective. Ann Acad Med Singapore 2013;42:567-74.
9. Chiong W, Kim AS, Huang IA, Farahany NA, Josephson SA. Testing the presumption of consent to emergency treatment for acute ischemic stroke. JAMA 2014;311:1689-91.
10. Chiong W, Kim AS, Huang IA, Farahany NA, Josephson SA. Inability to consent does not diminish the desirability of stroke thrombolysis. Ann Neurol 2014;76:296-304.
11. Ciccone A, Sterzi R, Crespi V, Defanti CA, Pasetti C. Thrombolysis for acute ischemic stroke: the patient's point of view. Cerebrovasc Dis 2001;12:335-40.

Appendix 1
Patient Questionnaire

Attitudes and Perceptions on the Informed Consent Process / Decision-making on Intravenous Tissue Plasminogen Activator (IV TPA).

You have been invited to participate in this survey because you have recently suffered a stroke. This survey aims to determine the attitudes and perceptions of the informed consent process, as well as factors that influence decision-making for the clot-busting drug treatment for stroke. There is no right or wrong answer. Your answers will be kept strictly confidential.

You may complete the form on your own by ticking (☑) the box. Alternatively, our trial coordinator can assist you by writing down your verbal answers. Please direct any questions you may have to the trial coordinator.

SC

1. Please indicate the language or dialect that you are most fluent with. (You may choose more than one answer)

☐ 1) English
☐ 2) Mandarin
☐ 3) Malay
☐ 4) Tamil
☐ 5) Others including dialect: _____

Lng

2. Marital status

☐ 1) Single
☐ 2) Married
☐ 3) Widowed
☐ 4) Divorced
☐ 5) Separated

Sta

3. Do you have any surviving children aged 21 and above?

☐ 1) Yes
☐ 2) No

Chi

4. Do you have any surviving siblings (brothers/sisters)?

☐ 1) Yes
☐ 2) No

Sib

An ischemic stroke occurs when a blood vessel in the brain is blocked. Thrombolysis treatment – a clot-busting drug called alteplase - attempts to unblock the blood vessel. This drug must be given within 4.5 hours of the stroke onset. The advantage of this treatment is that it increases the likelihood of patients recovering their physical and mental abilities. Delay in initiating this treatment reduces its benefits and increases the bleeding risk. The main complication of this treatment is bleeding in the brain. You were not offered this clot busting drug treatment. This may be because you were admitted beyond the proven time window or it may be due to contraindications based on your medical history and laboratory findings.

Attitudes and Perceptions on the Informed Consent Process / Decision-making on Intravenous Tissue Plasminogen Activator (IV TPA).

Please read the Patient Information Sheet before answering the following questions.

Scenario 1: If you were suitable and eligible for this clot busting drug treatment and your doctors advised it, how agreeable would you be to receive it?

S1

☐ 1) Strongly agree
☐ 2) Agree
☐ 3) Undecided or unsure what to do
☐ 4) Disagree
☐ 5) Strongly disagree

Reasons:_____

_____

Stroke can affect mental functioning. Hence some patients are not able to make decisions for themselves due to their stroke symptoms. The following scenarios 2-5 are based on such potential situations.

Scenario 2: The doctor has discussed this clot-busting drug treatment with your family or next of kin and advised that in the circumstances this treatment is in your best interests. Your family or next of kin gave consent for you to receive this treatment. Do you agree with your family or next of kin's decision? (Please give your reasons in the space below.)

S2

☐ 1) Strongly agree
☐ 2) Agree
☐ 3) Undecided
☐ 4) Disagree
☐ 5) Strongly disagree

Reasons:_____

_____

Scenario 3: Your family or next of kin were not available to discuss the treatment options with your doctors. The doctors decided to give you the clot busting treatment because they thought it was in your best interests. Do you agree with the doctors' decision? (Please specify your reasons in the space provided below.)

S3

☐ 1) Strongly agree
☐ 2) Agree
☐ 3) Undecided
☐ 4) Disagree
☐ 5) Strongly disagree

Reasons:_____

_____

Attitudes and Perceptions on the Informed Consent Process / Decision-making on Intravenous Tissue Plasminogen Activator (IV TPA).

Scenario 4: The stroke has affected your mental functioning so you are unable to make a decision whether to accept or reject the clot-busting drug treatment. If this had happened to you, whom would you prefer to make that decision on your behalf? (Please specify your reasons in the space provided.)

S4

☐ 1) Family or next of kin ☐ 2) Doctor

Reasons:

_____

_____

Scenario 5: The stroke has affected your mental functioning so you are unable to make a decision whether to accept or reject the clot-busting drug treatment. The doctor has advised you should be treated with the clot-busting drug called alteplase. The doctor has discussed this treatment with your family or next of kin and advised that in the circumstances this treatment is in your best interests. Your family or next of kin declined consent for you to receive this treatment. You would prefer that:

S5

☐ 1) The treatment is given in accordance with the doctor's advice

☐ 2) The decision of my family or next of kin is accepted and treatment not given

6. When you read through the Patient Information Sheet, how did you find it?

PIS2

☐ 1) Very easy to understand ☐ 4) Confusing

☐ 2) Easy to understand ☐ 5) Very confusing

☐ 3) Adequate to understand

7. Do you think the Patient Information Sheet is useful if ever you will make a decision about the clot busting treatment?

PIS3

☐ 1) Not useful, it will make my decision harder ☐ 3) Unsure if useful or not

☐ 2) Useful, it will make my decision easier

8. Was the Patient Information Sheet…

PIS4

☐ 1) Too long

☐ 2) Length about right

☐ 3) Too short, requires more information

9. Which is your preferred format of the Patient Information Sheet?

PIS5

☐ 1) Written

☐ 2) Illustrated

☐ 3) Both written and illustrated

10. The current Patient Information Sheet is in English. Would you prefer it to be translated into a language you are more comfortable with?

PIS6

☐ 1) Yes

☐ 2) No

☐ 3) Does not matter as long as it was adequately explained or verbally translated to me

☐ 4) Not applicable as English is my primary language

Attitudes and Perceptions on the Informed Consent Process / Decision-making on Intravenous Tissue Plasminogen Activator (IV TPA).

What other information do you think is important when making a decision regarding this clot-busting drug treatment, but is lacking or needs more emphasis in the Patient Information Sheet?

Thank you for participating in this survey. If you have any comments about this clot-busting drug treatment or about the informed consent process, or suggestions to improve this survey questionnaire, please write them in the space provided below.

Appendix 2
NOK Questionnaire

Attitudes and Perceptions on the Informed Consent Process / Decision-making on Intravenous Tissue Plasminogen Activator (IV TPA).

You have been invited to participate in this survey because your relative has recently suffered a stroke. This survey aims to determine the attitudes and perceptions of the informed consent process, as well as factors that influence decision-making for the clot-busting drug treatment for stroke. There is no right or wrong answer. Your answers will be kept strictly confidential.

You may complete the form on your own by ticking (☑) the box. Alternatively, our trial coordinator can assist you by writing down your verbal answers. Please direct any questions you may have to the trial coordinator.

SC

1. Age:_____

Age

2. Gender: ☐ 1) Female ☐ 2) Male

Sex

3. Race/ethnicity
☐ 1) Chinese ☐ 3) Indian
☐ 2) Malay ☐ 4) Mixed/Others (please indicate) _____

Rac

4. Please indicate the language or dialect that you are most fluent with. (You may choose more than one answer)
☐ 1) English ☐ 3) Malay ☐ 5) Others including dialect:_____
☐ 2) Mandarin ☐ 4) Tamil

Lng

5. What is your relationship to the patient?
☐ 1) Parent ☐ 3) Child ☐ 5) Others (please indicate): _____
☐ 2) Sibling ☐ 4) Spouse

Rel

An ischemic stroke occurs when a blood vessel in the brain is blocked. Thrombolysis treatment – a clot-busting drug called alteplase - attempts to unblock the blood vessel. This drug must be given within 4.5 hours of the stroke onset. The advantage of this treatment is that it increases the likelihood of patients recovering their physical and mental abilities. Delay in initiating this treatment reduces its benefits and increases the bleeding risk. The main complication of this treatment is bleeding in the brain. Please read the Patient Information Sheet before answering the following questions.

Scenario 1
The doctors have assessed your relative (the patient) and advised that he/she should be treated with the clot-busting drug treatment called alteplase. The doctor has discussed this treatment with your relative and advised that in the circumstances this treatment is in your relative's best interests. Your relative is prepared to make the treatment decision. As a family member, would you like the doctor to ask for your opinion before your relative makes the treatment decision?

1

☐ 1) Yes
☐ 2) No, because the patient is competent, and can therefore decide on his / her own

Attitudes and Perceptions on the Informed Consent Process / Decision-making on Intravenous Tissue Plasminogen Activator (IV TPA).

Scenario 2

The doctors have assessed your relative (the patient) and advised that he/she should be treated with the clot-busting drug called alteplase. The doctor has discussed this treatment with your relative and advised that in the circumstances this treatment is in your relative's best interests. Your relative (the patient) is undecided and asks you as family member to make a decision on his/her behalf. How willing are you to make the decision about this clot busting drug treatment for your relative? (Please specify your reasons in the space provided below.)

☐ 2

☐ 1) Very willing
☐ 2) Willing
☐ 3) Undecided or unsure what to do
☐ 4) Unwilling
☐ 5) Very unwilling

Reasons:

_____

_____

Scenario 3

The stroke has affected your relative's mental functioning and he/she is unable to make a decision whether to accept or reject the clot-busting drug treatment called alteplase. The doctors advised that in the circumstances this treatment is in your relative's best interests. How comfortable are you in letting the doctors make the decision on behalf of your relative and give him/her the clot-busting drug treatment? (Please specify your reasons in the space provided below.)

☐ 3

☐ 1) Very comfortable
☐ 2) Comfortable
☐ 3) Undecided or unsure what to do
☐ 4) Uncomfortable
☐ 5) Very uncomfortable

Reasons:

_____

_____

Scenario 4

The stroke has affected your relative's mental functioning and he/she is unable to make a decision whether to accept or reject the clot-busting drug treatment called alteplase. The doctors advised that in the circumstances this treatment is in your relative's best interests. How willing are you to make this treatment decision on your relative's behalf and sign an informed consent on his/her behalf?

☐ 4

☐ 1) Very willing
☐ 2) Willing
☐ 3) Undecided or unsure what to do
☐ 4) Unwilling
☐ 5) Very unwilling

Reasons:

_____

_____

Attitudes and Perceptions on the Informed Consent Process / Decision-making on Intravenous Tissue Plasminogen Activator (IV TPA).

