



AAMS

Annals of the Academy of Medicine, Singapore

MCI(P) 004/11/2013

VOLUME 43

NUMBER 5

FREE PAPERS

MAY 2014



Reproduced with permission from:
Hu Min Sheng

*"And pluck till time and times are done,
The silver apples of the moon..."*

From: Song of Wandering Aengus (1899)
WB Yeats (1965 – 1939)
Irish poet

CONTENTS

Editorial

- 248 **Schizophrenia: No Health Without Physical Health**

Jimmy Lee, Tih-Shih Lee, Gary Remington

Original Articles

- 250 **Use of Endobronchial Ultrasound-guided Transbronchial Needle Aspiration (EBUS-TBNA) in the Diagnosis of Granulomatous Mediastinal Lymphadenopathy**

Su Ying Low, Mariko S Koh, Thun How Ong, et al

- 255 **Systemic Candidiasis in Extremely Low Birthweight (ELBW) Neonates Despite the Routine Use of Topical Miconazole Prophylaxis: Trends, Risk Factors and Outcomes over an 11-Year Period**

Bhavani Sriram, Pratibha K Agarwal, et al

- 263 **The Looi Suture Technique for Anchoring the Lateral Tarsal Strip to the Lateral Orbital Wall**

Joy BM Chan, Audrey LG Looi

Review Article

- 267 **The Golden Hours in Paediatric Septic Shock—Current Updates and Recommendations**

Shu Ling Chong, Gene YK Ong, et al

Clinical Update

- 275 **Anticoagulation Needs in Asians with Atrial Fibrillation: A Mythbuster**

Zeenathnisa M Aribou, Adrian Mondry

Please see inside Contents for the full list of articles.

Schizophrenia: No Health Without Physical Health

Jimmy Lee,^{1,2,3} MBBS, MMed, MCI, Tih-Shih Lee,⁴ MD, PhD, FRCPC, Gary Remington,^{3,5} MD, PhD, FRCPC

Introduction

Schizophrenia is a severe and chronic mental disorder, with onset routinely occurring in late adolescence. It is associated with the poorest outcomes among all described psychotic conditions, and there is currently no cure. However, effective treatments are available to mitigate some of the psychiatric symptoms, and more recent studies have suggested that outcome in schizophrenia may not be as pessimistic as once thought. For example, we now know from longer-term follow-up studies that about one-third of individuals with schizophrenia can achieve recovery at some point over a 10-year interval.¹

It remains, though, that schizophrenia is for many a debilitating illness. The recently completed Global Burden of Disease Study (2010) ranked schizophrenia as one of the 5 leading causes of disability among all mental and substance use disorders. Notably, schizophrenia appeared to make a larger contribution to years lived with disability (YLD) than years of life lost (YLL) because mental disorders are rarely fatal. However, what is not considered in the computation of burden is the increased risk of physical illnesses and consequent reduced life expectancy frequently observed in individuals with schizophrenia. The unfortunate reality is that individuals with schizophrenia are at greater risk for medical illnesses and chronic medical conditions.² All these exact significant burden with a consequent impact on morbidity and mortality.

Schizophrenia and Mortality

The life expectancy for individuals with schizophrenia has been estimated to be 20% shorter, which translates to about 15 years less than the general population.³ Deaths from natural causes account for up to 63% of the excess mortality.⁴ Reflecting this, mortality from digestive, infectious and respiratory diseases has been reported to range from 4- to 5-fold higher than the general population. Paradoxically, mortality rates for schizophrenia have increased in recent decades, contrary to what is observed

in the general population.⁵

These statistics are sobering, and while one can argue that they were not obtained from Singapore there is no reason to believe that Singapore bucks the global trend. In fact, data gathered locally in recent years point to increased rates of obesity, metabolic disorders and higher cardiovascular risk in individuals with schizophrenia.⁶⁻⁸ In short, these results suggest that the local population would not be any different from other countries.

Possible Reasons for Increased Mortality

When we examine the possible reasons for the mortality gap, several uncomfortable findings emerge. Mortality from cardiovascular causes account for the greatest majority, and schizophrenia has been linked to increased cardiovascular risks. Reasons for this increased risk included lifestyle and dietary factors, inherent genetic vulnerability and psychotropic medications. However, these reasons might be insufficient to explain the non-cardiovascular mortality causes.

Schizophrenia is a highly stigmatised mental disorder that has often been misunderstood by the public as well as healthcare workers not practising in the mental health field. Could this misunderstanding and stigma act as an invisible barrier when individuals with schizophrenia attempt to access care? This does not diminish the fact that access to care is a 2-way street. From the patients' perspective, their ability to be aware that something warrants medical attention and/or to communicate their concerns clearly to the healthcare provider highlights possible opportunities where this might go awry. Conversely, from the clinicians' perspective, one has to be mindful of diagnostic overshadowing, whereby physical symptoms are misattributed to mental illnesses.⁹ This is an understudied area, deserving greater attention, as cognitive biases of this sort can be addressed.

There is, in fact, evidence that individuals with schizophrenia receive suboptimal medical care. A recent meta-analysis concluded that such individuals (which

¹Department of General Psychiatry 1, Institute of Mental Health, Singapore

²Office of Clinical Sciences, Duke-NUS Graduate Medical School, Singapore

³Schizophrenia Division, Centre for Addiction and Mental Health, Canada

⁴Neuroscience & Behavioral Disorders, Duke-NUS Graduate Medical School, Singapore

⁵Department of Psychiatry, University of Toronto, Canada

Address for Correspondence: Dr Jimmy Lee, Department of General Psychiatry, Institute of Mental Health, 10 Buangkok View, Singapore 539747.

Email: jimmy_lee@imh.com.sg

includes those with other severe mental illnesses) are prescribed significantly lower quantities of several common medications, especially cardiovascular medications.¹⁰ Along similar lines, another study found that individuals with mental illnesses fared poorer in all measured parameters of quality of diabetes care received.¹¹ When we look at preventive medical care, the evidence once again points to individuals with mental illnesses receiving lower rates of preventive services.¹²

The above highlights not only a treatment gap in physical healthcare for schizophrenia, but a glaring disparity in most aspects of medical care provided to this vulnerable group. As psychiatrists, it behooves us to look for ways to close this gap by highlighting these pertinent issues and acting as patient advocates. Particularly with the severely mentally ill, it is all too easy to focus only on the psychiatric symptoms when, in fact, they warrant the same attention to medical risks as their non-psychiatric counterparts. We expect no less from medical practitioners and have gone to considerable lengths to ensure that they screen for psychiatric symptoms.

As noted, many of the highlighted studies relate not just to schizophrenia, but to most mental illnesses. The mind and body are not separate—mental and medical health care are bi-directional and should be seen as such across all levels of training. While gains have been made, it remains that too often the different disciplines work in parallel when closer collaboration between psychiatrists, family physician and medical specialist would ensure better and more timely care in both directions.

To this end, alternative models of care delivery need to be considered and evaluated. One such alternative is collocation of medical clinics with mental health services, a strategy that reduces the physical barrier to care access and can allow for training a dedicated team with tailored preventive care algorithms. Evidence is already in place to support such a strategy, indicating improved quality of preventive medical care and, more importantly, outcomes of medical care.¹³

Conclusion

It may well be the case that psychiatry has contributed to the present situation, divesting itself of attention to medical care but, at the same time, not ensuring alliances that would address this gap are in place. In an environment that fosters subspecialisation, it is not even so surprising that care would be partitioned. Now clearly recognised, though, it is time to address this service gap and disparity, advocating and working collaboratively with our medical counterparts to provide equitable care for this vulnerable group.

Acknowledgements

Dr Jimmy Lee is supported by the Singapore Ministry of Health's National Medical Research Council under its Transition Award (Grant No.: NMRC/TA/002/2012).

REFERENCES

1. Austin SF, Mors O, Secher RG, Hjorthøj CR, Albert N, Bertelsen M, et al. Predictors of recovery in first episode psychosis: the OPUS cohort at 10 year follow-up. *Schizophr Res* 2013;150:163-8.
2. Leucht S, Burkard T, Henderson J, Maj M, Sartorius N. Physical illness and schizophrenia: a review of the literature. *Acta Psychiatr Scand* 2007;116:317-33.
3. Hennekens CH. Increasing global burden of cardiovascular disease in general populations and patients with schizophrenia. *J Clin Psychiatry* 2007;68 Suppl 4:4-7.
4. Harris EC, Barraclough B. Excess mortality of mental disorder. *Br J Psychiatry* 1998;173:11-53.
5. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch Gen Psychiatry* 2007;64:1123-31.
6. Lee J, Nurjono M, Wong A, Salim A. Prevalence of metabolic syndrome among patients with schizophrenia in Singapore. *Ann Acad Med Singapore* 2012;41:457-62.
7. Tay YH, Nurjono M, Lee J. Increased Framingham 10-year CVD risk in Chinese patients with schizophrenia. *Schizophr Res* 2013;147:187-92.
8. Lee J, Seow C, Wong S, Govindasamy A, Quek E, Phang A, et al. Annual Review Clinic: A chronic disease management model of care for schizophrenia and delusional disorder in Singapore. *ASEAN Journal of Psychiatry* 2013;14.
9. Jones S, Howard L, Thornicroft G. 'Diagnostic overshadowing': worse physical health care for people with mental illness. *Acta Psychiatr Scand* 2008;118:169-71.
10. Mitchell AJ, Lord O, Malone D. Differences in the prescribing of medication for physical disorders in individuals with v. without mental illness: meta-analysis. *Br J Psychiatry* 2012;201:435-43.
11. Frayne SM, Halanych JH, Miller DR, Wang F, Lin H, Pogach L, et al. Disparities in diabetes care: impact of mental illness. *Arch Intern Med* 2005;165:2631-8.
12. Druss BG, Rosenheck RA, Desai MM, Perlin JB. Quality of preventive medical care for patients with mental disorders. *Medical Care* 2002;40:129-36.
13. Druss BG, Rohrbach RM, Levinson CM, Rosenheck RA. Integrated medical care for patients with serious psychiatric illness: a randomized trial. *Arch Gen Psychiatry* 2001;58:861-8.

Use of Endobronchial Ultrasound-guided Transbronchial Needle Aspiration (EBUS-TBNA) in the Diagnosis of Granulomatous Mediastinal Lymphadenopathy

Su Ying Low, ¹*BMBCh*, Mariko S Koh, ¹*MBBS*, Thun How Ong, ¹*MBBS*, Ghee Chee Phua, ¹*MBBS*, Devanand Anantham, ¹*MBBS*

Abstract

Introduction: This study assessed the clinical utility of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for the diagnosis of suspected granulomatous mediastinal lymphadenopathy. **Materials and Methods:** Retrospective chart review of all patients who underwent EBUS-TBNA for suspected granulomatous mediastinal lymphadenopathy at Singapore General Hospital between December 2008 and December 2011 inclusive. **Results:** Over a period of 3 years, a total of 371 patients underwent EBUS-TBNA of whom 33 (9%) had the procedure performed for evaluation of suspected granulomatous mediastinal lymphadenopathy — 18 for suspected tuberculosis (TB) and non-tuberculous mycobacterial (NTM) lymphadenitis, and 15 for suspected sarcoidosis. EBUS-TBNA was diagnostic in 9 of the 13 patients with a final diagnosis of TB/NTM. EBUS-TBNA cultures were positive in 6 of them (46%), 1 showed acid-fast bacilli (AFB) although cultures were negative, and 2 had necrotising granulomatous inflammation from EBUS-TBNA biopsies and sputum cultures grew TB. EBUS-TBNA was diagnostic in 9 of the 14 patients with a final diagnosis of sarcoidosis through histology showing non-caseating granulomatous inflammation. The sensitivities of EBUS-TBNA for diagnosis of TB/NTM, sarcoidosis and overall granulomatous mediastinal lymphadenopathy were 69%, 64%, 64%; the negative predictive values were 56%, 17%, 33%; and accuracies were 78%, 67%, 70%, respectively. **Conclusion:** EBUS-TBNA can be useful in the diagnosis of suspected granulomatous mediastinal lymphadenopathy with sensitivities and accuracies of >60%.

Ann Acad Med Singapore 2014;43:250-4

Key words: Lymphadenitis, Non-tuberculous mycobacterial, Sarcoidosis, Tuberculosis

¹Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Singapore

Address for Correspondence: Dr Su Ying Low, Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Outram Road, Singapore 169608.

Email: low.su.ying@sgh.com.sg

Use of Endobronchial Ultrasound-guided Transbronchial Needle Aspiration (EBUS-TBNA) in the Diagnosis of Granulomatous Mediastinal Lymphadenopathy

Su Ying Low, ¹*BMBCh*, Mariko S Koh, ¹*MBBS*, Thun How Ong, ¹*MBBS*, Ghee Chee Phua, ¹*MBBS*, Devanand Anantham, ¹*MBBS*

Abstract

Introduction: This study assessed the clinical utility of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for the diagnosis of suspected granulomatous mediastinal lymphadenopathy. **Materials and Methods:** Retrospective chart review of all patients who underwent EBUS-TBNA for suspected granulomatous mediastinal lymphadenopathy at Singapore General Hospital between December 2008 and December 2011 inclusive. **Results:** Over a period of 3 years, a total of 371 patients underwent EBUS-TBNA of whom 33 (9%) had the procedure performed for evaluation of suspected granulomatous mediastinal lymphadenopathy — 18 for suspected tuberculosis (TB) and non-tuberculous mycobacterial (NTM) lymphadenitis, and 15 for suspected sarcoidosis. EBUS-TBNA was diagnostic in 9 of the 13 patients with a final diagnosis of TB/NTM. EBUS-TBNA cultures were positive in 6 of them (46%), 1 showed acid-fast bacilli (AFB) although cultures were negative, and 2 had necrotising granulomatous inflammation from EBUS-TBNA biopsies and sputum cultures grew TB. EBUS-TBNA was diagnostic in 9 of the 14 patients with a final diagnosis of sarcoidosis through histology showing non-caseating granulomatous inflammation. The sensitivities of EBUS-TBNA for diagnosis of TB/NTM, sarcoidosis and overall granulomatous mediastinal lymphadenopathy were 69%, 64%, 64%; the negative predictive values were 56%, 17%, 33%; and accuracies were 78%, 67%, 70%, respectively. **Conclusion:** EBUS-TBNA can be useful in the diagnosis of suspected granulomatous mediastinal lymphadenopathy with sensitivities and accuracies of >60%.

Ann Acad Med Singapore 2014;43:250-4

Key words: Lymphadenitis, Non-tuberculous mycobacterial, Sarcoidosis, Tuberculosis

Introduction

The clinical utility and safety of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in the diagnosis and mediastinal staging of patients with non-small cell lung has been well established with diagnostic accuracies reported at 85% to 100%, and a negative predictive value of 11% to 97.4%.¹ Of all the other conditions, sarcoidosis has been the most extensively studied, and publications have reported diagnostic sensitivities of EBUS-TBNA of 79.5% to 93%.²⁻¹⁰ These studies were done in patients with a high pretest probability of sarcoidosis and in countries with an incidence rate of 1 to 50 per 100,000, and prevalence rate of 3 to 200 per 100,000

population.¹¹ Published data on tuberculous mediastinal lymphadenopathy are scarce — one report described the utility of EBUS-TBNA in the diagnosis of tuberculosis in 2 retroviral patients with mediastinal lymphadenopathy for evaluation,¹² whilst 2 other studies have shown sensitivities of EBUS-TBNA for diagnosis of tuberculous mediastinal lymphadenopathy of 84.2% (19 patients) and 94% (156 patients).^{9,13} In geographic areas where tuberculosis (TB) is endemic, it can be clinically challenging to distinguish between TB and thoracic sarcoidosis as both may present similarly with mediastinal and hilar lymphadenopathy with or without systemic manifestations of cough, fever,

¹Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Singapore

Address for Correspondence: Dr Su Ying Low, Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Outram Road, Singapore 169608.

Email: low.su.ying@sgh.com.sg

and weight loss. In Singapore, the incidence of TB is 35 per 100,000 and that of sarcoidosis is 0.56 per 100,000 population.¹⁴ It would be imperative to differentiate between these 2 conditions as therapeutic management is markedly different. As such, this study set out to evaluate the clinical utility of EBUS-TBNA for suspected granulomatous mediastinal lymphadenopathy at our institution.

Materials and Methods

A retrospective chart review was carried out on all consecutive patients who underwent EBUS-TBNA for suspected granulomatous mediastinal lymphadenopathy at the Singapore General Hospital, a tertiary care university-affiliated teaching hospital, between December 2008 and December 2011 inclusive. Completeness of data were ensured by a centralised database that was set up at the time of introduction of EBUS-TBNA to our institution. The database utilised billing to track procedures. All patients had a computed tomography (CT) of the thorax done prior to EBUS-TBNA.

EBUS-TBNA was performed by attending respiratory physicians trained and experienced in this procedure under local anaesthesia with conscious sedation (midazolam and fentanyl). Local anaesthesia was attained using nebulised 1% lignocaine solution (4 mL) and 4% lignocaine solution sprayed into the pharynx (4 mL). Bolus doses of 2 mL 1% lignocaine were administered topically to the airway via the working channel of the bronchoscope as needed. Patients were monitored throughout the procedure by electrocardiogram (ECG), pulse oximetry and blood pressure. A linear array bronchoscope (BF-UC260F-OL8, Olympus, Tokyo, Japan) was introduced via the oral route and used to perform ultrasonic examination. A dedicated 22-gauge needle (NA-201SX-4022, Olympus, Tokyo, Japan) was used to perform biopsies of the pathology in question. Typically, 2 needle passes were performed at each lymph node station with at least 1 core specimen obtained. After obtaining a sample, the needle was withdrawn from the working channel of the bronchoscope and the stylet introduced to expel the core specimen out onto a filter paper which was then put into a bottle of formalin for histological evaluation. The stylet was then removed and 1 mL of normal saline followed by air was introduced into the needle to expel any remaining material into a bottle of normal saline for microbiological evaluation. Rapid on-site evaluation (ROSE) was not utilised routinely. Standard haematoxylin and eosin (H&E) stain was used in processing the histological specimens. Microbiological specimens were sent to the Central Tuberculosis Laboratory, Singapore General Hospital, for identification of acid-fast bacilli (AFB) and mycobacteria cultures. We did not routinely use polymerase chain reaction (PCR) to detect mycobacterium

tuberculosis. Patients whose histology from core specimens of the lymph nodes showed necrotising granulomatous inflammation, and/or lymph node aspirate microbiology positive for AFB and mycobacteria culture were considered to have a diagnostic EBUS-TBNA evaluation for TB/NTM mediastinal lymphadenitis. Patients whose histology from the core specimens showed non-caseating granulomatous inflammation with negative microbiology were considered to have a diagnostic EBUS-TBNA evaluation for sarcoidosis. Statistical analysis was done with SPSS 16 statistical software (SPSS Inc, Chicago, Illinois). The study was approved by the Singhealth Centralized Institutional Review Board (2008/458/B).

Results

Over a period of 3 years, a total of 371 patients underwent EBUS-TBNA whose indications are shown in Table 1. Baseline characteristics and clinical presentations of the 33 patients with suspected granulomatous mediastinal lymphadenopathy (18 patients with suspected TB lymphadenitis, 15 with suspected sarcoidosis) are shown in Table 2. A total of 49 lymph node stations were sampled whose characteristics are shown in Table 3. Core biopsies were attained in 45/49 (92%) of the lymph nodes.

EBUS-TBNA results for suspected TB/NTM lymphadenitis are shown in Table 4. Of the 9 patients in whom EBUS-TBNA was diagnostic, EBUS-TBNA cultures were positive in 6 patients — 5 grew mycobacterium tuberculosis complex (MTC), and 1 had mycobacterium avian complex (MAC). Two of these 6 patients were HIV positive. The remaining 3 patients had negative EBUS-TBNA cultures. One patient's EBUS-TBNA showed AFB but cultures were negative. This patient was HIV positive and further biopsy of a cervical lymph node grew MAC. The last 2 patients had necrotising granulomatous inflammation from EBUS-TBNA biopsies and sputum cultures were

Table 1. Indications for EBUS-TBNA

Indication	No. of Patients (%)
Suspected or known lung cancer and known cancer with suspected lung metastases	293 (79)
Suspected granulomatous mediastinal lymphadenopathy	33 (9)
Mediastinal lymphadenopathy for evaluation	25 (7)
Mediastinal lymphadenopathy in patients with underlying interstitial lung disease	8 (2)
Suspected lymphoma	7 (2)
Thyroid mass	2 (0.5)
Probable bronchogenic cyst	2 (0.5)
Mediastinal mass of uncertain aetiology	1 (0.3)

EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration

Table 2. Baseline Characteristics and Clinical Presentations of 33 Patients who Underwent EBUS-TBNA for Suspected Granulomatous Mediastinal Lymphadenopathy

Characteristics	No. of Patients (%)
Age (years)	47 ± 18
Male	18 (54.5)
Fever	16 (48.5)
Weight loss	12 (36.4)
Cough	18 (54.5)
Dyspnoea	7 (21.2)
Rash	6 (18.2)
Arthralgia/arthritis	3 (9.1)
Uveitis	3 (9.1)
CT thorax findings	
Lung parenchymal abnormalities	1 (3)
Intrathoracic lymphadenopathy	8 (24.2)
Parenchymal abnormalities and lymphadenopathy	24 (72.7)
Median follow-up duration (months, range)	11 (0.5 to 36)

EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration; CT: Computed tomography

Table 3. Characteristics of the 49 Lymph Nodes Biopsied

Variable	Number
Median size of lymph node (mm, range)	17 (8 to 30)
Median number of passes per lymph node (n, range)	2 (1 to 5)
Lymph node location	(n, %)
2R	2 (4.1)
4R	16 (32.7)
4L	3 (6.1)
7	21 (42.9)
10R	3 (6.1)
10L	1 (2)
11R	2 (4.1)
11L	1 (2)

eventually positive for MTC. They both tested negative for HIV. All cultures of MTC were sensitive to first-line anti-tuberculous drugs. In the 4 patients in whom EBUS-TBNA was non-diagnostic for TB/NTM lymphadenitis, histology from 2 showed lymphocytes, and the other 2 showed necrotic material.

EBUS-TBNA results for suspected sarcoidosis are shown in Table 4. EBUS-TBNA evaluation for sarcoidosis was considered diagnostic if the histology from core specimens of the lymph nodes showed non-caseating granulomatous inflammation and microbiology was negative for mycobacterial disease. In the 5 patients in whom EBUS-TBNA was non-diagnostic, histology was non-diagnostic in 2, and showed lymphocytes in 3 of them.

The sensitivities of EBUS-TBNA for diagnosis of TB/NTM, sarcoidosis, and overall granulomatous mediastinal lymphadenopathy were 69%, 64%, 64%, the negative predictive values were 56%, 17%, 33%, and diagnostic accuracies were 78%, 67%, 70%, respectively. We had no false positives in our study and there were no major complications requiring further intervention from the procedure.