The next 2 scenarios are your views if you personally suffered an ischemic stroke

Scenario 5a: You have suffered an ischemic stroke. The doctor has advised you should be treated with the clot-busting drug called alteplase. The stroke has affected your mental functioning so you are unable to make a decision whether to accept or reject the clot-busting drug treatment. The doctors have discussed this treatment with your family or next of kin and advised that in the circumstances you should be treated with alteplase. You would prefer that:

☐ 1) The treatment is given in accordance with your doctor's advice
☐ 2) The decision of my family or next of kin is accepted, even if they decline consent for me to be treated with alteplase

☐ 5a

Scenario 5b: You have suffered an ischemic stroke. The doctor has advised you should be treated with the clot-busting drug called alteplase. The doctor has assessed that you have the mental capacity to make the decision whether to accept or decline treatment. Who do you think should make this treatment decision?

☐ 1) You
☐ 2) The doctor
☐ 3) Your family members or next of kin

☐ 5b

Reasons:

_____

_____

6. When you read through the Patient Information Sheet, how did you find it?

☐ 1) Very easy to understand
☐ 2) Easy to understand
☐ 3) Adequate to understand
☐ 4) Confusing
☐ 5) Very confusing

☐ PIS2

7. Do you think the Patient Information Sheet is useful when making a decision about the clot busting treatment?

☐ 1) Not useful, it will make my decision harder
☐ 2) Useful, it will make my decision easier
☐ 3) Unsure if useful or not

☐ PIS3

8. Is the Patient Information Sheet…

☐ 1) Too long
☐ 2) Length about right
☐ 3) Too short, requires more information

☐ PIS4

9. Which is your preferred format of the Patient Information Sheet?

☐ 1) Written
☐ 2) Illustrated
☐ 3) Both written and illustrated

☐ PIS5

Attitudes and Perceptions on the Informed Consent Process / Decision-making on Intravenous Tissue Plasminogen Activator (IV TPA).

10. The current Patient Information Sheet is written in English. Would you prefer it to be translated into a language you are more comfortable with?

PIS6

☐ 1) Yes
☐ 2) No
☐ 3) Does not matter as long as it was adequately explained or verbally translated to me
☐ 4) Not applicable as English is my primary language

What other information do you think is important when making a decision regarding this clot-busting drug treatment, but is lacking or needs more emphasis in the Patient Information Sheet?

_____

_____

Thank you for participating in this survey. If you have any comments about this clot-busting drug treatment or about the informed consent process, or suggestions to improve this survey questionnaire, please write them in the space provided below.

_____

_____

Appendix 3
Patient Information Sheet

INTRAVENOUS ALTEPLASE FOR ACUTE ISCHAEMIC STROKE
Patient Information Sheet

What is Alteplase?

Alteplase acts as an agent to dissolve clots by breaking up the blockage in blood vessels.

Why do I need this treatment?

You have been diagnosed with stroke due to blockage in one of the blood vessels supplying blood to your brain. If alteplase is given within 4 and a half hours from the onset of the stroke, you are more likely to achieve recovery to the extent of independence in carrying out self-care activities (e.g. toileting, feeding, walking) within 3 months as compared to 30 - 45% who achieve functional independence with standard stroke therapy. Your physician will assess your suitability to receive this alteplase treatment. As the assessment is based on the information which you provide, you are encouraged to co-operate in providing accurate information to the best of your knowledge.

What does it involve?

Alteplase will be given into your vein (intravenous) over 1 hour.

What are the risks of the treatment?

The main complication arising from alteplase is bleeding, both inside and outside the brain. The risk of bleeding inside the brain with alteplase is up to 10 times higher than standard stroke therapy. This degree of risk is dependent on the severity of stroke and time from stroke onset, and will be explained to you by your physician. Some patients may die from this complication despite medical care, however the overall 3-month risk of death is similar between patients who receive this treatment and those who do not. Despite the risk of bleeding, patients who receive alteplase are still more likely to be functionally independent at 3 months compared to standard stroke therapy.

Less than 5% of patients will develop an allergic reaction to alteplase. Allergic reactions may range from rashes, breathing difficulties, drop in blood pressure and death. Medication and ventilatory support may be required.

What can I expect after the treatment?

You will be admitted to the Neurology high-dependency or intensive care ward and monitored closely over the few days following the treatment, especially in the first 24 hours. A brain scan will be repeated in the next day or two.

What are your options?

You may choose to decline treatment with alteplase. If you decline, you will be admitted to the Neurology ward, managed by a team of healthcare professional and receive standard stroke therapy. This includes close monitoring and treatment for complications, medications to reduce stroke recurrence, assessment and management of risk factors and rehabilitation.

Original Article

Percutaneous Endovascular Treatment to Salvage Non-Maturing Arteriovenous Fistulas in a Multiethnic Asian Population

Wei Ping Tham, [1]*MBCHB, FRCR (UK), MMED (Diagnostic Radiology)*, Mark C Burgmans, [2]*MD, FAMS*, Bien Soo Tan, [1]*MBBS, FRCR, FAMS*, Kiang Hong Tay, [1]*MBBS, FRCR, FAMS*, Farah G Irani, [1]*MBBS, FRCR*, Apoorva Gogna, [1]*MBBS, FRCR, FAMS*, Ankur Patel, [1]*MBCHB, MRCS, FRCR*, Richard HG Lo, [1]*MBBS, FRCR, FAMS*, Siew Ping Chng, [3]*MBCHB, MRCS, FAMS*, Hui Lin Choong, [4]*MBBS, MMED, FAMS*, Shaun XJM Chan, [1]*MBBS, FRCR, FAMS*

Abstract

Introduction: An arteriovenous fistula (AVF) is the preferred method for haemodialysis in patients with end-stage renal failure. Previous studies have shown value in attempting percutaneous transluminal angioplasty (PTA) to salvage AVFs that fail to mature, but they are relatively small in size and mainly reported in Western populations. We reviewed our data of PTA in non-maturing AVFs to establish whether this technique is translatable to our local multiethnic population. Materials and Methods: We retrospectively reviewed the medical records and procedural images of 105 patients who had PTA for non-maturing AVFs performed at our department from January 2008 to January 2011. Technical success was defined as ≤30% residual stenosis after angioplasty. Clinical success was defined as at least 1 successful haemodialysis session within 4 weeks after PTA. Results: All 105 patients underwent angioplasty for at least 1 haemodynamically significant stenosis. Six (5.7%) had additional embolisation of accessory veins. Technical success was achieved in 95.2% of cases. The clinical success rate was 76.2%. Primary patency rates at 3, 6 and 12 months were 83%, 45% and 28%, respectively. Secondary patency rates at 3, 6 and 12 months were 90%, 79% and 70%, respectively. The minor complication rate was 18.1%. No major complications were encountered. An average of 1.7 interventions per access-year was required to maintain AVF patency. Patients with a preoperative vein size >2.0 mm and age <55 years were more likely to achieve clinical success, although not statistically significant. Conclusion: PTA is a viable option to help salvage non-maturing AVFs in a multiethnic Asian population.

Ann Acad Med Singapore 2017;46:64-71

Key words: Angioplasty, Chronic renal disease, Haemodialysis, Interventional radiology

Introduction

End-stage renal failure (ESRF) is an important global cause of morbidity and mortality.[1] A 2008 World Health Organization (WHO) bulletin estimated the number of people requiring renal replacement therapy (RRT) at 1.4 million with an estimated 8% increase per annum.[2] In Singapore, the number of patients with ESRF requiring RRT has steadily increased with an estimated prevalence of 4895 patients in December 2011 compared with 3565 in 2005.[3] Haemodialysis is the mainstay of RRT with good evidence that dialysis via arteriovenous fistula (AVF) is associated with lower mortality, complication rate and overall cost when compared with other options such as arteriovenous graft (AVG) or haemodialysis catheters (HC).[4,5]

Up to 28% to 60% of autologous AVFs will fail to mature adequately to allow effective dialysis with reported associations to female sex and previous tunnelled catheter use.[6,7] The characteristics of a mature AVF are summed up by the United States' National Kidney Foundation in the Kidney Disease Outcome Quality Initiative (KDOQI) "rule of 6s" (6 mm vein, <6 mm under the skin and ≥600 mL/min flow). AVFs that fail to mature are small, non-palpable or have inadequate blood flow for dialysis.

There is growing literature on the efficacy of percutaneous transluminal angioplasty (PTA) to salvage AVFs that fail to mature. The techniques include angioplasty to assist AVF

[1]Department of Diagnostic Radiology, Singapore General Hospital, Singapore
[2]Department of Radiology, Leiden University Medical Centre, Netherlands
[3]Department of Vascular and Endovascular Surgery, Singapore General Hospital, Singapore
[4]Department of Renal Medicine, Singapore General Hospital, Singapore
Address for Correspondence: Dr Tham Wei Ping, Department of Diagnostic Radiology, Block 2 Level 1, Singapore General Hospital, Outram Road, Singapore 169608.
Email: tham.wei.ping@sgh.com.sg

maturation and embolisation of collateral veins to channel blood flow through a single outflow vein. However, most of these studies have focused on Western populations who have larger vessel sizes.[8-15] Those studies done in Asian populations have small sample sizes.[16-20] As a tertiary interventional centre which performs a significant number of cases, we performed a retrospective analysis to see if PTA of non-maturing AVF is a viable option in our patient population and to determine the factors that influence a successful outcome.

Materials and Methods

For this retrospective study, approval was obtained from our Institutional Review Board. Informed consent was waived. From our computerised database of 1968 PTA's for AVFs performed between January 2008 and January 2011, we found that 105 angioplasties were for salvage of non-maturing AVFs. We retrospectively reviewed the medical records and procedural images of all 105 procedures. The cases were performed or supervised by interventional radiologists with >5 years of experience.

We extracted information on patient and AVF characteristics, possible factors contributing to non-maturation, procedure details and treatment outcomes. Patient demographic data included age, gender and ethnicity. For the AVFs, we looked at the date of creation, type of AVF and calibre of anastomosed vessels. To determine possible factors contributing to non-maturation, we recorded information on the number and location of any stenoses, the presence of competing collateral veins and whether these were treated. For each procedure, we noted the date it was performed, angioplasty balloon characteristics, complications, technical success and any residual stenosis. Outcomes measured include clinical success, primary and secondary patency rates, as well as number and type of secondary interventions.

AVF Evaluation

In our institution, all AVFs were reviewed by a surgeon 4 to 6 weeks after creation. If there was clinical suspicion that the AVF was not maturing, further evaluation was performed with duplex ultrasound. Patients with significant stenosis on ultrasound examination were referred to our department for fistulography and assisted maturation.

Intervention

For each case, the AVF was initially assessed using ultrasound and/or fistulography. The fistulography was performed by injecting contrast through a 21G butterfly needle or 19 to 22G cannula inserted into the juxta-anastomotic segment of the AVF. In cases where spontaneous reflux of contrast into the feeding artery was not seen, we inflated a blood pressure cuff around the upper arm during contrast injection to achieve contrast reflux opacification of the anastomosis. When there was difficulty in puncturing the juxta-anastomotic segment, we performed the fistulography via a brachial artery approach.

After fistulography and documentation of the underlying lesions, interventions were performed using a venous approach. The draining vein was punctured, either antegrade or retrograde as appropriate, and a vascular sheath inserted to obtain access. In a few cases, both approaches were required to treat all the lesions. When the stenosis could not be crossed via the venous approach, brachial artery access was used. After externalisation of the guidewire through the venous sheath, the angioplasty balloon was advanced from the venous approach to treat the stenosis.

Anastomotic and juxta-anastomotic stenoses were treated using angioplasty balloons with a diameter of 3 mm to 6 mm (Fig. 1). Stenoses in the draining vein were treated using angioplasty balloons with a diameter of 5 mm to 8 mm (Fig. 2). Central vein stenoses were treated using angioplasty balloons with a diameter of 10 mm to 14 mm.

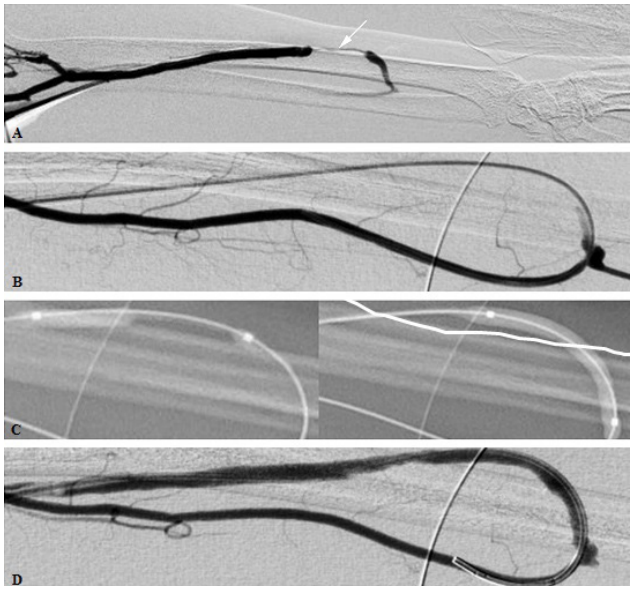

Fig. 1. Percutaneous angioplasty of a non-maturing radiocephalic AVF. A) Venogram obtained after insertion of a 5F sheath in the cephalic vein shows a 3 cm tight stenosis (arrow) in the juxta-anastomotic cephalic vein. B) A 4F catheter and 0.035 guidewire were manipulated across the stenosis into the proximal radial artery. C) Images obtained during inflation of a 4 mm x 40 mm conventional angioplasty balloon show balloon 'waisting' at 6 atm, and full effacement of the balloon waist at 12 atm. D) Post-angioplasty angiogram obtained by injection of contrast through a 4F catheter in the radial artery. No residual stenosis is seen.

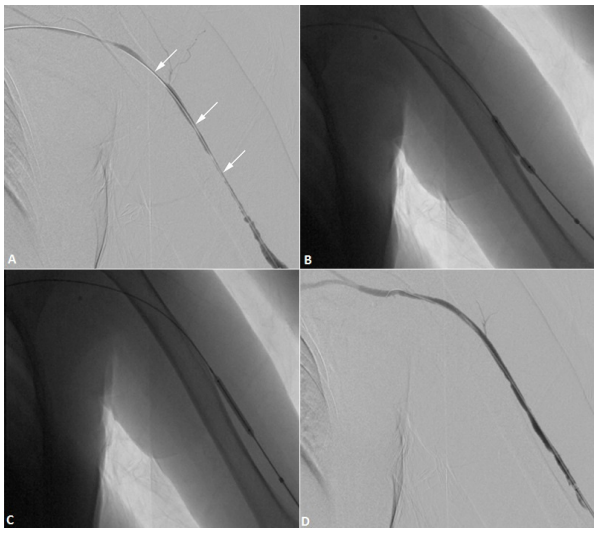

Fig. 2. Percutaneous angioplasty of a non-maturing brachiocephalic AVF. A) Venography shows several stenoses (arrows) in the outflow cephalic vein. B) Inflation of a 5 mm x 40 mm conventional angioplasty balloon with balloon 'waisting' at 10 atm. C) Full effacement of a high-pressure balloon at 20 atm. D) Post-angioplasty venogram shows good results with no residual stenosis.

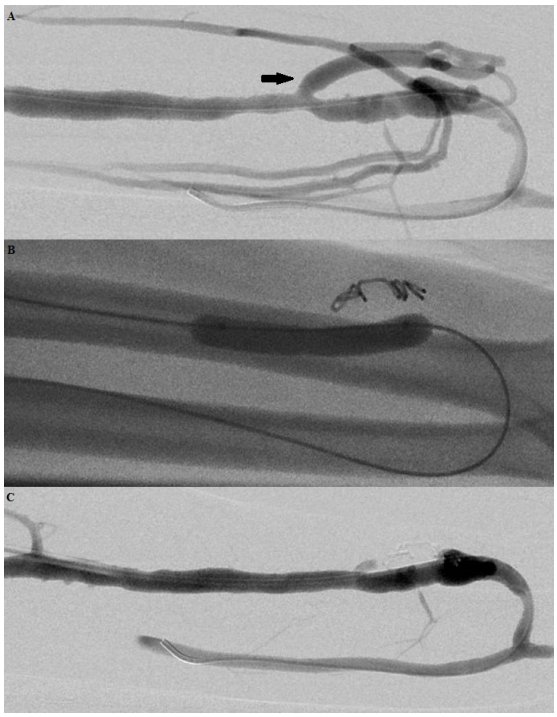

Fig. 3. Coil embolisation of an accessory vein. A) Venography shows a non-maturing AVF due to competing venous collateral (arrow). B) Balloon-assisted coil embolisation of the competing venous collateral. C) The post-embolisation venogram shows obliteration of the competing venous collateral, with a single main outflow vein.

We used conventional angioplasty balloons (Powerflex; Cordis, Miami, FL, USA or Sterling; Boston Scientific, Natick, MA, USA) as the first-line treatment option. High-pressure balloons capable of inflation pressures up to 26 atmospheres (Conquest; BARD, Tempe, AZ, USA) were utilised when conventional balloons did not achieve satisfactory effacement.

Six patients had embolisation of accessory veins performed to assist AVF maturation (Fig. 3). Three of the patients had embolisation with coils performed during the initial angioplasty. The others were done post-angioplasty at 14, 17 and 26 weeks, respectively when their AVFs did not mature. An additional patient had surgical ligation of an accessory collateral vein performed 12 weeks after initial angioplasty.

Definitions

Technical success was defined as ≤30% residual stenosis on angiographic images for all treated lesions which follows the recommendations of the Society of Interventional Radiology (SIR).[21] For embolisation of competing collateral veins, technical success was defined as successful occlusion of competing collateral flow on angiographic images.

Clinical success was defined as at least 1 successful haemodialysis session within 4 weeks after PTA using the treated AVF without creation of a new haemodialysis access (AVF or AVG), surgical revision or insertion of a peritoneal or vascular dialysis catheter. This reflects the standard practice at our institution where the patient is reviewed 4 weeks post-procedure to assess the treatment result.

Primary patency was defined as the interval between the initial salvage procedure and the next thrombosis or repeat intervention (surgical or radiological).

Secondary patency was defined as the lifetime of the AVF from the initial salvage procedure, including its maintenance by PTA, until it is surgically revised or abandoned for any reason.

Complications were categorised into minor and major complications according to the SIR classification system.[21]

Statistical Analysis

We used the chi-square test to determine if any of the variables mentioned earlier showed association with clinical success. Primary and secondary patency rates were measured with Kaplan-Meier survival analysis based on the time of the initial intervention to the last known status of the AVF. The 7 patients that underwent embolisation or surgical ligation of accessory veins were not included in our analysis of patency rates. Multivariate analysis was performed using the Cox regression model.

A P value of <0.05 was taken as the threshold value for statistical significance. We performed the statistical analysis with SPSS 16.0 software.

Results

Within the study period, a total of 105 patients had PTA for non-maturing AVF. The mean age was 63 years (range, 33 to 84 years) with 57.1% (n = 60) of them being male. The majority were of Chinese ethnicity (68%) while the rest were of Malay (31%) and Indian (6%) ethnicity. Most AVFs (74.3% [n = 78]) were radiocephalic, 21.9% (n = 23) were brachiocephalic, and 3.8% (n = 4) were brachiobasilic vein transposition.

The time interval between AVF creation to PTA ranged from 0.9 to 17.6 months (mean 4.6 months; median 3.9 months).

Thirteen patients (12.4%) had PTA of the AVF attempted more than 6 months after creation. In 7 cases, the decision was made to try an alternate option first. Of these 7 patients, 3 had tunnelled dialysis catheters inserted for long-term haemodialysis. Another 3 had a second AVF created on the opposite arm and only after this failed were they referred for PTA of the first non-maturing AVF. The last patient had surgical ligation of an accessory vein to aid maturation before being referred for PTA.

Of the remaining 6 patients, 4 had AVFs created in preparation for dialysis but PTA was delayed as renal function did not deteriorate as quickly as expected. Two patients were referred for PTA but initial fistulography did not reveal a stenosis. Repeat fistulography after 6 months showed significant stenosis for which PTA was performed.

Altogether, 156 stenoses of ≥50% were found, with a mean of 1.5 stenoses per patient (range, 1 to 4). In 59.0% of cases (n = 62), an isolated stenosis was present. In the rest, 34.3% (n = 36) had 2 stenoses, 5.7% (n = 6) had 3 stenoses, and 1.0% (n = 1) had 4 stenoses. The locations of the stenoses are shown in (Table 1).

Technical success was attained in 95.2% (n = 100) of angioplasties and 100% of coil embolisations.

In all cases, a venous approach was first attempted. The majority of the cases (90.5%, n = 95) were treated via a standard venous approach, retrograde and/or antegrade as appropriate. Arterial access was required in 9.5% (n = 10) of patients. In 14.3% (n = 15) of cases, a 0.018" (versus a standard 0.035") platform was needed to cross the stenosis. Three cases were done using an arterial approach while the other 12 through standard venous access.

In 93.3% (n = 98) of cases, angioplasty was successful in using conventional balloons while the other 6.7% (n = 7) necessitated the use of high-pressure balloons.

Minor complications were seen in 18.1% (n = 19) of cases. In 10 cases, angioplasty resulted in vein rupture which was successfully controlled by manual external compression and/or prolonged balloon inflation, with maintenance of AVF patency. Dislodgement of a coil occurred during one of the embolisation procedures and was retrieved with a snare. Other complications included puncture site haematoma in 6 patients, pseudoaneurysm formation in 1 patient and non-flow-limiting dissection in another. All these complications were managed conservatively. There were no major complications.