Discussion

The overall sensitivity, negative predictive value, and diagnostic accuracy of EBUS-TBNA in this cohort of patients were 64%, 33%, and 70%, respectively. This is slightly lower than a previous study on granulomatous mediastinal lymphadenopathy which reported a sensitivity, negative predictive value, and diagnostic accuracy of 81%, 43%, and 83%, respectively,⁹ but in agreement with the general consensus that EBUS-TBNA is less accurate in conditions not pertaining to mediastinal staging of lung cancer. In the subgroup of patients with sarcoidosis and TB/NTM mediastinal lymphadenitis, we found sensitivities, negative predictive values, and diagnostic accuracies of 64%, 17%, 67%, and 69%, 56%, 78%, respectively. This whilst lower than previous reports,^{2-10,12,13} still enabled a definitive diagnosis to be attained in a significant proportion of patients without subjecting them to more invasive investigations which would entail the risks of general anaesthesia, surgical morbidity and mortality, and possible chronic tuberculous sinus formation.¹⁵

Our comparative lower diagnostic yield could be attributable to the fact that previous studies were largely from dedicated interventional pulmonary units where EBUS-TBNA procedure was performed by world experts. In some cases, the procedure was performed via rigid endoscopy on patients under general anaesthesia.⁷ The endoscopists involved in our study, although experienced and trained in EBUS-TBNA, are likely to be more reflective of the practice standard that is more widely available. Another reason for our lower diagnostic yield could be due to the fact that we only used histology without cytology for the diagnosis of granulomatous inflammation. The histopathological hallmark of granulomatous lymphadenitis is the identification of granulomas which are composed of epithelioid and giant cells with or without central necrosis. The use of cytological assessment of lymph node aspirates is more controversial because whilst it may demonstrate epithelioid histiocytes in a background of lymphocytes and plasma cells, the absence of giant cells makes it less specific for true granulomatous disease,¹⁰ although the cytological diagnosis of sarcoidosis has been shown to be feasible.¹⁶ The addition of cytology to histology may be important especially for ROSE of specimen adequacy. Presence of granulomas

Table 4. EBUS-TBNA Results in the 18 Patients with Suspected TB/NTM Lymphadenitis and 15 Patients with Suspected Sarcoidosis

Final Diagnosis (n)	TB/NTM (13)	Not TB/NTM (5)	Sarcoidosis (14)	Not Sarcoidosis (1)
EBUS-TBNA diagnostic	9	0	9	0
EBUS-TBNA culture positive	6		0	
EBUS-TBNA histology	• 2 necrotising granulomatous inflammation • 3 necrotic • 1 lymphocytes			
EBUS-TBNA culture negative	3		9	
EBUS-TBNA histology	• 2 necrotising granulomatous inflammation • 1 necrotic, AFB smear positive			
EBUS-TBNA non-diagnostic	4	5	5	1
Final diagnosis based on:				
Bronchial washings	1 TB			
Transbronchial lung biopsy			1	
Mediastinoscopy	1 NTM			1 TB
Transthoracic needle biopsy		1 meliodosis		
Video-assisted thoracoscopic surgery		1 infected bronchogenic cyst		
Clinical and radiological follow-up	2 responded to empirical TB treatment	3 benign	4 showed lymph node stability (3 on treatment, 1 not)	

EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration; TB: Tuberculosis; NTM: Non-tuberculous mycobacteria; AFB: Acid-fast bacilli

on ROSE may prompt the endoscopist to consider diagnoses related to granulomatous inflammation, which may not have been a consideration initially and thus direct further investigations accordingly e.g. sending additional specimens for mycobacterial and fungal smears and cultures. However, we would also caution the over-reliance of ROSE cytology interpretation as granulomas and granulomatous inflammation are known to exist around malignancies such as cancer and lymphoma.¹⁰ Therefore, ROSE may be misleading in some situations. We acknowledge that perhaps the addition of cytological evaluation to our histologic one may have increased our EBUS-TBNA diagnostic yield. In spite of these shortcomings, our results still support the use of EBUS-TBNA as an initial mode of evaluation of suspected granulomatous mediastinal lymphadenopathy, and more invasive investigations should be reserved for cases with clinical doubt.

Previous studies have demonstrated that the diagnostic yield for sarcoidosis via EBUS-TBNA can be further improved by combining with random endobronchial and transbronchial lung biopsies.^{3,7,8,10} We had a similar finding where the addition of transbronchial lung biopsy increased our diagnostic sensitivity from 64% to 71%.

We were able to obtain a positive microbiological culture in 46%, and combined smear and culture positivity of 54%. This is similar to previously reported microbiological yield for EBUS-TBNA (culture 47%, smear and culture 53%),¹³ and compatible with other modalities such as mediastinoscopy (culture 41%),¹⁵ and fine needle aspirates of lymph nodes (culture 49%, smear and culture 57%).¹⁷ The low microbiological yield is postulated to reflect the variable bacillary load within lymph nodes.

The main limitation of our study is its small numbers and retrospective nature. Despite this, we were able to obtain comparable results with the published data. Recent studies have suggested that a bigger EBUS-TBNA needle (19-gauge or 21-gauge) may provide better histologic specimens for better characterisation of diseases including lymphoma and sarcoidosis.¹⁸⁻²⁰ We believe by adopting these practices, we will be able to further improve our diagnostic accuracy.

Conclusion

EBUS-TBNA has a lower diagnostic yield in patients who do not present with suspected or known lung cancer. The limited negative predictive value mandates that cases without a definitive diagnosis should undergo either

further investigation or clinico-radiological follow-up until resolution. Nevertheless, our study supports the use of EBUS-TBNA, by virtue of being a safe, minimally invasive, and an outpatient procedure, in the diagnosis of granulomatous mediastinal lymphadenopathy with a sensitivity and diagnostic accuracy of >60%, thereby obviating more invasive testing in a significant number of patients.

REFERENCES

- Varela-Lema L, Fernandez-Villar A, Ruano-Ravina A. Effectiveness and safety of endobronchial ultrasound-transbronchial needle aspiration: a systematic review. *Eur Respir J* 2009;33:1156-64.
- Oki M, Saka H, Kitagawa C, Tanaka S, Shimokata T, Kawata Y, et al. Real-time endobronchial ultrasound-guided transbronchial needle aspiration is useful for diagnosing sarcoidosis. *Respirology* 2007;12:863-8.
- Garwood S, Judson MA, Silvestri G, Hoda R, Fraig M, Doelken P. Endobronchial ultrasound for the diagnosis of pulmonary sarcoidosis. *Chest* 2007;132:1298-304.
- Wong M, Yasufuku K, Nakajima T, Herth FJF, Sekine Y, Shibuya K, et al. Endobronchial ultrasound: new insight for the diagnosis of sarcoidosis. *Eur Respir J* 2007;29:1182-6.
- Tremblay A, Stather DR, MacEachern P, Khalil M, Field SK. A randomized controlled trial of standard vs endobronchial ultrasonography-guided transbronchial needle aspiration in patients with suspected sarcoidosis. *Chest* 2009;136:340-6.
- Nakajima T, Yasufuku K, Kurosu K, Takiguchi Y, Fujiwara T, Chiyo M, et al. The role of EBUS-TBNA for the diagnosis of sarcoidosis – comparisons with other bronchoscopic diagnostic modalities. *Respir Med* 2009;103:1796-800.
- Tournoy KG, Bolly A, Aerts JG, Pierard P, De Pauw R, Leduc D, et al. The value of endoscopic ultrasound after bronchoscopy to diagnose thoracic sarcoidosis. *Eur Respir J* 2010;35:1329-35.
- Plit M, Pearson R, Havryk A, Da Costa J, Chang C, Glanville AR. Diagnostic utility of endobronchial ultrasound-guided transbronchial needle aspiration compared with transbronchial and endobronchial biopsy for suspected sarcoidosis. *Intern Med J* 2012;42:434-8.
- Caglayan B, Salepci B, Fidan A, Kiral N, Comert SS, Yavuzer D, et al. Sensitivity of convex probe endobronchial sonographically guided transbronchial needle aspiration in the diagnosis of granulomatous mediastinal lymphadenitis. *J Ultrasound Med* 2011;30:1683-9.
- Navani N, Booth HL, Kocjan G, Falzon M, Capitanio A, Brown JM, et al. Combination of endobronchial ultrasound-guided transbronchial needle aspiration with standard bronchoscopic techniques for the diagnosis of stage I and stage II pulmonary sarcoidosis. *Respirology* 2011;16:467-72.
- Hosoda Y, Yamaguchi M, Hiraga Y. Global epidemiology of sarcoidosis. What story do prevalence and incidence tell us? *Clin Chest Med* 1997;18:681-94.
- Steinfort DP, Johnson DF, Connell TG, Irving LB. Endobronchial ultrasound-guided biopsy in the evaluation of intrathoracic lymphadenopathy in suspected tuberculosis: a minimally invasive technique with a high diagnostic yield. *J Infect* 2009;58:309-11.
- Navani N, Molyneaux PL, Breen RA, Connell DW, Jepson A, Nankivell M, et al. Utility of endobronchial ultrasound-guided transbronchial needle aspiration in patients with tuberculous intrathoracic lymphadenopathy: a multicentre study. *Thorax* 2011;66:889-93.
- Anantham D, Ong SJ, Chuah KL, Fook-Chong S, Hsu A, Eng P. Sarcoidosis in Singapore: epidemiology, clinical presentation and ethnic differences. *Respirology* 2007;12:355-60.
- Farrow PR, Jones DA, Stanley PJ, Bailey JS, Wales JM, Cookson JB. Thoracic lymphadenopathy in Asians resident in the United Kingdom: role of mediastinoscopy in initial diagnosis. *Thorax* 1985;40:121-4.
- Kitamura A, Takiguchi Y, Kurosu K, Takigawa N, Saegusa F, Hiroshima K, et al. Feasibility of cytological diagnosis of sarcoidosis with endobronchial US-guided transbronchial aspiration. *Sarcoidosis Vasc Diffuse Lung Dis* 2012;29:82-9.
- Gupta SK, Chugh TD, Sheikh ZA, al-Rubah NA. Cytodiagnosis of tuberculous lymphadenitis. A correlative study with microbiologic examination. *Acta Cytol* 1993;37:329-32.
- Herth FJF, Morgan RK, Eberhardt R, Ernst A. Endobronchial ultrasound-guided miniforceps biopsy in the biopsy of subcarinal masses in patients with low likelihood of non-small cell lung cancer. *Ann Thorac Surg* 2008;85:1874-9.
- Nakajima T, Yasufuku K, Takahashi R, Shingyoji M, Hirata T, Itami M, et al. Comparison of 21-gauge and 22-gauge aspiration needle during endobronchial ultrasound-guided transbronchial needle aspiration. *Respirology* 2011;16:90-4.
- Herth FJF, Schuler H, Gompelmann D, Kahn N, Gasparini S, Ernst A, et al. Endobronchial ultrasound-guided lymph node biopsy with transbronchial needle forceps: a pilot study. *Eur Respir J* 2012;39:373-7.