Table 1. Distribution of Stenoses by Location

Location of Stenosis	Number (n)	% Stenosis
Inflow artery	15	9.6%
AV anastomosis	40	25.6%
Juxta-anastomotic vein	32	20.5%
Peripheral outflow vein	67	42.9%
Central vein	2	1.3%
Total stenoses	156	100%

AV: Arteriovenous

Clinical success was achieved in 76.2% of patients (n = 80). A preoperative anastomotic vein diameter of >2.0 mm was found to be a significant positive predictor for clinical success (PR = 1.29; 95% CI, 1.03 to 1.62; P = 0.024), while an age of ≥55 years was a negative predictor for clinical success (PR = 0.78; 95% CI, 0.65 to 0.94; P = 0.043) (Table 2).

The mean follow-up period was 356 days. During this time, 134 further interventions were performed (120 angioplasties, 10 thrombolysis procedures, 3 collateral vein embolisations and 1 surgical ligation of an accessory vein). From the 80 patients who had clinical success, 50% (n = 40) required further interventions to maintain AVF patency. There was an average of 1.7 interventions per access-year. The mean interval from the initial angioplasty to the next intervention was 5.8 months (range, 1.6 to 17.8 months). None of the patients underwent renal transplantation during the period of follow-up.

The primary patency rates following angioplasty at 3 months, 6 months and 1 year were 83%, 45% and 28%, respectively (Fig. 4A). The corresponding secondary patency rates were 90%, 79% and 70%, respectively (Fig. 4B). The mean duration of primary patency was 9.0 months with a median of 5.8 months. For secondary patency, this was 20.8 months and 29.5 months, respectively.

We found that patients with a preoperative vein size of >2.0 mm tend to have better long-term patency (Fig. 5). At 3, 6, and 12 months' post-intervention, they showed primary patency rates of 92%, 53%, and 40% and secondary patency rates of 95%, 88%, and 83%, respectively. This is compared to primary patency rates of 75%, 39%, and 26% and secondary patency rates of 84%, 73% and 60%, respectively, for patients with a preoperative vein size of

Table 2. Factors Affecting Clinical Success

Variable	Total	Clinical Success			
	n (%)	n (%)	Prevalence Ratio	(95% CI)	*P* Value
Overall	105 (100.0)	80 (76.2)	-	-	-
Age					
<55 years' old	24 (22.9)	22 (91.7)	1.00	(reference)	-
≥55 years' old	81 (77.1)	58 (71.6)	0.78	(0.65 – 0.94)	0.043
Gender					
Male	60 (57.1)	49 (81.7)	1.00	(reference)	-
Female	45 (42.9)	31 (68.9)	0.84	(0.67 – 1.06)	0.128
Ethnicity					
Chinese	68 (64.8)	51 (75.0)	1.00	(reference)	-
Malay	31 (29.5)	24 (77.4)	1.03	(0.82 – 1.31)	0.794
Indian	6 (5.7)	5 (83.3)	1.11	(0.76 – 1.63)	0.648
Time from AVF creation to PTA angioplasty					
<6 months	84 (80.0)	66 (78.6)	1.00	(reference)	-
≥6 months	21 (20.0)	14 (66.7)	0.85	(0.62 – 1.17)	0.252
Type of AVF					
Forearm (RC)	78 (74.3)	58 (74.4)	1.00	(reference)	-
Upper arm (BC, BBT)	27 (25.7)	22 (81.5)	1.10	(0.88 – 1.37)	0.454
Preoperative size of artery					
≤2.0 mm	24 (22.9)	16 (66.7)	1.00	(reference)	-
>2.0 mm	68 (64.8)	52 (76.5)	1.15	(0.84 – 1.57)	0.347
No information	13 (12.4)	12 (92.3)	-	-	-
Preoperative size of vein					
≤2.0 mm	48 (45.7)	32 (66.7)	1.00	(reference)	-
>2.0 mm	50 (47.6)	43 (86.0)	1.29	(1.03 – 1.62)	0.024
No information	7 (6.7)	5 (71.4)	-	-	-
Number of sites stenosed					
Single stenosis	62	47	1.00	(reference)	-
Multiple stenoses	43	33	1.01	(0.82 – 1.26)	0.912

AVF: Arteriovenous fistula; BBT: Brachiobasilic vein transposition; BC: Brachiocephalic; CI: Confidence interval; PTA: Percutaneous transluminal angioplasty; RC: Radiocephalic

≤2.0 mm. However, this difference was not statistically significant (Kaplan-Meier log rank test: $P = 0.591$ for primary patency rate and $P = 0.099$ for secondary patency rate). The average secondary patency for patients with a preoperative vein size of >2.0 mm was 685 days (95% CI, 572 to 798), as compared to 517 days (95% CI, 407 to 627) for patients with a preoperative vein size of ≤2.0 mm ($P = 0.099$).

Discussion

This is a large retrospective study looking at the results of PTA to salvage non-maturing AVF in a multiethnic Asian population. The ethnic distribution of our patients is reflective of that seen in HD prevalence for our local population, which in 2011 stood at 67.6% Chinese, 24.3% Malay and 7% Indian. This distribution has been generally stable since 1999, with a similar pattern seen in the incidence of patients starting HD and incidence of chronic kidney disease stage 5.[3] The technical success rate for PTA was high at 95.2%, with clinical success achieved in 76.2% of cases. While our technical success rates are comparable to prior studies which showed technical success rates of between 87% to 97%, our clinical success rates are slightly lower compared to those of other studies (83% to 98%).[8,10-15,18-20]

Our overall primary and secondary patency rates were 28% and 70% at 12 months, respectively. These values are marginally lower than those obtained in previous Western studies of 34% to 39 % primary patency and 68% to 79 %

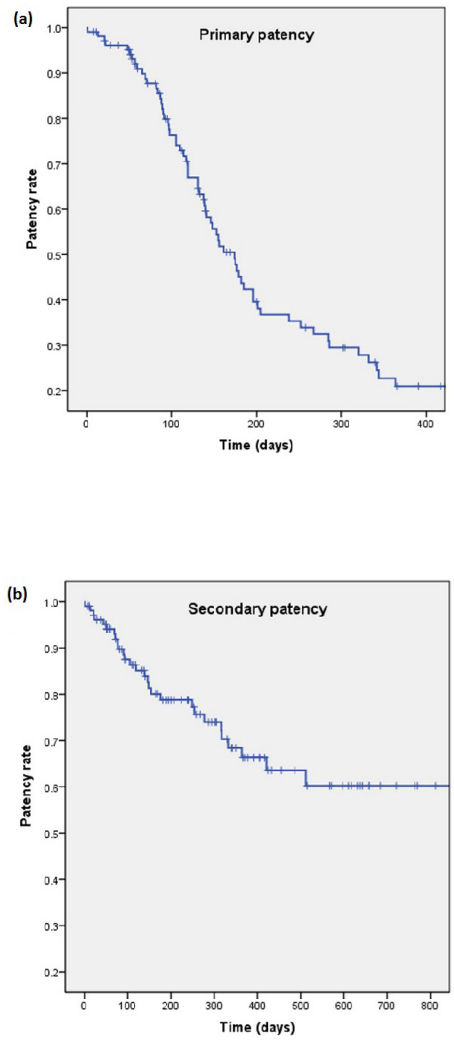

Fig. 4. A) Overall primary and B) overall secondary patency rates.

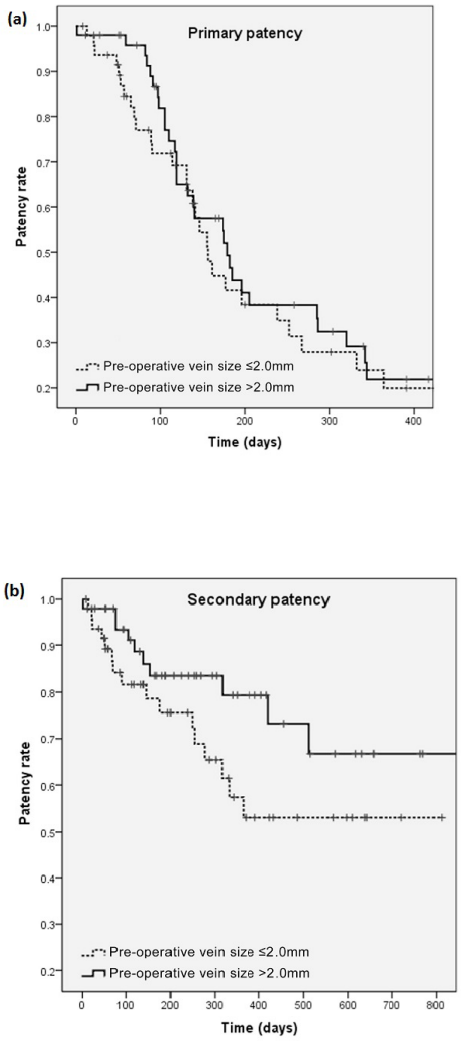

Fig. 5. A) Primary and B) secondary patency rates, compared by preoperative vein size.

secondary patency.[8,10,12,14,22] We postulate that our results could be attributable to factors such as vessel (artery and vein) size, age and diabetes prevalence that are known to affect clinical success and AVF patency.[23,24]

In this study, 45.7% of the preoperative veins were less than 2 mm, which is well researched and below the widely accepted cut-off vein size associated with a lower chance of AVF maturation.[25-27] Our study findings are also consistent with the prevailing evidence, showing that patients having a preoperative vein size of <2 mm had a significantly reduced chance of clinical success (66.7% vs 86.0%). They also tended to have lower primary and secondary patency rates although this did not attain statistical significance. Population studies have shown that Caucasians tend to have larger vein sizes compared with other races, and this is probably a contributing factor to better outcomes in the Western studies.[28,29]

In addition, 22.9% of our patients had a preoperative artery size of <2 mm which is the minimum recommended diameter for successful creation of radiocephalic (RC) AVF.[30]

Our patients were also of slightly older age – mean of 63 years, compared with mean of 58 to 60 years in previous studies.[8,10,14] A meta-analysis of RC AVFs in elderly patients found increased primary failure rate and poorer patency rates at all time points.[31] This could be due to the increased burden of atherosclerotic disease or other comorbidities such as diabetes. Our analysis revealed that an age of ≥55 years was also associated with a reduced chance of clinical success (71.6% vs 91.7%), which is in agreement with the previous meta-analysis. However, there are also studies which dispute the finding of age as a significant factor with

regard to AVF maturation.[32] Based on current information, we do not feel that age should be a determining factor in patient selection for PTA.

Finally, a possible reason could be the higher prevalence of diabetes in our study population. The estimated prevalence of diabetes in Singapore is 12.8% compared with 10.0% in Taiwan and 9.1% in Europe.[33] The incidence of local patients on haemodialysis due to diabetic nephropathy stands at 64.9% in 2014, an increase from 36.9% in 1999.[34] There is evidence that diabetics with AVFs have poorer patency rates.[23,24] However, this is still largely speculative, given that we did not track the prevalence of diabetes in our study population.