Systemic Candidiasis in Extremely Low Birthweight (ELBW) Neonates Despite the Routine Use of Topical Miconazole Prophylaxis: Trends, Risk Factors and Outcomes over an 11-Year Period

Bhavani Sriram,¹ MBBS, MRCP (Paeds), Pratibha K Agarwal,¹ MD (Paeds), DNB (Paeds), Mmed (Paeds), Nancy WS Tee,² MBBS, FRCPA, Victor S Rajadurai,¹ MRCP, DCH, FAMS

Abstract

Introduction: This study aims to determine the incidence, trends of systemic candidiasis and meningitis in extremely low birthweight (ELBW) neonates (<1000 gms) despite the routine use of topical miconazole prophylaxis and to compare the risk factors, adverse outcomes and comorbidities with controls. **Materials and Methods:** Retrospective cohort study of ELBW neonates with systemic candidiasis and meningitis over an 11-year period (1997 to 2007). Matched case control analyses were performed to determine the risk factors and comorbidities which were severe intraventricular haemorrhage (IVH), severe retinopathy of prematurity (ROP), patent ductus arteriosus (PDA) requiring treatment, necrotising enterocolitis (NEC), chronic lung disease (CLD) and cholestatic jaundice. Mortality and end organ involvement secondary to systemic candidiasis were identified as adverse outcomes. **Results:** Of the 757 ELBW neonates, 51 (6.7%) had evidence of systemic candidiasis with a significant 3-fold increase in trend noted in 2007 as compared against 1997 (12.1% vs 3.8%) (RR 1.2, 95% CI, 1.06 to 1.36, $P < 0.001$). This corresponds to a significant increasing trend of preceding or co-existent bacterial blood stream infections (BSI) in neonates with systemic candidiasis (0% in 1997 vs 7.1% in 2007, RR 1.40, 95% CI, 1.04 to 1.25, $P = 0.005$). On logistic regression analysis, decreasing gestational age was an independent risk factor for systemic candidiasis (OR 2.0, 95% CI, 1.52 to 2.63, $P < 0.001$). Candida meningitis was detected in 4/38 (10.5%) and end organ involvement in 17 (33%). The organisms isolated were *Candida parapsilosis* 31 (61%), *Candida albicans* 17 (33%) and *Candida glabrata* 3 (5.8%). Significantly higher mortality was seen in cases when compared to controls 10/51 (19.6%) vs 76/706 (10.7%) (OR 2.02, 95% CI, 1.02 to 4.40, $P < 0.001$). **Conclusion:** Increasing trend in the incidence of systemic candidiasis despite routine use of topical miconazole prophylaxis is of concern and future studies comparing the use of systemic fluconazole versus oral nystatin may need to be considered.

Ann Acad Med Singapore 2014;43:255-62

Key words: Antifungal prophylaxis, Extremely preterm, Invasive candidiasis

¹Department of Neonatology, KK Women's and Children's Hospital, Singapore

²Department of Pathology and Laboratory Medicine, KK Women's and Children's Hospital, Singapore

Address for Correspondence: Dr Bhavani Sriram, Department of Neonatology, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899.
Email: Bhavani.Sriram@khh.com.sg

Systemic Candidiasis in Extremely Low Birthweight (ELBW) Neonates Despite the Routine Use of Topical Miconazole Prophylaxis: Trends, Risk Factors and Outcomes over an 11-Year Period

Bhavani Sriram,¹ MBBS, MRCP (Paeds), Pratibha K Agarwal,¹ MD (Paeds), DNB (Paeds), Mmed (Paeds), Nancy WS Tee,² MBBS, FRCPA, Victor S Rajadurai,¹ MRCP, DCH, FAMS

Abstract

Introduction: This study aims to determine the incidence, trends of systemic candidiasis and meningitis in extremely low birthweight (ELBW) neonates (<1000 gms) despite the routine use of topical miconazole prophylaxis and to compare the risk factors, adverse outcomes and comorbidities with controls. **Materials and Methods:** Retrospective cohort study of ELBW neonates with systemic candidiasis and meningitis over an 11-year period (1997 to 2007). Matched case control analyses were performed to determine the risk factors and comorbidities which were severe intraventricular haemorrhage (IVH), severe retinopathy of prematurity (ROP), patent ductus arteriosus (PDA) requiring treatment, necrotising enterocolitis (NEC), chronic lung disease (CLD) and cholestatic jaundice. Mortality and end organ involvement secondary to systemic candidiasis were identified as adverse outcomes. **Results:** Of the 757 ELBW neonates, 51 (6.7%) had evidence of systemic candidiasis with a significant 3-fold increase in trend noted in 2007 as compared against 1997 (12.1% vs 3.8%) (RR 1.2, 95% CI, 1.06 to 1.36, $P < 0.001$). This corresponds to a significant increasing trend of preceding or co-existent bacterial blood stream infections (BSI) in neonates with systemic candidiasis (0% in 1997 vs 7.1% in 2007, RR 1.40, 95% CI, 1.04 to 1.25, $P = 0.005$). On logistic regression analysis, decreasing gestational age was an independent risk factor for systemic candidiasis (OR 2.0, 95% CI, 1.52 to 2.63, $P < 0.001$). Candida meningitis was detected in 4/38 (10.5%) and end organ involvement in 17 (33%). The organisms isolated were *Candida parapsilosis* 31 (61%), *Candida albicans* 17 (33%) and *Candida glabrata* 3 (5.8%). Significantly higher mortality was seen in cases when compared to controls 10/51 (19.6%) vs 76/706 (10.7%) (OR 2.02, 95% CI, 1.02 to 4.40, $P < 0.001$). **Conclusion:** Increasing trend in the incidence of systemic candidiasis despite routine use of topical miconazole prophylaxis is of concern and future studies comparing the use of systemic fluconazole versus oral nystatin may need to be considered.

Ann Acad Med Singapore 2014;43:255-62

Key words: Antifungal prophylaxis, Extremely preterm, Invasive candidiasis

Introduction

Systemic candidiasis in extremely low birth weight (ELBW) neonates is associated with a high mortality, as well as short- and long-term morbidities. The incidence of systemic candidiasis in the very low birth weight neonates is less than 10% but it is higher in the ELBW cohort.¹ It varies in different centres with some reporting an increasing trend.^{2,3} Numerous risk factors predisposing to systemic candidiasis have been implicated. Extreme prematurity with relative immunodeficiency⁴ and presence of immature and fragile skin⁵ are considered as important host factors. Other risk factors are the use of third-generation cephalosporins,

H₂-receptor antagonists, parenteral steroids, prolonged ventilatory support, presence of central venous catheters, previous gastrointestinal (GI) surgery and prolonged hyperalimentation.⁶

Pre-existing fungal colonisation and increased density of colonisation of the skin and mucosal surfaces are significant risk factors for systemic disease.⁷ Strategies have focused on prevention of systemic disease from the colonised sites by use of topical antifungal agents with limited success.⁸ By comparison, prophylactic systemic antifungals have shown promising results.

¹Department of Neonatology, KK Women's and Children's Hospital, Singapore

²Department of Pathology and Laboratory Medicine, KK Women's and Children's Hospital, Singapore

Address for Correspondence: Dr Bhavani Sriram, Department of Neonatology, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899.
Email: Bhavani.Sriram@khh.com.sg

Mortality and end organ involvement secondary to systemic candidiasis still remains high but a declining trend is noted with improved neonatal care.⁹ In this study, we evaluated the incidence, trends and clinical presentation of ELBW neonates with systemic candidiasis and compared the risk factors, mortality and comorbidities in neonates with and without systemic candidiasis in our institution over an 11-year period.

Materials and Methods

Study population consisted of all ELBW neonates with evidence of systemic candidiasis/candida meningoencephalitis admitted to the neonatal intensive care unit (NICU) at KK Women's and Children's Hospital (KKH) Singapore, between January 1997 and December 2007. KKH is the largest tertiary perinatal centre in Singapore with approximately 12,000 deliveries annually. Control population included all ELBW neonatal survivors beyond 72 hours of life without systemic candidiasis. Maternal, perinatal and neonatal data were prospectively captured from a standardised very low birth weight (VLBW) database and review of case records. Approval was obtained from the hospital ethics committee.

Topical miconazole prophylaxis was used for all ELBW neonates commencing from the day of admission and continued until full enteral feeds were established. The preparation that is used in our institution is Daktarin oral gel™ (Miconazole 20 mg in 1 g), which is applied with an applicator to cover the mucosal surface of the oral cavity. Strict handwashing and hand hygiene measures were practised with periodic audits.

Antibiotic policy was based on customised antibiograms but neonates with presumed nosocomial infection would be initially treated with cloxacillin and an aminoglycoside pending antibiotic sensitivity. Neonates with confirmed bacterial blood stream infection (BSI) would be treated with 2 weeks of appropriate broad spectrum antibiotic therapy, or 3 weeks, if there was proven meningeal involvement in the presence of gram negative infections. Routine surveillance cultures for detecting fungal colonisation was not a practice in our institution.

Definitions

Systemic candidiasis was defined as isolation of candida species from a peripheral blood culture. Blood cultures were drawn between 3rd and 5th day after appropriate antifungal therapy to document clearance of systemic infection. Persistence of systemic candidiasis was defined as isolation of candida species from peripheral venous culture 10 days after the first isolate despite appropriate treatment. Mortality secondary to systemic candidiasis was

defined as death within one week of documented sepsis. Combined adverse outcomes analysed were mortality and end organ involvement secondary to systemic candidiasis. Evidence of end organ involvement was performed within 2 weeks after commencing therapy and involvement of the central nervous system, hepatobiliary system and kidneys were scanned by ultrasonography to look for evidence of fungal abscess. 2D echocardiography was done to look for vegetations. Ophthalmological evaluation was done to look for fungal chorioretinitis. Candida meningitis was diagnosed if the cerebrospinal fluid (CSF) showed pleocytosis or isolation of candida species from CSF cultures.

Antenatal risk factors analysed were use of antenatal steroids, presence of maternal chorioamnionitis, pregnancy induced hypertension and mode of delivery. Postnatal risk factors analysed were birthweight, gestation, Apgar scores at 1 and 5 minutes of age, need for intubation during resuscitation, surfactant therapy, presence of pneumothorax, presence of umbilical lines prior to the onset of sepsis, use of parenteral steroids and need for GI surgery, duration of ventilator support in the form of positive pressure ventilation and duration of percutaneously inserted central catheters (PICC). Presence of bacterial BSI either preceeding the onset of systemic candidiasis or occurring concomitantly was also evaluated. The risk factors evaluating the combined adverse outcomes were the types of candida species, presence of PICC beyond 48 hours of positive cultures and persistence of positive cultures beyond 10 days of appropriate therapy.

Associated comorbidities secondary to systemic candidiasis analysed were presence of chronic lung disease (CLD), severe intraventricular haemorrhage (IVH), necrotising enterocolitis (NEC), severe retinopathy of prematurity (ROP) and patent ductus arteriosus (PDA) requiring treatment. CLD was defined as requirement of supplemental oxygen at 36 weeks post-conceptual age indicating severe form of CLD.¹⁰ The Papile grading system was used to define the different grades of IVH.¹¹ Severe IVH was defined as Grade III/IV IVH. ROP was considered severe if grading by the paediatric ophthalmologist was Stage III ROP or presence of plus disease.¹² Necrotising enterocolitis (NEC) was graded using Bell's classification.¹³ Stage II or more was considered as a significant morbidity. Haemodynamically significant PDA confirmed by 2D echocardiography would be treated medically and failure of resolution would warrant surgical ligation. Duration of hospitalisation and duration of total parenteral nutrition (TPN) were also evaluated as associated comorbidities as there was an increased need for resource utilisation.

Amphotericin as a single agent was used for treatment of systemic candidiasis and combination of antifungal drugs (flucytosine, fluconazole) was used only in the presence of end organ involvement or persistence of cultures beyond

10 days of monotherapy. Amphotericin at 1 mg/kg/day was commenced and a cumulative dose of 20 mg was used in the absence of end organ involvement and 40 mg in the presence of end organ involvement.

Microbiology

In neonates with presumed sepsis, one millilitre of blood was drawn by a venipuncture using standardised sterile precautions. Blood for bacterial culture was inoculated into Bactec Paed (d2) blood culture vials and incubated for 5 days in Bactec 9240 (BD, USA), a continuous monitoring blood culture system. *Candida* isolates were identified using API 20C AUX (bioMerieux, France). The isolate was plated on cornmeal agar to determine its microscopic morphology.

Computerised data were analysed using SPSS software version 14. Categorical data were analysed using Fischer's exact test or chi-square tests and continuous data using Student's t-test. Parametric data were expressed as mean $\pm$ standard deviation and non-parametric data expressed as median (range). Logistic regression model was used for trend analysis and for predicting risk factors. Significance was declared at P values <0.05 and odds ratio with 95% confidence interval was expressed.

Results

There were a total of 757 ELBW neonates during the study period. Of them, 51 (6.7%) had systemic candidiasis with a total of 55 episodes (7.3%). The mean gestation and the mean birthweight of the study population were 24.5 ± 1.2 weeks (range, 23 to 29 weeks) and 673 ± 127 g (range, 390 to 1000 g) respectively. A 3-fold increase in the incidence of systemic candidiasis was noted from 3.8% in 1997 to

12.1% in 2007 and logistic regression analyses showed a significant increase in the trend of systemic candidiasis over the years (RR 1.2, 95% CI, 1.06 to 1.36, $P < 0.001$ (Fig. 1)). *Candida meningitis* was detected in 4/38 (10.5%) and 2 of them had evidence of cerebral abscess. Thirteen neonates had no cerebrospinal fluid (CSF) analyses done as they were critically ill. CSF analysis was performed between 2 to 18 days (median 5 days) in neonates with systemic candidiasis. The mean age of onset of sepsis was 20.4 ± 13.7 days (range, 7 to 60 days) and the mean duration to clearance of sepsis was 10.4 ± 5.4 days (range, 3 to 28 days).

Of the 51 cases, *C. parapsilosis* was the predominant organism isolated in 31 (61%), followed by *C. albicans* in 17 (33%) and *C. glabrata* in 3 (5.8%). Clinical presentation at the onset of illness was increased respiratory distress requiring ventilatory support in 48 (94%), hypotension requiring inotropes in 27 (54%), feed intolerance in 27 (52%) and neurological symptoms like lethargy and seizures in 4 (7.8%) cases.

Maternal, perinatal and neonatal demographic risk factors in the study and control groups are described in Table 1.

On univariate analysis, significant risk factors for systemic disease were maternal chorioamnionitis, need for intubation during resuscitation, lower birth weight and decreasing gestation, surfactant therapy, presence of pneumothorax, duration of umbilical lines prior to the onset of systemic candidiasis, need for GI surgery and bacterial blood stream infections. It is interesting to note that not only was there a significant increase in the presence of preceding or concomitant bacterial (BSI) in neonates with systemic candidiasis compared to controls 29 (51%) vs 166 (23.5%) (OR 4.2, 95% CI, 2.31 to 7.97, $P < 0.001$) but also a significant increase in trend in the incidence of bacterial

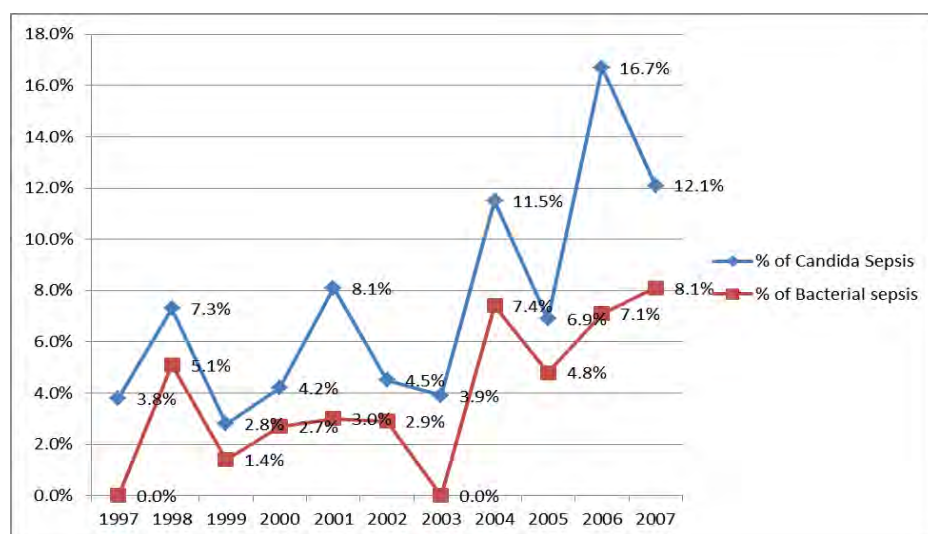


Fig. 1. Trends in the incidence of systemic candidiasis and comparison with the trend of preceding or co-existent bacterial BSI (January 1997 – December 2007).

Table 1. Patient Demographics and Risk Factors Associated with Systemic Candidiasis: Univariate Analysis

Risk Factors	Numbers	Cases (%)	Controls (%)	OR	95% CI	P Value
Number of cases	n = 757	n = 51	n = 706			
Maternal chorioamnionitis	735	25 (49)	212 (31)	2.1	(1.20 – 3.79)	0.008
Antenatal steroids	752	38(76)	521 (74)	1.1	(0.56 – 2.15)	0.78
Cesarean section	757	34 (67)	310 (44)	2.6	(1.40 – 4.65)	0.002
Maternal pregnancy-induced hypertension	754	4 (8)	163 (23)	0.3	(0.1 – 0.79)	0.037
Need for positive pressure ventilation	709	48 (94)	515 (78)	0.2	(0.07 – 0.73)	0.007
Apgar scores <7 at 5 minutes	750	37 (72)	563 (80)	0.6	(0.33 – 1.21)	0.168
Surfactant therapy	753	44 (86)	454 (65)	3.4	(1.52 – 7.73)	0.002
Birthweight (g) Mean ($\pm$ 2SD)	757	673 $\pm$ 127	810.47 $\pm$ 136.23	1.0	(0.991 – 0.996)	<0.001
Gestation (weeks) Mean ($\pm$ 2SD)	757	24 $\pm$ 1	26.81 $\pm$ 2.16	2.2	(1.4 – 2.8)	<0.001
Postnatal parenteral steroids	691	17 (44)	150 (23)	258	(1.33 – 4.99)	0.004
Presence of pneumothorax	755	14 (27)	72 (10)	3.3	(1.71 – 6.43)	<0.001
Gastrointestinal surgery	757	12 (24)	41 (5.8)	4.9	(2.27 – 10.7)	<0.001
Preceding or concomitant bacterial sepsis	757	29 (57)	166 (23.5)	4.2	(2.31 – 7.97)	<0.001
Duration of umbilical arterial catheter prior to the onset of sepsis (days) Mean ($\pm$ SD)	692	8 $\pm$ 5	5 $\pm$ 5	1.1	(1.04 – 1.14)	0.003
Duration of umbilical venous catheter prior to the onset of sepsis (days) Mean ($\pm$ SD)	696	6 $\pm$ 3	4 $\pm$ 2.9	1.2	(1.11 – 1.34)	<0.001
Duration of TPN (days) Mean ($\pm$ SD)	696	45.66 $\pm$ 29.38	28.39 $\pm$ 17	2.65	(22.49 – 12.06)	0.00
Duration of PICC (days) Mean ($\pm$ SD)	757	41 $\pm$ 25	27 $\pm$ 17	1.02	(1.02 – 1.04)	0.00
Duration of ventilatory support (days) Mean $\pm$ SD	750	49 $\pm$ 40	20 $\pm$ 29	1.01	(1.01 – 1.02)	0.00

OR: Odds ratio; TPN: Total parental nutrition; PICC: Peripherally inserted central catheter

BSI between 1997 and 2007 (0% vs 7%) (RR 1.14, 95% CI, 1.04 to 1.25, $P = 0.005$) (Fig. 1). There were 29 (57%) cases of bacterial BSI preceding or concomitantly occurring in neonates with systemic candidiasis. Gram-negative BSI occurred in 18/29 (62%), gram-positive in 7/29 (24%) and a combination of gram-positive and gram-negative organisms were present in 4/29 (14%). There is a preponderance of gram-negative organisms in this cohort with a corresponding use of broad spectrum antibiotics like the third-generation cephalosporins and the carbapenams. It was noted in our study that 36/51 (76%) of neonates with systemic candidiasis received broad spectrum antibiotics. In the control group, there were 166 (23.5%) cases of bacterial BSI of which 81/166 (49%) were gram-negative organisms, 70/166 (42%) were gram-positive and 15/166 (9%) were a combination of both. However, logistic regression analysis revealed that the only significant risk factor for predicting sepsis was decreasing gestational age (OR 2.0, 95% CI, 1.52 to 2.63, $P < 0.001$). Presence of pregnancy-induced hypertension appears to have protective effect 7.8% vs 23%, (OR 0.28, 95% CI, 0.1 to 0.79, $P \leq 0.01$).

In neonates with systemic candidiasis, the overall mortality was 16/51 (31%) but deaths secondary to systemic candidiasis occurred only in 10 neonates (19.6%). End organ involvement occurred in 17 (33%) neonates and the sites were hepatic abscesses in 4 (24%), renal fungal balls in 2 (12%), cerebral abscess in 2 (12%) and cavitatory lung lesions in 1 (6%) neonate; gastrointestinal perforation occurred in 8 (47%) neonates, of whom 6 had mycelia isolated from histopathology specimens resected during surgery. Risk factors associated with significant adverse outcomes (mortality secondary to systemic candidiasis and end organ involvement) were presence of *C. albicans* sepsis $P = 0.034$ (Table 2) and the presence of PICC beyond 48 hours of positive cultures ($P = 0.00$, OR 3.13, 95% CI, 1.10 to 7.92) (Table 3). Persistence of culture positivity >10 days despite appropriate antifungal treatment was not associated with a significant increase in mortality or end organ involvement in our series as the mean day of clearance of sepsis was 10.4 ± 5.4 days (OR 1.79, 95% CI, 1.97 to 6.45, $P = 0.46$). Thirty (59%) babies needed only amphotericin deoxycusate while 21(41%) cases needed

Table 2. Comparison of Types of *Candida* Species Predicting Adverse Outcomes

Adverse Outcomes	No. of Cases n = 51	<i>C. Albicans</i> n = 17 (35%)	<i>C. Parapsilosis</i> n = 31 (61%)	<i>C. Glabrata</i> n = 3 (4%)	P Value
Mortality secondary to systemic candidiasis	10 (19.6%)	6 (35%)	2 (6.5%)	2 (67%)	0.02
End organ involvement secondary to systemic candidiasis	17 (33%)	6 (35%)	10 (32%)	1 (34%)	0.45
Combined adverse outcomes	27 (53%)	12 (71%)	12 (39%)	3 (100%)	0.04

Table 3. Risk Factors for Predicting Adverse Outcomes Secondary to Systemic Candidiasis

Risk Factors for Predicting Adverse Outcomes Mortality n = 10 End Organ n = 17	Neonates with Systemic Candidiasis n = 51	Adverse Outcomes Present n = 27 (53%)	Adverse Outcomes not Present n = 24 (47%)	OR 95% CI	P Value
Removal of PICC <48 hours after culture positivity	22 (43%)	8/22 (36%)	14/22 (64%)	OR 3.12 95% CI, 1.10 – 7.92	P = 0.00
Removal of PICC >48 hours after culture positivity	29 (57%)	19/29 (66%)	10/29 (34%)		
Persistence of systemic candidiasis >10 days of appropriate therapy	28 (55%)	13/28 (46%)	15/28 (54%)	OR 1.79 95% CI, 1.97 – 6.45	P = 0.46
Clearance of systemic candidiasis <10 days after appropriate therapy	23 (45%)	14/23 (61%)	9/28 (39%)		

PICC: Peripherally inserted central catheter; OR: Odds ratio

Table 4. Comparison of Mortality and Comorbidities in ELBW Neonates With and Without Candidiasis