Our rates are also slightly lower compared with the study by Liang et al (the largest similar study in an Asian population to date) at 44.9% and 85.4%, respectively.[20] One possible explanation could be related to the time from AVF creation to intervention. Our mean time was 4.6 months (range, 0.9 to 17.6), compared with just 7.9 weeks (range, 3 to 12). Therefore, our patients had a generally longer interval between AVF creation and intervention which could impact our success rate. In our study and another by Renaud et al,[7] the clinical success rate was slightly lower for patients in whom intervention was performed later than 6 months (although this did not achieve statistical significance). One reason for the relative delay in intervention was that some AVFs had been created earlier in anticipation for dialysis; as a result, the surgeon was willing to take a more conservative approach to management.

We did not find any correlation between successful salvage rates and gender although previous studies have suggested female sex to be a negative predictive factor for AVF maturation.

Our study had a few limitations. Firstly, it was a retrospective study, with data collection limited to what can be gleaned from clinical notes and procedure reports. For example, preoperative artery and vein sizes were missing in 12.4% (n = 13) and 6.7% (n = 7) of our cases. Given that the surgeon would be more inclined to mention a small vessel in his report, we had probably overestimated the actual proportion of patients with small vessels in our study population. Secondly, we did not compare our results with any alternative treatment options for non-maturing AVFs, such as surgical revision. However, surgical revision would inevitably result in loss of available vessel for future access, unlike PTA where the original AVF is still salvaged.

Conclusion

Increased population longevity and a rising prevalence of diabetes will result in an ever larger number of patients developing ESRF requiring RRT. AVFs are the preferred option for haemodialysis but a significant number of AVFs fail to mature after creation. Our institution has a policy of creating an AVF first for haemodialysis, and veins of small calibre are utilised by our surgeons to create a lower arm AVF rather than resorting to an AVF in the upper arm or an AVG. This strategy has the advantage of preserving the patient's arm veins for future access creation. Despite the smaller vein sizes, we have shown that in our multiethnic Asian population, PTA is a viable method for salvaging non-maturing AVFs and it should be attempted before abandoning any non-maturing AVFs.

REFERENCES

1. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, et al. Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol 2006;17:2034-47.
2. White SL, Chadban SJ, Jan S, Chapman JR, Cass A. How can we achieve global equity in provision of renal replacement therapy? Bull World Health Organ 2008;86:229-37.
3. Ministry of Health, Singapore. National Registry of Diseases Office. Singapore renal registry report no. 9. Trends in chronic kidney failure in Singapore 2010 - 2011. Available at: https://www.nrdo.gov.sg/docs/librariesprovider3/Publications---Kidney-Failure/trendsinrenal2010-2011.pdf?sfvrsn=0&AspxAutoDetectCookieSupport=1. Accessed on 5 July 2016.
4. Vascular Access Work Group. Clinical practice guidelines for vascular access. Am J Kidney Dis 2006;48:S248-73.
5. Malas MB, Canner JK, Hicks CW, Arhuidese IJ, Zarkowsky DS, Qazi U, et al. Trends in incident hemodialysis access and mortality. JAMA Surg 2015;150:441-8.
6. Irani FG, Tan BS, Taneja M, Lo R, Tay KH. Hemodialysis access interventions: an Asian perspective. In: Rajan DK, editor. Essentials of percutaneous dialysis interventions. New York: Springer; 2011. p. 379-93.
7. Renaud CJ, Pei JH, Lee EJ, Robless PA, Vathsala A. Comparative outcomes of primary autogenous fistulas in elderly, multiethnic Asian haemodialysis patients. J Vasc Surg 2012;56:433-9.
8. Clark TW, Cohen RA, Kwak A, Markmann JF, Stavropoulos SW, Patel AA, et al. Salvage of nonmaturing native fistulas by using angioplasty. Radiology 2007;242:286-92.
9. Falk A. Maintenance and salvage of arteriovenous fistulas. J Vasc Interv Radiol 2006;17:807-13.
10. Nassar GM, Nguyen B, Rhee E, Achkar K. Endovascular treatment of the "failing to mature" arteriovenous fistula. Clin J Am Soc Nephrol 2006;1:275-80.
11. McLafferty RB, Pryor RW 3rd, Johnson CM, Ramsey DE, Hodgson KJ. Outcome of a comprehensive follow-up program to enhance maturation of autogenous arteriovenous haemodialysis access. J Vasc Surg 2007;45:981-5.
12. Miller GA, Hwang W, Preddie D, Khariton A, Savransky Y. Percutaneous salvage of thrombosed immature arteriovenous fistulas. Semin Dial 2011;24:107-14.

13. Miller GA, Goel N, Khariton A, Friedman A, Savransky Y, Trusov I, et al. Aggressive approach to salvage non-maturing arteriovenous fistulae: a retrospective study with follow-up. J Vasc Access 2009;10:183-91.
14. Manninen HI, Kaukanen E, Mäkinen K, Karhapää P. Endovascular salvage of nonmaturing autogenous hemodialysis fistulas: comparison with endovascular therapy of failing mature fistulas. J Vasc Interv Radiol 2008;19:870-6.
15. Asif A, Roy-Chaudhury P, Beathard GA. Early arteriovenous fistula failure: a logical proposal for when and how to intervene. Clin J Am Soc Nephrol 2006;1:332-9.
16. Shin SW, Do YS, Choo SW, Lieu WC, Choo IW. Salvage of immature arteriovenous fistulas with percutaneous transluminal angioplasty. Cardiovasc Intervent Radiol 2005;28:434-8.
17. Song HH, Won YD, Kim YO, Yoon SA. Salvaging and maintaining non-maturing Brescia-Cimino haemodialysis fistulae by percutaneous intervention. Clin Radiol 2006;61:404-9.
18. Hong HP, Kim SK. Usefulness of percutaneous intervention with transarterial approach in the salvage of nonmaturing native fistulas status-post transvenous approach failure: transarterial approach in the salvage of nonmaturing native fistulas. Cardiovasc Intervent Radiol 2009;32:1252-6.
19. Hsieh MY, Lin L, Tsai KC, Wu CC. Radial artery approach to salvage nonmaturing radiocephalic arteriovenous fistulas. Cardiovasc Interv Radiol 2013;36:957-63.
20. Liang HL, Fu JH, Wang PC, Chen MC, Wang CC, Lin YH, et al. Endovascular salvage of immature autogenous haemodialysis fistulas. Cardiovasc Intervent Radiol 2014;37:671-8.
21. Gray RJ, Sacks D, Martin LG, Trerotola SO. Reporting standards for percutaneous interventions in dialysis access. J Vasc Interv Radiol 2003;14:S433-42.
22. Zangan SM, Falk A. Optimizing arteriovenous fistula maturation. Semin Intervent Radiol 2009;26:144-50.
23. Smith GE, Gohil R, Chetter IC. Factors affecting the patency of arteriovenous fistulas for dialysis access. J Vasc Surg 2012;55:849-55.
24. Aktas A, Bozkurt A, Aktas B, Kirbas I. Percutaneous transluminal balloon angioplasty in stenosis of native haemodialysis arteriovenous fistulas: technical success and analysis of factors affecting postprocedural fistula patency. Diagn Interv Radiol 2015;21:160-6.
25. Lauvao LS, Ihnat DM, Goshima KR, Chavez L, Gruessner AC, Mills JL. Vein diameter is the major predictor of fistula maturation. J Vasc Surg2009;49:1499-504.
26. Mendes RR, Farber M, Marston W, Dinwiddie LC, Keagy B, Burnham SJ. Prediction of wrist arteriovenous fistula maturation with preoperative vein mapping with ultrasonography. J Vasc Surg 2002;36:460-3.
27. Silva MB Jr, Hobson RW 2nd, Pappas PJ, Jamil Z, Araki CT, Goldberg MC, et al. A strategy for increasing use of autogenous haemodialysis access procedures: Impact of preoperative noninvasive evaluation. J Vasc Surg 1998;27:302-8.
28. Ishaque B, Zayed MA, Miller J, Nguyen D, Kaji AH, Lee JT, et al. Ethnic differences in arm vein diameter and arteriovenous fistula creation rates in men undergoing haemodialysis access. J Vasc Surg 2012;56:424-31.
29. Fronek A, Criqui MH, Denenberg J, Langer RD. Common femoral vein dimensions and hemodynamics including Valsalva response as a function of sex, age, and ethnicity in a population study. J Vasc Surg 2001;33:1050-6.
30. Tordoir J, Canaud B, Haage P, Konner K, Basci A, Fouque D, et al. EBPG on vascular access. Nephrol Dial Transplant 2007;22:ii88-117.
31. Lazarides MK, Georgiadis GS, Antoniou GA, Staramos DN. A meta-analysis of dialysis access outcome in elderly patients. J Vasc Surg 2007;45:420-6.
32. Bashar K, Zafar A, Elsheikh S, Healy DA, Clarke-Moloney M, Casserly L, et al. Predictive parameters of arteriovenous fistula functional maturation in a population of patients with end-stage renal disease. PLoS One 2015;10:e0119958.
33. International Diabetes Federation. IDF Diabetes Atlas – 7th ed. Available at: http://www.diabetesatlas.org/. Accessed on 5 July 2016.
34. Health Promotion Board. National Registry of Diseases Office. Singapore renal registry annual registry report 1999-2014 (interim). Available at: https://www.nrdo.gov.sg/docs/librariesprovider3/Publications---Kidney-Failure/report-1999-till-2014-interim.pdf?sfvrsn=0&AspxAutoDetectCookieSupport=1. Accessed on 5 July 2016.

Acute Inflammatory Polyarthritis: A Rare Presentation of Secondary Syphilis

Dear Editor,

Syphilis can present in a myriad of ways. Recognition of this "great imitator", which can be easily treated, will greatly reduce morbidity.

A 46-year-old Chinese male presented with intense inflammatory polyarthritis of his bilateral metacarpophalangeal, wrists, elbows, knees, ankles and metatarsophalangeal joints for 2 weeks. Joint tenderness was alleviated with movement and associated with early morning stiffness lasting more than 30 minutes. He also reported rashes over his chest, scalp, hands and feet over the previous 3 months. Two days prior to the onset of the above symptoms, he experienced vomiting, abdominal pain and non-bloody diarrhoea which resolved spontaneously. He was subsequently admitted for worsening arthritis which had resulted in inability to weight-bear. He denied any history of fever, loss of appetite and loss of weight. There was no axial or gluteal pain and no urethral symptoms. Family history for autoimmune diseases was unremarkable. The patient denied any prior sexual exposure. Treatment from his physicians consisted of topical clotrimazole for his rashes and prednisolone (3 mg bd) for his arthritis, which did not significantly improve his condition.

On physical examination, erythematous papulosquamous plaques were noted over his sternum, palms and soles (Figs. 1 to 3). Of note, there was faint macular hyperpigmentation over his palms. Intense synovitis was present over the aforementioned joints with tense effusion over his left knee and dactylitis of multiple toes. Conjunctival injection, cervical lymphadenopathy and right thumb onycholysis were noted. There were no genital lesions or urethral discharge.