Mortality and Comorbidities	Numbers n = 757	Cases (%) n = 51	Controls (%) n = 706	OR	95% CI	P Value
Overall mortality	757	16 (31.3%)	76 (10.7%)	3.78	(1.906 – 7.474)	0.00
Mortality secondary to systemic candidiasis	757	10 (19.61%)	76 (10.7%)	2.02	(1.021 – 4.396)	0.009
Stage II and above NEC/GI perforation	757	12 (24%)	58 (8%)	3.43	(1.60 – 7.25)	0.00
PDA requiring treatment and surgical ligation	746	45 (90%)	442 (64%)	5.1	(2.02 – 13.19)	0.00
Severe IVH	755	11 (22%)	81 (12%)	2.1	(1.07 – 4.41)	0.028
Chronic lung disease at 36 weeks (in survivors)	689	28/35 (50%)	177/644 (25%)	10.5	(4.3 – 27)	0.001
Severe ROP (in survivors)	677	22/36 (61%)	123/641 (19%)	6.6	(3.29 – 13.30)	0.00
Duration of hospitalisation (days) Mean (± SD)		121 ± 78	97 ± 52	8.04	(8.48 – 40.06)	0.037
Cholestatic jaundice	756	26 (51%)	194 (28%)	2.74	(1.49 – 5.05)	0.005
Duration of TPN (days) Mean (± SD)	696	45.66 ± 29.38	28.39 ± 52.42	2.65	(22.49 – 12.06)	0.00

ELBW: Extremely low birth weight; NEC: Necrotising enterocolitis; GI: Gastrointestinal; IVH: Intraventricular haemorrhage; ROP: Retinopathy of prematurity; TPN: Total parental nutrition; OR: Odds ratio

a combination therapy with flucytosine/fluconazole for clearance of sepsis.

Neonates with systemic candidiasis had a significantly higher incidence of comorbidities such as CLD, severe IVH, PDA requiring treatment, NEC, cholestatic jaundice and severe ROP compared to controls (Table 4). Resource utilisation in the form of prolonged duration of TPN and duration of hospital stay were also significantly higher in those with systemic candidiasis.

Discussion

Despite significant improvement in the survival of VLBW neonates, the surviving neonates are immunocompromised and susceptible to systemic blood stream infections. *Candida* species is an emerging pathogen with *C. albicans* reported as the third most frequent organism in neonates with nosocomial sepsis.¹ In our institution, there was a significant rise in the trend of systemic candidiasis with an incidence of 3.7% in 1997 to 12.1% in 2007 despite the routine use of topical miconazole as a prophylactic agent. Except for a decline in the incidence in 2005 to 6.9%, there appears to be an increase noted since 2004. Bacterial BSI before the onset of systemic candidiasis is an important risk factor for systemic candidiasis.¹² We noted in our study that not only was there a significant increase in the incidence of preceding or concomitant BSI in neonates with systemic candidiasis when compared to controls 29 (56.9%) vs 166 (23.5%)) but also a significant increase in trend in the incidence of bacterial blood stream infections from 0% in 1997 to 7.1% in 2007. It is interesting to note that the incidence of gram-negative infections preceding or occurring concomitantly in those with systemic candidiasis was 62%, leading to the use of broad spectrum antibiotics. Though the antibiotic policy in our institution for nosocomial infection is cloxacillin and an aminoglycoside in the presence of proven blood stream infection secondary to gram-negative infection, broad spectrum antibiotics like the third-generation cephalosporins or carbapenam would be used for 2 weeks depending on the antibiotic sensitivity pattern. Prolonged antimicrobial use promotes colonisation of the neonate with *Candida* species and this could be one of the reasons for the rising trend of systemic candidiasis noted in our institution. We also cannot ignore the fact that there was use of broad spectrum antibiotics in 76% of the cases prior to the onset of systemic candidiasis. High density colonisation of the skin and mucosal surfaces is important for spread of systemic disease and is associated with prolonged antimicrobial use especially third-generation cephalosporins.⁶

Other risk factors commonly implicated are lower birthweight and decreasing gestation, use of parenteral steroids, duration of central lines, duration of assisted ventilation and previous GI surgery similar to our study.^{6,14,15}

Pregnancy-induced hypertension was noted to be protective with a lower incidence of sepsis in our study similar to the study reported by Cotten et al.³

Systemic candidiasis predominantly occurs between 2nd and 3rd week of life but in our study, the mean age of onset of sepsis was between the 3rd and 4th week of life.¹⁶ The clinical presentations are non-specific and difficult to distinguish from other bacterial infections. However, positive cultures can usually be obtained within 72 hours¹⁷ and aids physicians to discontinue empiric antifungal therapy if warranted. In our study, all positive cultures were available within 72 hours.

C. albicans was considered the predominant pathogen for systemic disease but recent trends show that *C. parapsilosis* is the predominant organism in the NICU¹⁶ and this was also noted in our study. Systemic candidiasis is associated with a high mortality rate of more than 25%⁹ and our series also showed a rate of 19.6%. End organ involvement secondary to dissemination is well documented with systemic candidiasis and was seen in 17 (33%) of our cases.¹⁸ Screening for end organ involvement is essential to guide duration of treatment and aids in prognostication.

Spontaneous intestinal perforation, described as a distinct clinical entity in ELBW neonates, is associated with systemic candidiasis or coagulase negative staphylococcal infection.¹⁹ In our study, 8 (16%) babies had isolated intestinal perforation, of which, 6 had evidence of myelia in the histopathology specimens. Increased incidence of mortality and end organ involvement are reported in those with *Candida albicans* sepsis, persistently positive cultures and failure of removal of PICC more than 24 hours after detection of candida sepsis.^{20,21} In our study, removal of PICC beyond 48 hours and presence of *Candida albicans* sepsis were associated with significant combined adverse outcomes. Persistence of culture positivity >10 days despite treatment was not associated with significant adverse outcomes in our series as the mean duration to clearance of sepsis in our series was (10.4 ± 5.4) days.

Associated comorbidities like CLD, severe IVH, cholestatic jaundice, significant PDA and severe ROP were reported to be significantly higher in neonates who survive candida sepsis both in our study and in the literature.^{22,23}

Amphotericin B is used as monotherapy in proven fungal sepsis.²⁴ Amphotericin was used in 30 (59%) of our cases with combination of antifungals being used only in the presence of complications.

The limitations of the study are failure to evaluate some of the essential risk factors in the cohort between cases and controls, like the use of third-generation cephalosporins, use of H2 blockers and fungal surveillance cultures. It would indeed be useful to identify the above-mentioned risk factors which are commonly implicated as predisposing factors to

subsequent development of systemic infection. This would certainly help us in future to look at our antibiotic policies and use of H2 blockers.

Systemic candidiasis is associated with a high disease burden in the VLBW neonates and therefore strategies to decrease the incidence of systemic candidiasis have been extensively studied. The use of prophylactic antifungal agents in the VLBW neonates has been of great interest recently as it decreases the intensity of fungal colonisation and thereby preventing systemic spread.²⁵

The prophylactic antifungal agents evaluated are topical miconazole, oral nystatin and systemic fluconazole. Selection of prophylactic agents will depend on the disease burden in the nursery, safety and efficacy of the agent and cost-benefit analysis.

Use of topical miconazole was studied by Warner et al,²⁶ showing a reduction in the incidence of fungal colonisation but no difference in the rates of systemic candidiasis. Miconazole as a topical prophylactic agent was used for all high-risk neonates in our unit and despite the routine use, we noted a steady rise in the incidence of systemic candidiasis in the ELBW neonates. We understand that the increase in incidence of systemic candidiasis is likely to be due to multifactorial causes. However, we need to address the rising trend of candida sepsis in our institution by considering the use of other antifungal prophylactic agents. Systemic oral nystatin as a prophylactic agent has been successfully shown to decrease the incidence of systemic candidiasis.²⁷⁻²⁹

Concerns about use of oral nystatin as a prophylactic agent is due to the high osmolality of the medication and its association with gastrointestinal morbidities (NEC and solitary intestinal perforation).³⁰

Fluconazole as a systemic prophylactic antifungal agent has been evaluated with promising results and has shown significant decline in the incidence of systemic candidiasis.³¹⁻³³ Despite the success, concerns still exist on reports of reversible elevated liver enzymes, fluconazole resistant candida species and emergence of filamentous fungi as pathogens with the use of routine fluconazole prophylaxis.³⁴⁻³⁶ A prospective study comparing the efficacy of nystatin and systemic fluconazole has shown promising results with the use of nystatin with minimal GI side effects.³⁷

Conclusion

The incidence of systemic candidiasis in our institution has shown an increasing trend despite the routine use of prophylactic topical miconazole of *C. parapsilosis* which was the predominant pathogen in our nursery. Systemic candidiasis was associated with a significantly high mortality and morbidity. The limited impact of topical antifungal prophylaxis has prompted physicians to consider use of

systemic agents like fluconazole targeted to neonates <800 gms. With ongoing concerns about the use of systemic agents, a prospective randomised trial comparing the efficacy of fluconazole with nystatin should be considered.

REFERENCES

1. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Late-onset sepsis in very low birthweight neonates: the experience of the national institute of child health and human development Neonatal Research Network. *Paediatrics* 2002;110:285-91.
2. Kossoff EH, Buescher ES, Karlowicz MG. Candidemia in a neonatal intensive care unit: trends during fifteen years and clinical features of 111 cases. *Pediatr Infect Dis J* 1998;17:504-8.
3. Cotten CM, McDonald S, Stoll BJ, Goldberg RN, Poole K, Benjamin DK Jr, et al. The association of third-generation cephalosporin use and systemic candidiasis in extremely low birth-weight infants. *Paediatrics* 2006;118:717-22.
4. Bektas S, Goetze B, Speer CP. Decreased adherence, chemotaxis and phagocytic activities of neutrophils in preterm neonates. *Acta Paediatrica Scand* 1990;79:1031-8.
5. Rowen JL, Atkinds JT, Levy ML, Baer SC, Baker CJ. Invasive fungal dermatitis in the < or = 1000-gram neonate. *Paediatrics* 1995;95:682-7.
6. Saiman L, Ludington E, Pfaller M, Rangel-Frausto S, Wiblin RT, Dawson J, et al. Risk factors for candidemia in Neonatal Intensive Care Unit patients. The National Epidemiology of Mycosis Survey study group. *Pediatr Infect Dis J* 2000;19:319-24.
7. Manzoni P, Faruna D, Galleto P, Leonessa M, Priolo C, Arisio R, et al. Type and number of sites colonized by fungi and risk of progression to systemic fungal infection in preterm neonates in neonatal intensive care unit. *J Perinatal Med* 2007;35:220-6.
8. Austin NC, Darlow B. Prophylactic oral antifungal agents to prevent systemic candida infection in preterm infants. *Cochrane Database Syst Rev* 2004;CD003478.
9. Benjamin DK Jr, Stoll BJ, Fanaroff AA, McDonald SA, Oh W, Higgins RD, et al. Neonatal candidiasis among extremely low birthweight infants: risk factors, mortality rates and neurodevelopmental outcomes at 18 to 22 months. *Pediatrics* 2006;117:84-92.
10. Shennan AT, Dunn MS, Oh Isson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants. Prediction from oxygen requirement in the neonatal period. *Paediatrics* 1988;82:527-32.
11. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular haemorrhage: a study of infants with birthweights less than 1,500gms. *J Pediatr* 1978;92:529-34.
12. An International Committee for the Classification of Retinopathy of Prematurity. The international classification of retinopathy of prematurity Revisited. *Arch Ophthalmol* 2005;123:991-9.
13. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Ann Surg* 1978;187:1-7.
14. Feja KN, Wu F, Roberts K, Loughrey M, Nesin M, Larson E, et al. Risk factors for candidaemia in critically ill infants: A matched case-control study. *J Paediatr* 2005;147:156-61.
15. Pera A, Byun A, Gribar S, Schwartz R, Kumar D, Parimi P. Dexamethasone therapy and candida sepsis in neonates less than 1250 grams. *J Perinatol* 2002;22:204-8.

16. Clerihew L, Lamagni TL, Brocklehurst P, McGuire W. Candida parapsilosis infection in very low birthweight infants. *Arch Dis Child Fetal Neonatal Ed* 2007;92:127-9.
17. Schelonka RL, Moser SA. Time to positive culture results in neonatal Candida septicemia. *J Pediatr* 2003;142:564-5.
18. Benjamin DK Jr, Poole C, Steinbach WJ, Rowen JL, Walsh TJ. Neonatal candidemia and end organ damage: A critical appraisal of the literature using meta-analytic techniques. *Paediatrics* 2003;112:634-40.
19. Adderson EE, Pappin A, Pavia AT. Spontaneous intestinal perforation in premature infants: A distinct clinical entity associated with systemic candidiasis. *J Pediatr Surg* 1998;33:1463-7.
20. Chapman RL, Faix RG. Persistently positive cultures and outcome in systemic neonatal candidiasis. *Pediatr Infect Dis J* 2000;19:822-7.
21. Karlowicz MG, Hashimoto LN, Kelly RE Jr, Buescher ES. Should central venous catheters be removed as soon as candidemia is detected in neonates? *Pediatrics* 2000;106:e63.
22. Friedman S, Richardson SE, Jacobs SE, O' Brein K. Systemic candida infection in extremely low birthweight infants: Short term morbidity and long-term neurodevelopment outcome. *Pediatr Infect Dis J* 2000;19:499-504.
23. Mittal M, Dhanireddy R, Higgins RD. Candida sepsis and association with retinopathy of prematurity. *Pediatrics* 1998;101:654-7.
24. Clerihew L, McGuire W. Systemic antifungal drugs for systemic fungal infection in preterm infants. *Cochrane Database Syst Rev* 2004;CD003953.
25. Manzoni P, Jacqz-Aigrain E, Rizzollo S, Franco C, Stronati M, Mostert M, et al. Antifungal prophylaxis in neonates. *Early Hum Dev* 2011;(87 Suppl 1):S59-60.
26. Warner S, Cooper PA, Funk E, Bental RY, Sandler DA, Patel J. Prophylactic miconazole oral gel for the prevention of neonatal fungal rectal colonization and systemic infection. *Paediatr Infect Dis J* 1992;11:713-6.
27. Ganesan K, Harigopal S, Neal T, Yoxall CW. Prophylactic oral nystatin for preterm babies under 33 weeks gestation decreases fungal colonization and systemic fungaemia. *Arch Dis Child Fetal Neonatal Ed* 2009;94:F275-8.
28. Howell AJ, Isaacs D, Halliday R, Australasian Study Group For Neonatal Infections. Oral nystatin prophylaxis and neonatal fungal infections. *Arch Dis Child Fetal Neonatal Ed* 2009;94:F429-33.
29. Ozturk MA, Gunes T, Koklu E, Cetin N, Koc N. Oral nystatin prophylaxis to prevent systemic candidiasis in neonatal intensive care unit. *Mycoses* 2006;49:484-92.
30. Ernst JA, Williams JM, Glick MR, Lemons JA. Osmolality of substances used in the intensive care nursery. *Pediatrics* 1983;72:347-52.
31. Violaris K, Carbone T, Bateman D, Olawepo O, Doraiswamy B, LaCorte M. Comparison of fluconazole and nystatin oral suspensions for prophylaxis of systemic fungal infection in very low birthweight infants. *Am J Perinatol* 2010;27:73-8.
32. Kaufman D. Fluconazole prophylaxis decreases the combined outcome of invasive candida infections or mortality in preterm infants. *Paediatrics* 2008;122:1158-9.
33. Manzoni P, Stofil I, Pugni L, Decembrino L, Magnani C, Vetrano G, et al. A multicentre randomized trial of prophylactic fluconazole in preterm neonates. *N Engl J Med* 2007;356:2483-95.
34. Aghai ZH, Mudduluru M, Nakhla TA, Amendolia B, Longo D, Kemble N, et al. Fluconazole prophylaxis in extremely low birth weight infants: association with cholestasis. *J Perinatol* 2006;26:550-5.
35. Brion LP, UKOSE, Goldman DL. Risk of resistance associated with fluconazole prophylaxis: systematic review. *J Infect* 2007;54:521-9.
36. Parikh TB, Naravati RN, Patankar CV, Rao S, Bisure K, Udani RH, et al. Fluconazole prophylaxis against fungal colonization and systemic fungal infection in very low birth weight infants. *Indian Paediatr* 2007;44:830-7.
37. Aydemir C, Oguz SS, Dizdar EA, Akar M, Sarikabadayi YU, Saygan S, et al. Randomised controlled trial of prophylactic fluconazole versus nystatin for the prevention of fungal colonization and invasive fungal infection in very low birthweight infants. *Arch Dis Child Fetal Neonatal Ed* 2011;96:F164-168.

The Looi Suture Technique for Anchoring the Lateral Tarsal Strip to the Lateral Orbital Wall

Joy BM Chan, ¹*MRCSEd*, Audrey LG Looi, ²*FRCS(Ed)*

Abstract

Introduction: The lateral tarsal strip procedure (LTS) was first reported by Anderson and Gordy in 1979 for the management of paralytic or senile eyelid laxity. Since its description, the LTS procedure has been subject to several modifications by various authors. In this study, we described the Looi suture technique, a small modification in the technique of suturing the LTS to the lateral orbital wall periosteum. Using this technique, the surgeon achieves a larger area of contact between the anterior surface of the tarsal strip and the lateral orbital wall periosteum, promoting a stronger adhesion. With a double-armed suture, the technique also allows for adjustment of the lower lid tension to avoid over- or under-correction of horizontal lid laxity. This study aimed to evaluate the technique. **Materials and Methods:** This was a retrospective non-comparative case series of 39 eyelids of 31 patients who underwent LTS with Looi suturing technique for the correction of involutional lower lid laxity which had resulted in either entropion or ectropion. In this procedure, a novel technique utilising a double armed 5/0 Ethibond suture is used to secure the LTS to the lateral orbital rim, with the aim of increasing appositional contact between the LTS and periosteum. **Results:** In 36 eyelids with entropion, the procedure was combined with lower lid retractor repair, and in 3 eyelids with ectropion, with medial tarsoconjunctivoplasty. Surgery was successful in 37 of 39 eyelids (94.87%) after one procedure. The remaining 2 eyelids required repeat procedures to achieve anatomical success. Both cases had been performed by trainee surgeons under supervision. Postoperative follow-up period ranged from 1 day (in a visiting overseas patient) to 2 years. **Conclusion:** This study described the Looi suturing technique in performing the LTS procedure and we found it a simple and effective modification when dealing with lower lid laxity.

Ann Acad Med Singapore 2014;43:263-6

Key words: Entropion, Lower lid laxity

¹Department of Ophthalmology, National University Hospital, Singapore

²General Cataract and Comprehensive Ophthalmology Service, Singapore National Eye Centre, Singapore

Address for Correspondence: Dr Joy Chan, Department of Ophthalmology, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074.

Email: drjoychan@gmail.com

The Looi Suture Technique for Anchoring the Lateral Tarsal Strip to the Lateral Orbital Wall

Joy BM Chan, ¹*MRCSEd*, Audrey LG Looi, ²*FRCS(Ed)*

Abstract

Introduction: The lateral tarsal strip procedure (LTS) was first reported by Anderson and Gordy in 1979 for the management of paralytic or senile eyelid laxity. Since its description, the LTS procedure has been subject to several modifications by various authors. In this study, we described the Looi suture technique, a small modification in the technique of suturing the LTS to the lateral orbital wall periosteum. Using this technique, the surgeon achieves a larger area of contact between the anterior surface of the tarsal strip and the lateral orbital wall periosteum, promoting a stronger adhesion. With a double-armed suture, the technique also allows for adjustment of the lower lid tension to avoid over- or under-correction of horizontal lid laxity. This study aimed to evaluate the technique. **Materials and Methods:** This was a retrospective non-comparative case series of 39 eyelids of 31 patients who underwent LTS with Looi suturing technique for the correction of involutional lower lid laxity which had resulted in either entropion or ectropion. In this procedure, a novel technique utilising a double armed 5/0 Ethibond suture is used to secure the LTS to the lateral orbital rim, with the aim of increasing appositional contact between the LTS and periosteum. **Results:** In 36 eyelids with entropion, the procedure was combined with lower lid retractor repair, and in 3 eyelids with ectropion, with medial tarsoconjunctivoplasty. Surgery was successful in 37 of 39 eyelids (94.87%) after one procedure. The remaining 2 eyelids required repeat procedures to achieve anatomical success. Both cases had been performed by trainee surgeons under supervision. Postoperative follow-up period ranged from 1 day (in a visiting overseas patient) to 2 years. **Conclusion:** This study described the Looi suturing technique in performing the LTS procedure and we found it a simple and effective modification when dealing with lower lid laxity.

Ann Acad Med Singapore 2014;43:263-6

Key words: Entropion, Lower lid laxity

Introduction

The lateral tarsal strip (LTS) procedure was first described by Anderson and Gordy in 1979 for the management of paralytic or senile eyelid laxity and lateral canthal tendon laxity. The procedure described by the authors involved lateral canthotomy and inferior cantholysis, dividing the lid into anterior and posterior lamellae, fashioning a tarsal strip from the posterior lamellae, and suturing the tarsal strip to the periosteum of the lateral orbital wall, thereby adjusting the height and tension of the lateral canthus.¹

Since its description, the tarsal strip procedure has been subject to several modifications by various authors. In 1991, Weber et al described several refinements in technique,

including electrosurgical deepithelialisation of conjunctiva and lid margin, use of a V-shaped needle, direct needle passage about the lateral orbital tubercle, and the parallel placement of a buried absorbable suture to unite the upper and lower lid margins and to maintain a long-lasting sharp canthal angle.² Baker et al performed lateral canthotomy using a CO₂ laser, and found 3 distinct advantages, namely a cleaner dissection allowing better visualisation of tissues, preservation of the lateral canthal angle, and prevention of epithelial inclusions by avoiding the violation of the conjunctival mucosa.³ Olver et al described a minimally invasive technique that performed a LTS and diagonal tightening of the orbital septum and lower lid retractors to

¹Department of Ophthalmology, National University Hospital, Singapore

²General Cataract and Comprehensive Ophthalmology Service, Singapore National Eye Centre, Singapore

Address for Correspondence: Dr Joy Chan, Department of Ophthalmology, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074.

Email: drjoychan@gmail.com

the lateral orbital rim via a 1-cm lateral canthal incision.⁴ Chang et al augmented the technique to reduce the vertical palpebral aperture in the management of paralytic ectropion and lagophthalmos. This consisted of a long strip (10 mm to 15 mm) that is attached to the outer temporal orbital rim, at a point higher than a conventional LTS. It included removal of a small part of the upper eyelid anterior lamella laterally to pass the long strip up high enough.⁵ The LTS procedure has also been combined with lower lid retractor repair,⁶ Quickert sutures⁷ and orbicularis resection⁸ in the management of lower lid entropion. In medial ectropion, the LTS procedure has been used to correct horizontal lid laxity, in combination with resection of the lower lid retractors subjacent to the punctal area⁹ and transconjunctival retractor plication¹⁰ to correct punctal eversion.