Investigations revealed elevated erythrocyte sedimentation rate (ESR) of 127 mm/h and C-reactive protein (CRP) of 133.5 mg/L. He was also noted to have hypoalbuminaemia of 25 g/L. Aside from iron deficiency anaemia, his full blood count, renal panel, liver function test and autoimmune serologies were unremarkable. No organisms were recovered from the blood cultures and fungal scrape of his

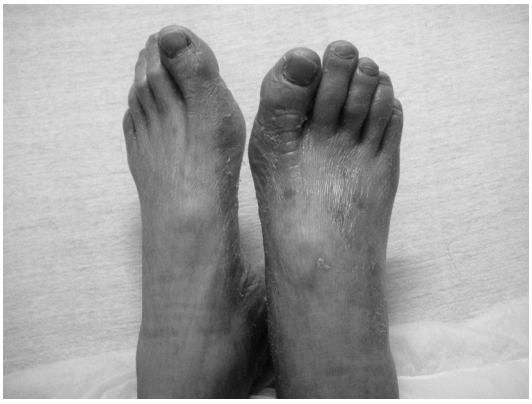

Fig 2. Erythematous papulosquamous plaques associated with dactylitis and post-inflammatory hyperpigmentation on both feet.

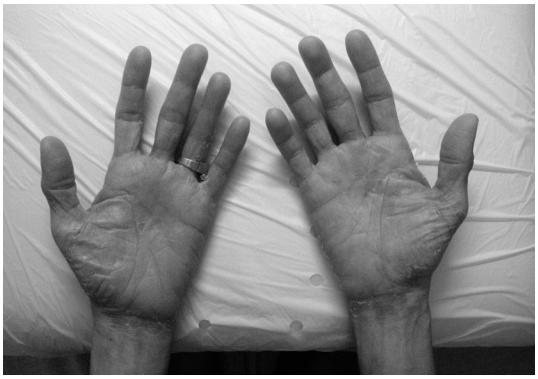

Fig 1. Scaly plaques with underlying erythema and post-inflammatory hyperpigmentation over the palmar surface of hands.

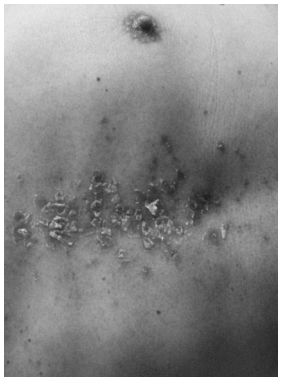

Fig.3. Scaly plaques with underlying post-inflammatory hyperpigmentation on the sternal region.

soles and palms were negative. Plain radiographs of his bilateral hands and ankle joints did not reveal bony erosions. Rapid plasma reagin (RPR) was performed despite patient's claim of no prior sexual exposure and it returned positive with a titre of 1:256. Enzyme immunoassay for syphilis IgG was also reactive. Human immunodeficiency virus (HIV), hepatitis B and C screening were recommended but the patient declined evaluation. One dose of benzathine penicillin G 2.4 MU was given during admission and by 2 weeks post-treatment, there was complete resolution of the patient's rashes and polyarthritis.

The prevalence of syphilis in Singapore has been increasing since 1999.[1] Groups who are particularly affected include men-who-have-sex-with-men and HIV-infected individuals.[2] Unfortunately, syphilis can present in many forms, mimicking other pathologies. This makes timely diagnosis and treatment difficult.

The differentials for the case above include spondyloarthropathies such as reactive arthritis (previously known as Reiter Syndrome), psoriatic arthritis and enteropathic arthropathy, which can all present with peripheral inflammatory polyarthropathy, dactylitis and nail dystrophy. However, the arthritis in reactive arthritis tends to occur 1 to 4 weeks after the infectious trigger. Despite the presence of conjunctival injection, the onset of arthritis in this case occurred too soon after the antecedent episode of self-limiting gastroenteritis. Moreover, reactive arthritis tends to present with asymmetrical oligoarthritis. Psoriatic arthritis does not usually present in such an explosive polyarticular fashion. There were no features of personal or family history to suggest inflammatory bowel disease.

The patient's rashes were papulosquamous but not psoriasiform, and post-inflammatory hyperpigmentation was present on his palms, a feature atypical of rashes in psoriasis and reactive arthritis. The abovementioned atypical joint and skin features prompted an evaluation with syphilitic serology, despite the patient's insistence of no prior sexual exposure. Beside palmoplantar papulosquamous eruption, the typical features of secondary syphilis include moth-eaten non-scarring alopecia and snail track oral ulcers. Other rare musculoskeletal manifestations include symmetrical acute inflammatory arthritis, dactylitis and onycholysis, which can occur in both congenital and acquired syphilis.[2,3] Characteristically, syphilitic arthritis is not painful on gentle passive movement, unlike rheumatic joint diseases. Presentation of joint involvement is protean. Early treatment allows for cure and improvement in patient outcomes.[2] Syphilitic dactylitis is triggered by flexor tenosynovitis.[4] Onycholysis occurs when syphilitic infiltration precipitates the formation of a nail bed granular layer leading to detachment of the distal nail plate.[5]

This case highlights polyarthritis as a rare presentation of secondary syphilis. It underscores the importance of ordering appropriate investigations for syphilis based on clinical suspicion despite an incongruent sexual history, as patients may not be forthcoming with the latter. An early diagnosis of syphilis will allow for prompt treatment and cure with antibiotics, reducing subsequent systemic complications from tertiary disease.

REFERENCES

1. Sen P, Chio MT, Tan HH, Chan RK. Rising trends of STIs and HIV infection in Singapore – a review of epidemiology over the last 10 years (1994 to 2003). Ann Acad Med Singapore 2006;35:229-35.
2. Lautenschlager S. Cutaneous manifestations of syphilis: recognition and management. Am J Clin Dermatol 2006;7:291-304.
3. Ashhurst A. A case of syphilitic dactylitis of the toe. JAMA 1906;XLVI:584.
4. Avenel G, Goeb V, Abboud P, Ait-Abdesselam T, Vittecoq O. Atypical forms of syphilis: two cases. Joint Bone Spine 2009;76:293-5.
5. Fitzgerald F. The great imitator, syphilis. West J Med 1981;134:424-32.

Xu Cong Ruan, [1,2]*BSc (Pharm)(Hons)*, Joel HL Lim,[2]*MBBS, MRCP (UK), MMed (Int Med)*, Hong Liang Tey, [2,3]*MBBS, FRCP (Edin), FAMS*

[1]Duke-NUS Medical School, Singapore
[2]Department of Dermatology, National Skin Centre, Singapore
[3]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

Address for Correspondence: Dr Tey Hong Liang, National Skin Centre, 1 Mandalay Road, Singapore 308205.
Email: teyhongliang111@yahoo.com

Group B *Streptococci* in Sushi and Sashimi

Dear Editor,

A large outbreak of invasive Group B *streptococcus* (GBS) infection occurred in Singapore in 2015 which was associated with the consumption of Chinese-style raw fish (yusheng) porridge.[1] The GBS clone responsible belonged to *serotype III, ST283*.[2] We sought to determine if GBS could also be found in Japanese-style sushi and sashimi.

We collected 17 fish sold ready-to-eat (12 salmon, 4 'tai', 1 tilapia) from various Japanese food outlets (n = 8), and supermarkets (n = 4). Fish purchased were kept in their original containers and immediately transported by ice-box back to the laboratory. The fish species were chosen because GBS tends to cause a problem with freshwater fish. 'Tai' is normally understood to be a saltwater fish, the red sea bream (*Pagrus major*). However, we wanted to know if cheaper freshwater fish was being used as a substitute for genuine 'tai' as this is a common practice in many countries.[3]

The fish meat was processed using a modification of the protocol described by van der Mee-Marquet et al;[4] 25 g of fish was macerated in 225 mL of Todd-Hewitt broth containing 8 µg/mL polymixin B and 32 µg/mL nalidixic acid using a stomacher before incubating 24 hours at 35˚C to 37˚C. The next day, 1 mL of the broth was removed and transferred to 5 mL of brain heart infusion containing 8 µg/mL polymixin B and 32 µg/mL nalidixic acid, and incubated at 35˚C to 37˚C for a further 24 hours. The following day, a loopful of the broth was plated onto chromID® Strepto B (bioMérieux) agar plates which were incubated at 35˚C to 37˚C for up to 48 hours. Pink, red, and violet colonies were selected for further workup. Polymerase chain reaction (PCR) serotyping was performed directly on deoxyribonucleic acid (DNA) extracted from the incubated broth if no GBS was isolated.[5]

Table 1. Characteristics of Group B *Streptococci* Isolated from Fish Meat

Fish Species	Salmon	Tilapia
PCR serotype	*II*	*Ia*
MLST	*ST1*	*ST7*
Antimicrobial susceptibility		
Penicillin	S*	S
Erythromycin	S	S
Clindamycin	S	S
Tetracycline	R†	S

MLST: Multi-locus sequence typing; PCR: Polymerase chain reaction
*Susceptible.
†Resistant.

We were able to isolate GBS from 2 samples (salmon and tilapia). The isolates were identified using matrix-assisted laser desorption ionisation-time of flight mass spectrometry (MALDI-TOF) and characterised by antimicrobial susceptibility testing,[6] PCR serotyping, and multi-locus sequence typing (MLST).[7] The results are summarised in Table 1. In addition, we were able to obtain PCR sequences consistent with GBS belonging to *serotype Ia* and *MLST ST7* from broth culture of 'tai' meat even though culture was unsuccessful.

PCR amplification and sequencing for the cytochrome *c* oxidase subunit *I gene* was performed on DNA extracts of the 4 'tai' samples.[8] The sequences were compared with those in the GenBank and the Fish-Bol database (http://www.fishbol.org/). Two samples were red sea bream *(Pagrus major)*. One was crimson snapper *(Lutjanus erythropterus)*, this was the broth sample that had sequences for *serotype Ia, ST7* GBS. The other sample was a Nile tilapia *(Oreochromis niloticus)*.

Foxman et al showed that fish consumption was an independent risk factor leading to the colonisation of the human gut with *serotype Ia* and *Ib* GBS.[9] *Serotype Ia, ST7* GBS is a well known fish pathogen and may be just emerging as a human pathogen.[10,11] The clinical significance of *serotype II, ST1* GBS is uncertain. It is possible that this is not a fish-specific clone and may have resulted from human contamination.

In this study, we did not find any virulent *serotype III, ST283* GBS. However, this could also be because the sample size was small, and it is improper to draw a firm conclusion on the absence of the virulent *serotype III, ST283* GBS, from fish meat. It is an important principle in science that the absence of evidence of a marker (or phenomenon) does not constitute evidence of the absence of that marker (or phenomenon). We were able to show the presence of other GBS and evidence of fish substitution, so there remains a potential for zoonotic GBS infection from the consumption of sushi/sashimi.

REFERENCES

1. Osada J. Recent GBS outbreak 'biggest in the world'. The Straits Times 2015 Dec 6;Sect A:10 (col 1).
2. Mehershahi KS, Hsu LY, Koh TH, Chen SL. Complete genome sequence of streptococcus agalactiae serotype III, multilocus sequence type 283 strain SG-M1.Genome Announc 2015;3:e01188-15.
3. Sampson S, Marlow I. Raw deal for sushi lovers. Toronto Star. 9 May 2009. Available at: https://www.thestar.com/life/2009/05/09/raw_deal_for_sushi_lovers.html. Accessed on 1 July 2016.
4. van der Mee-Marquet N, Domelier AS, Salloum M, Violette J, Arnault L, Gaillard N, et al. Molecular characterization of temporally and geographically matched Streptococcus agalactiae strains isolated from food products and bloodstream infections. Foodborne Pathog Dis 2009;10:1177-83.
5. Kong F, Ma L, Gilbert GL. Simultaneous detection and serotype identification of Streptococcus agalactiae using multiplex PCR and reverse line blot hybridization. J Med Microbiol 2005;54:1133-8.
6. CLSI (Clinical and Laboratory Standards Institute, Wayne, PA). Performance standards for antimicrobial susceptibility testing; Twenty-fifth informational supplement; 2015. CLSI document M100-S25.
7. Jones N, Bohnsack JF, Takahashi S, Oliver KA, Chan MS, Kunst F, et al. Multilocus sequence typing system for group B streptococcus. J Clin Microbiol 2003;41:2530-6.
8. Steinke D, Hanner R; FISH-BOL. The FISH-BOL collaborators' protocol. Mitochondrial DNA 2011;22 Suppl 1:10-4.
9. Foxman B, Gillespie BW, Manning SD, Marrs CF. Risk factors for group B streptococcal colonization: potential for different transmission systems by capsular type. Ann Epidemiol 2007;17:854-62.
10. Kayansamruaj P, Pirarat N, Kondo H, Hirono I, Rodkhum C. Genomic comparison between pathogenic Streptococcus agalactiae isolated from Nile tilapia in Thailand and fish-derived ST7 strains. Infect Genet Evol 2015;36:307-14.
11. Björnsdóttir ES, Martins ER, Erlendsdóttir H, Haraldsson G, Melo-Cristino J, Kristinsson KG, et al. Changing epidemiology of group B streptococcal infections among adults in Iceland: 1975-2014. Clin Microbiol Infect 2015;22:379.e9-379.e16.

Tse Hsien Koh, [1] *MD, PhD*, Delphine YH Cao, [1], Boon Ching Khoo, [1], Lan Huay Ong, [1], Fionicca Teo, [2], Terry WP Tan, [2]

[1]Diagnostic Bacteriology, Pathology Department, Singapore General Hospital, Singapore
[2]School of Applied Science, Temasek Polytechnic, Singapore

Address for Correspondence: A/Prof Koh Tse Hsien, Diagnostic Bacteriology, Pathology Department, Singapore General Hospital, 20 College Road, Academia, Level 7, Diagnostics Tower, Singapore 169856.
Email: koh.tse.hsien@singhealth.com.sg

Survey Study on the Injury Patterns, Dance Practices and Health Seeking Behaviour amongst Dancers in Singapore

Dear Editor,

Dancers are exposed to training loads that can lead to injuries, the majority of which are overuse in nature.[1] Their lower limbs and back are often injured.[1,2] There are a myriad of factors that can contribute to the injuries. However, there is relatively little local data on injury patterns among dancers in Singapore. The objective of the study is to gather data on the practices of dancers, the prevalence of dance injuries, and injury patterns among Singapore dancers.

Materials and Methods

Students at commercial dance and vocational schools, and professional dancers aged 21 years or older were recruited. The survey was conducted with anonymous self-administered questionnaires which were distributed via a dance instructor and administered prior to and after classes. Dancers also had the option of completing the survey online. A dance instructor was consulted on the design of the questionnaire which was made to be self-explanatory and could be completed in 10 minutes. To reduce ambiguity, each question was provided with mutually exclusive responses. The questions pertaining to injuries were modelled after those used in injury surveillance in sports.[3,4]

Biodata, experience and education in dance, genre(s) of dance practised, level of participation, weekly training load, location, recurrences, extent and diagnoses of current injuries, participation in other physical sports, physical conditioning practices, and response to injury were recorded.

Statistical Analysis

The responses were tabulated on Microsoft Excel 2013 version 14.0, statistical analysis was performed for data checking and descriptive analysis of the variables was performed.

Results

There were a total of 365 respondents. Three percent of the questions were left unanswered while 1% of the answers were found to be erroneous.

The average age of those surveyed was 25.4 years (CI, 24.4 to 26.4). All the respondents were female. The average body mass index (BMI) was 20.8 (CI, 19.6 to 22.0).

Thirty percent had 5 to 10 years of experience in dance while 26% had more than 10 years (Fig. 1). Two percent had a formal dance education while 32% and 13% were practising dance at semi-professional and professional levels, respectively.

The majority (77%) were engaged in at least 1 performance per year. Per week, 57% trained between 5 to 10 hours, 13% trained more than 10 hours, 49% had 3 or more rest days and 12% engaged in dance daily.

The results show that 67.4% of respondents participated in multiple genres of dance concurrently (Fig. 2).

Dance Injuries

Dance-related injuries were present in 53% of those surveyed, of which 40% resulted in absenteeism from dance for less than 1 week. A large proportion (69.9%) had 1 to 2 recurrent injuries. Of these, 40.7%, 35.0% and 24.3% were professional, semi-professional and recreational dancers, respectively. The differences in recurrent injuries between the groups did not reach statistical significance (Chi-square test, $P > 0.5$). Forty-three percent identified dance as an aggravating factor. The majority trained 5 to 10 hours per week and 69% were engaged in 1 or more performances per year.

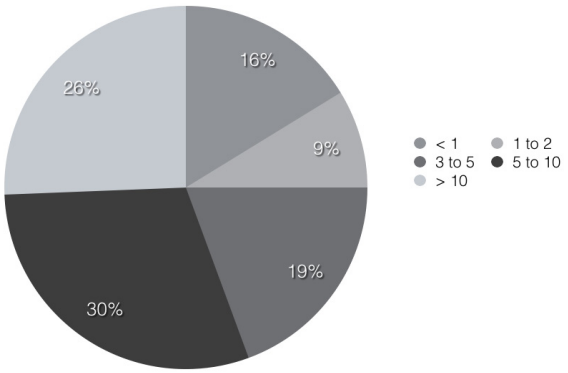

Fig. 1. Number of years in dance.

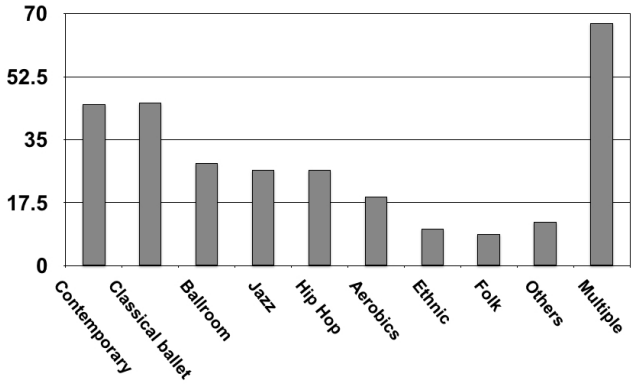

Fig. 2. Percentage of respondents and participation in dance genres.

Injuries of foot and ankle (53.8%), knee (48.9%) and back (34.1%) were the most common (Fig. 2). The majority (76.5%) of the injuries were overuse in nature, and 43.5% resulted in absenteeism from dance for 1 to 2 weeks and 14% required absenteeism of 5 weeks or more. Of the injured dancers that abstained from dance for more than 8 weeks, the majority (38.1%) were recreational dancers.

Of the injured, 42% chose to seek medical attention, 26.7% chose to ignore the injury and 32.7% abstained from dance to allow for recovery. Of the respondents that did not seek medical attention, 65.3% self managed with first aid.

Most of the injured dancers consulted a physiotherapist (33.3%), followed by a traditional physician (30.6%), medical specialist (20.6%) and primary care physician (16%).

Health Practices

Amongst the respondents, 64%, 92% and 44% were engaged in aerobic, flexibility and strength training, respectively.

Only 23% underwent musculoskeletal screening; 42.4% used massage as a form of recovery technique while 73.3% employed some form of active recovery (e.g. contrast bath, sauna). A large majority (94%) were non-smokers and half did not consume alcohol.

Discussion

The range of BMI from 15.1 to 34.0 is relatively wide compared to other studies of dancers[5,6] but the BMI mean is still lower than that in the general population of Singapore.[7]

Twelve percent of the dancers did not have a rest day from dance. The hours of weekly training and simultaneous participation in different genres of dance have been reported in other studies.[6] Fatigue as a result of over-training has been identified as a risk factor for dance injuries.[8]

The high prevalence and recurrence of dance injuries as well as its tendency to affect the lower limbs have also been previously reported.[1,2,6] This may reflect dance's intrinsically repetitive movements that may stress the foot and ankle regions, including other compensatory movements such as those needed to achieve turnout in ballet. The severity of dance injuries, as gauged by the duration of absenteeism from dance practice, is similar to most published data.[9]

Compared to other studies,[2,9] the proportion of dancers that sought medical treatment was low. Amongst collegiate dancers, medical professionals was ranked third as the primary source of advice for the management of dance injuries, with only 17.7% of them seeking medical help from physicians.[10]

A significant proportion of injured dancers sought treatment from traditional medical professionals or masseurs, consistent with the high prevalence of use of complementary and alternative medicine here.[11] While the majority of dancers engaged in flexibility training, only two-thirds engaged in regular aerobic training while less than half engaged in strength training. The relatively low rates of aerobic and strength training might suggest a lack of recognition of comprehensive physical conditioning in injury prevention.

The prevalence of smokers in the study is significantly lower than that of the national average while the proportion of non-drinkers was close to the national average of 54%.[7]

Limitations

The study population was heterogeneous in the proficiency and level of participation in dance. The anonymous nature of the survey made it impossible to ensure that there had been more than 1 form submitted for each individual. Furthermore, there remains the possibility of inadvertent selection bias in the recruitment process. However, the anonymous nature of the study also made it impossible to study the characteristics of non-respondents or estimate the extent of selection bias.

Conclusion

This survey showed that Singapore dancers share similar characteristics and injuries with dancers in other studies and thus, they may benefit from dance prevention measures that are already in practice in international communities. Efforts to improve accessibility to medical care for dancers would have to take into account local usage of complementary and alternative medicine as well as the level of knowledge of medical professionals in the management of dance injuries.

Dance screening could be a useful measure for detecting and managing injuries early amongst dancers. Despite its limitation, the study provides previously unavailable information on the local dance population.

REFERENCES

1. Sobro FJ, de la Cuadra C, Guillén P. Overuse injuries in professional ballet: injury-based differences among ballet disciplines. Orthop J Sports Med 2015;3:2325967115590114.
2. Shah S, Weiss DS, Burchette RJ. Injuries in professional modern dancers: incidence, risk factors, and management. J Dance Med Sci 2012;16:17-25.
3. Junge A, Engebretsen L, Alonso JM, Renström P, Mountjoy M, Aubry M, et al. Injury surveillance in multi-sport events: the International Olympic Committee approach. Br J Sports Med 2008;42:413-21.
4. Dick R, Agel J, Marshall SW. National Collegiate Athletic Association Injury Surveillance System commentaries: introduction and methods. J Athl Train 2007;42:173-82.
5. Ferrari EP, Silva DA, Martins CR, Fidelix YL, Petroski EL. Morphological characteristics of professional ballet dancers of the Bolshoi theater company. Coll Antropol 2013;37:37-43.
6. Bowling A. Injuries to dancers: prevalence, treatment, and perceptions of causes. BMJ 1989;298:731-4.
7. Ministry of Health, Singapore. National Health Survey 2010. Available at: https://www.moh.gov.sg/content/moh_web/home/Publications/Reports/2011/national_health_survey2010.html. Accessed on 19 August 2016.
8. Liederbach M, Schanfein L, Kremenic IJ. What is known about the effect of fatigue on injury occurrence among dancers? J Dance Med Sci 2013;17:101-8.
9. Weiss DS, Shah S, Burchette RJ. A profile of the demographics and training characteristics of professional modern dancers. J Dance Med Sci 2008;12:41-6.
10. Air ME, Grierson MJ, Davenport KL, Krabak BJ. Dissecting the doctor-dancer relationship: health care decision making among American collegiate dancers. PM R 2014;6:241-9.
11. Lim MK, Sadarangani P, Chan HL, Heng JY. Complementary and alternative medicine use in multiracial Singapore. Complement Ther Med 2005;13:16-24.

Jason KK Chia, [1] *MBBS (S'pore), MSpMed (Australia), DFD*

[1]Department of Orthopaedic Surgery, Tan Tock Seng Hospital, Singapore

Address for Correspondence: Dr Jason Chia, Department of Orthopaedic Surgery, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433. Email: jason_chia@ttsh.com.sg

Incidental Multiple Pulmonary Nodules in a Middle-Aged Woman

A 54-year-old lady underwent a screening cardiac computed tomography (CT) scan for coronary calcium which found incidental multiple sub-centimetre pulmonary nodules of varying sizes present in both lungs. This finding was confirmed on a CT of the chest (Fig. 1). Plain chest radiography was not done before surgery. She was a lifelong non-smoker with a history of total hysterectomy 15 years ago for menorrhagia secondary to fibroids. Her father had colon and lung cancer. Her mother had pulmonary tuberculosis, colon, lung and breast cancer. The patient had no cough, dyspnoea or constitutional symptoms including fever, night sweats, loss of weight and appetite. Physical examination was unremarkable. She had a recent mammography which was normal. Positron emission tomography-computed tomography (PET-CT) scan was performed to evaluate for the presence of malignancy elsewhere with lung metastases, but no hypermetabolic primary malignancy was detected. Autoimmune workup was negative.

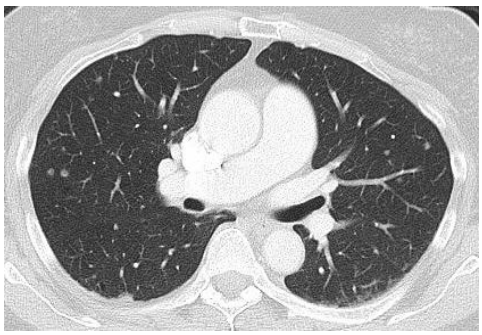

Fig. 1.Computed tomography scan of the chest demonstrates multiple sub-centimetre pulmonary nodules in both lungs.

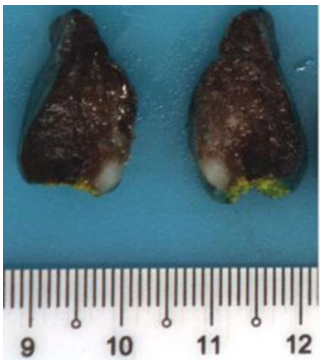

Fig. 2. Cut sections of the lung showing circumscribed whitish nodules.

The patient eventually underwent a video-assisted thoracoscopic (VATS) wedge resection of the right middle and lower lobes, which showed multiple small circumscribed firm whitish nodules (Fig. 2). Histologic findings showed circumscribed nodules with surrounding lung parenchyma (Fig. 3A), composed of a proliferation of interlacing fascicles of bland spindle cells featuring cigar-shaped nuclei with eosinophilic fibrillary cytoplasm, accompanied by a few entrapped tubules (Fig. 3B). Immunohistochemistry showed strong and diffuse staining for smooth muscle marker caldesmon (Fig. 3C) and oestrogen receptor (Fig. 3D) in the spindle cells. Ki-67 immunolabelling highlighted a very low proliferation index (F).

What is the diagnosis?

A. Miliary tuberculosis
B. Metastatic lung cancer
C. Sarcoidosis
D. Benign metastasising leiomyoma
E. Nodular pulmonary amyloidosis

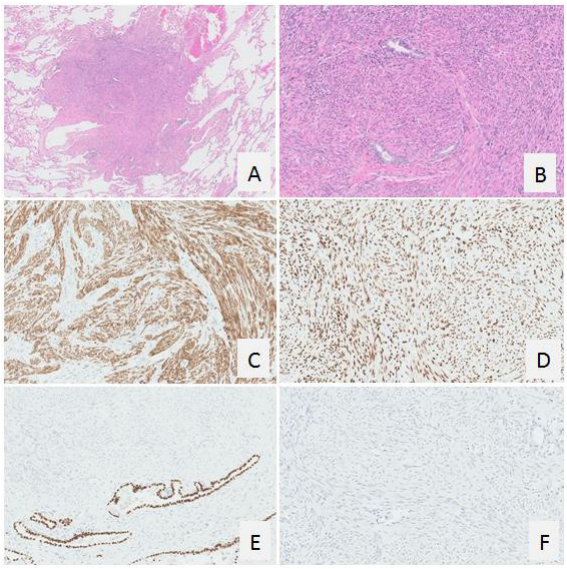

Fig. 3. A) Hematoxylin and eosin stain, x1; B) Hematoxylin and eosin stain, x10; C) Immunohistochemical stain positive for smooth muscle marker caldesmon and D) oestrogen receptor in the spindle cells; E) Entrapped tubules lined by TTF-1 positive bronchial epithelial cells; and F) Ki-67 immunolabelling demonstrated a very low proliferation index.

Answer: D

Discussion

Multiple pulmonary nodules in a patient with a strong family history of cancer and previous exposure to a close contact with pulmonary tuberculosis raised suspicion for an undiagnosed malignancy with lung metastases, or infections like tuberculosis. The PET-CT scan did not reveal any primary malignancy. The resected lung specimen was negative for bacterial, mycobacterial and fungal cultures. There was no evidence from the history or physical examination to suggest other differentials including inflammatory processes like sarcoidosis, rheumatoid nodules, nodular pulmonary amyloidosis and granulomatosis with polyangiitis.

A final diagnosis of benign metastasising leiomyoma (BML) was established based on the histopathological findings of multiple smooth muscle nodules found in the lungs. Leiomyosarcoma is not likely given the bland nature of the spindle cells, absence of necrosis and mitotic activity, as well as a low Ki-67 index. BML may closely resemble lymphangioleiomyomatosis (LAMS), but can be differentiated from the latter using immunohistochemical stain with melanocytic markers such as human melanoma black (HMB-45), which was negative in our patient. Multiple pulmonary fibroleiomyomatous harmatomas is another consideration with similar histopathological features, but the given history of a previous hysterectomy for fibroids would favour a diagnosis of BML in our patient.

Several hypotheses have been proposed to explain the pathogenesis of BML, the most widely accepted of which refers to these lesions as haematogenous metastases from histologically benign uterine tumours. A majority of women with BML underwent previous myomectomy or hysterectomy, raising the possibility of surgically induced vascular spread. Some authors suggest BML represents lung metastases from low grade leiomyosarcoma. Others postulate a multifocal smooth muscle proliferation theory, but the presence of oestrogen and progesterone receptors, as well as positive bcl-2 expression in most reported cases of BML does not support this notion. Moreover, studies have demonstrated that BMLs and uterine leiomyomas are clonally related.[1]

Most patients with BML remain asymptomatic although some rapidly progress to respiratory failure and death. Management would depend on the extent and progression of disease, hormone receptor positivity and age of the patient. Asymptomatic patients with stable lung lesions may not require treatment. Patients with solitary enlarging lung lesions are recommended for primary surgical excision. Those with progressive disease or unresectable lesions with positive expression of oestrogen receptors should be considered for hormonal manipulation via surgical oophorectomy or pharmacological means, such as selective oestrogen receptor modulator therapy, long acting gonadotropin releasing hormone (GnRH) analogues in combination with aromatase inhibitors.[2] Spontaneous regression of lesions due to the effects of natural hormonal changes after menopause has been reported.[3] Our patient received no further treatment but she remained on surveillance with 3-monthly chest radiographs, and was scheduled for a repeat CT chest after 12 months.

This case illustrates benign metastasising leiomyoma as an important differential to consider in patients with a history of fibroids and uterine surgery who present with multiple pulmonary nodules. VATS wedge resection of the lung is a useful means to obtain tissue for diagnosis. Although most cases follow an indolent course of progression, there is potential for some to develop progressive respiratory failure especially in premenopausal patients. Surgical resection and anti-oestrogen hormonal therapy are recommended treatment options for patients with progressive disease.

REFERENCES

1. Patton KT, Cheng L, Papavero V, Blum MG, Yeldandi AV, Adley BP, et al. Benign metastasizing leiomyoma: clonality, telomere length and clinicopathologic analysis. Mod Pathol 2006;19:130-40.
2. Lewis EI, Chason RJ, DeCherney AH, Armstrong A, Elkas J, Venkatesan AM. Novel hormone treatment of benign metastasizing leiomyoma: an analysis of five cases and literature review. Fertil Steril 2013;99:2017-24.
3. Arai T, Yasuda Y, Takay T, Shibayama M. Natural decrease of benign metastasizing leiomyoma. Chest 2000;117:921-2.

Ken CH Lee, [1]*MBBS, MRCP*, Kah Weng Lau, [2]*DPhil (Oxon)*

[1]Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Singapore
[2]Department of Pathology, Singapore General Hospital, Singapore

Address for Correspondence: Dr Ken Lee Cheah Hooi, Department of Respiratory and Critical Care Medicine, Singapore General Hospital, 20 College Road, Singapore 169856.
Email: ken.lee.c.h@sgh.com.sg