In this study, we describe a small modification in the technique of suturing the LTS to the periosteum of the lateral orbital wall. Using this technique, the surgeon achieves a larger area of contact between the anterior surface of the tarsal strip and the lateral orbital wall periosteum, promoting more stable adhesion and improving apposition between the lower lid and the globe. The technique also allows for adjustment of the lower lid tension to avoid over- or under-correction of horizontal lid laxity. We call this the Looi suture technique.

Materials and Methods

This was a retrospective noncomparative case series of 39 eyelids of 31 patients who underwent the Looi suture technique either by a single subspecialty-trained oculoplastic surgeon (AL), or by ophthalmology residents operating under direct supervision, from 1 January 2007 to 30 April 2009.

Using the Looi suture technique, the LTS is prepared as previously described. This involves lateral canthotomy and inferior cantholysis, followed by excision of the anterior lamella at the lateral end of the tarsal plate. The extent of excision is determined by the degree of horizontal lid laxity, and the distance between the lateral end of the lower lid and the lateral orbital wall periosteum. This is aided intraoperatively by stretching the lateral end of the lid to the intended suture-anchoring site on the lateral orbital wall. Deepithelialisation of the conjunctiva is performed using diathermy and scraping of the diathermised area with a 15-G blade.

Following this, the lateral orbital rim periosteum is exposed with the aid of curved Westcott scissors. The blades of the scissors are stretched apart to allow visualisation of the periosteum between the blades. A cotton tip applicator is used to push the orbital contents away to aid visualisation. A double-armed 5/0 Ethibond suture with a half-circle reverse

cutting needle (Ethicon, Inc) is then passed through the orbital wall periosteum posterior to the orbital rim and at a height that allows good cosmetic apposition of the lower lid against the globe (Figs. 1 and 2).

The 2 ends of the suture are then passed through the LTS in a parallel fashion from the anterior surface to the posterior surface, then back to the anterior surface, going from a lateral-to-medial direction (Fig. 3). The strip is then glided along the length of the Ethibond suture towards the lateral orbital rim, and the 2 ends of the suture are firmly tied to secure the lid position. Postoperatively, all patients were given a regime of topical antibiotic cream to the skin wound, and topical antibiotic/steroid eyedrops. No systemic antibiotics were given.

In our series, this modified technique of LTS procedure was either performed in conjunction with lower lid retractor repair in cases of entropion, or with medial conjunctivoplasty in cases of ectropion. Success was defined as good postoperative lid-globe apposition, with no inturning of the lash margin in cases of entropion, and no punctal eversion in cases of ectropion.



Fig. 1. The Looi suture technique. The 5/0 Ethibond suture has been secured to the lateral orbital wall periosteum, and the two arms of the suture have been passed through the LTS from the anterior surface to the posterior surface, then back to the anterior surface again.

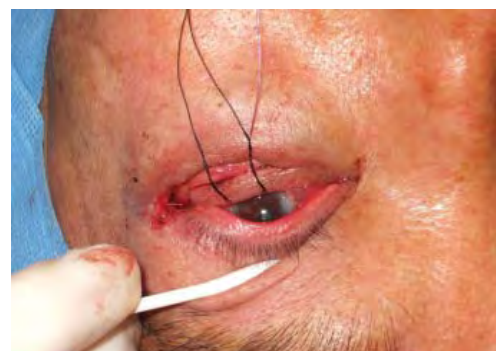


Fig. 2. The end result is a correction of lower lid laxity with stable lid-globe apposition. The two ends of the 5/0 Ethibond suture have been tied.

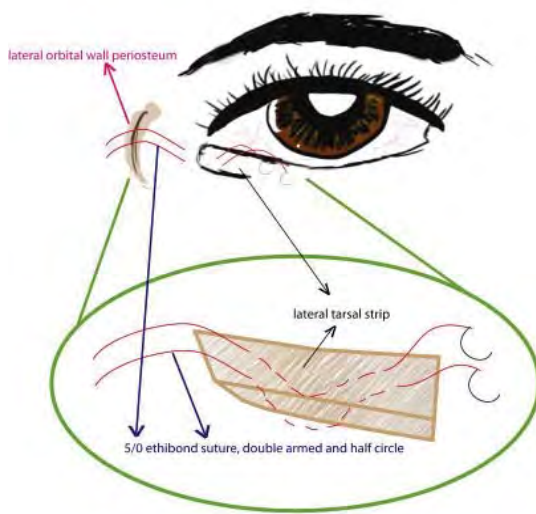


Fig. 3. Diagrammatic representation of the surgical technique.

Results

In total, 39 procedures using this technique were performed on 31 patients during the period of review. Twelve patients were male and the remaining 19 were female. The ethnicity of patients were as follows: 29 Chinese, 1 Malay and 1 Indian. The average age was 75.5 years (range, 54 to 92 years). Nine patients underwent bilateral procedures, while the remaining 21 patients underwent unilateral procedures. The indications for surgery included involutional entropion (28 patients) and involutional ectropion (3 patients). Postoperative follow-up duration ranged from 1 day in a foreign patient from Indonesia to 2 years. Mean follow-up duration was 7.25 months. All cases were either performed by the senior author (17 cases), or by residents under her supervision (22 cases). No cases were performed by residents without supervision.

Patients were reviewed on the first postoperative day, then again within the first postoperative week. At the second visit, the skin sutures were removed. Patients were then reviewed again at the first postoperative month.

At each review, subjective symptoms of each patient were recorded. Patients were examined for lid position, eyelash margin position, punctal position and lid-globe apposition.

Thirty-seven out of 39 procedures were successful (94.87%). In these 37 cases, good postoperative lid-globe apposition was achieved, with no inturning of the lash margin in cases of entropion, and no punctal eversion in cases of ectropion.

In the early postoperative period, mild lower lid bruising

was reported in all patients but no complications such as lymphedema, conjunctival chemosis or suture granuloma were seen.

In our series, 2 cases were unsuccessful after the first procedure. In the first case of unilateral involutional entropion in a 74-year-old female, surgery was uncomplicated, and recurrence of lower eyelid laxity occurred only 4 months later. During the second surgery, the LTS was noted to be attached to the lateral orbital wall periosteum. It was felt that there was undercorrection of the horizontal lid laxity in the first operation. The lower eyelid position remained stable on follow-up over the following 18 months, with no recurrence of entropion.

The second case was a case of bilateral involutional entropion in an 84-year-old female, for which bilateral surgery was done. The patient was well with bilateral good lid-globe apposition at the first 2 postoperative visits, at days 1 and 5. On the 15th postoperative day, the entropion was noted to have recurred, and a repeat LTS procedure was performed the same day. Intraoperatively, a large hematoma was noted in the lateral canthus wound, and the Ethibond suture had completely cheesewired off the lateral orbital wall periosteum, leaving the LTS completely detached. The LTS was re-attached during this procedure. Unfortunately, on review 5 days later, the wound was noted to be gaping, and entropion had recurred for a second time, necessitating a third procedure the following day. Intraoperatively, the LTS was found to be again detached from the lateral orbital wall, and by this time the lateral orbital wall periosteum was frayed from repeated attempts at reattachment. A decision was made to reattach the LTS to the superior limb of the lateral canthal ligament instead. This proved successful, and lid-globe apposition and stability has been maintained in the 1-year postoperative period to date.

Discussion

The Looi suture technique is a small modification in the technique of suturing the LTS to the periosteum of the lateral orbital wall in the management of involutional lower eyelid laxity. This study has demonstrated its high degree of efficacy (94.87%) after a single procedure.

This technique is also relatively simple to perform. In our series, 22 out of 39 (56.41%) of procedures were performed by ophthalmology residents undergoing training, under the direct supervision of a subspecialty-trained oculoplastic surgeon (AL). These residents were all in their 4th to 6th years of ophthalmic training, and had 6 months or less experience in oculoplastic surgery. Despite their relative inexperience, the residents achieved a success rate of 90.09%.

The surgical success rates can be improved by paying

particular attention to the degree of horizontal tightening required for the horizontal lid laxity. Ideally, the result should be a lid that is well apposed to the globe without excess tension on the canthal tendons and without any sclera show. In the 2 cases that required repeat surgery, one was likely due to undercorrection. The other was possibly caused by some eye rubbing that led to wound dehiscence and haemorrhage. In this second case, it has to be emphasised that the passage of the needle through the periosteum can be traumatic to the periosteum if one does not take care to follow the curve of the needle. Using a 1/2 circle needle helps with atraumatic placement of the suture through the lateral orbital wall periosteum.

Conclusion

In summary, this study described the Looi suture technique, a modification in the technique of anchoring the LTS to the periosteum of the lateral orbital wall. This technique is easy to perform and has a high success rate, making it an ideal suturing technique when performing the LTS procedure.

REFERENCES

1. Anderson RL, Gordy DD. The tarsal strip procedure. *Arch Ophthalmol* 1979;97:2192-6.
2. Weber PJ, Popp JC, Wulc AE. Refinements of the tarsal strip procedure. *Ophthalmic Surg* 1991;22:687-91.
3. Baker SS, Pham RT. Lateral canthal tendon suspension using the carbon dioxide laser. A modified technique. *Dermatol Surg* 1995;21:1071-3.
4. Olver JM, Barnes JA. Effective small-incision surgery for involutional lower eyelid entropion. *Ophthalmology* 2000;107:1982-8.
5. Chang L, Olver J. A useful augmented lateral tarsal strip tarsorrhaphy for paralytic ectropion. *Ophthalmology* 2006;113:84-91.
6. Yip CC, Choo CT. The correction of Oriental lower lid involutional entropion using the combined procedure. *Ann Acad Med Singapore* 2000;29:463-6.
7. Ho SF, Pherwani A, Elsherbiny SM, Reuser T. Lateral tarsal strip and quickert sutures for lower eyelid entropion. *Ophthal Plast Reconstr Surg* 2005;21:345-8.
8. Corin S, Veloudious A, Harvey JT. A modification of the lateral tarsal strip procedure with resection of orbicularis muscle for entropion repair. *Ophthalmic Surg* 1991;22:606-8.
9. O'Donnell FE Jr. Medial ectropion: association with lower lacrimal obstruction and combined management. *Ophthalmic Surg* 1986;17:573-6.
10. Fong KC, Mavrikakis I, Sagili S, Malhotra R. Correction of involutional lower eyelid medial ectropion with transconjunctival approach retractor plication and lateral tarsal strip. *Acta Ophthalmol Scand* 2006;84:246-9.

The Golden Hours in Paediatric Septic Shock—Current Updates and Recommendations

Shu Ling Chong,¹ MBBS, MRCPCH (UK), Gene YK Ong,¹ MBBS, MRCPCH (UK), Anantharaman Venkataraman,² MBBS, FRCP (Edin), FRCSEd (A&E), Yoke Hwee Chan,³ MBBS, M Med (Paeds), MRCP (Paeds) (UK)

Abstract

Introduction: Paediatric sepsis is a global health problem. It is the leading cause of mortality in infants and children worldwide. Appropriate and timely initial management in the first hours, often termed as the “golden hours”, has great impact on survival. The aim of this paper is to summarise the current literature and updates on the initial management of paediatric sepsis. **Materials and Methods:** A comprehensive literature search was performed via PubMed using the search terms: ‘sepsis’, ‘septic shock’, ‘paediatric’ and ‘early goal-directed therapy’. Original and review articles were identified and selected based on relevance to this review. **Results:** Early recognition, prompt fluid resuscitation and timely administration of antibiotics remain key in the resuscitation of the septic child. Use of steroids and tight glycaemic control in this setting remain controversial. **Conclusion:** The use of early goal-directed therapy has had significant impact on patient outcomes and protocolised resuscitation of children in septic shock is recommended.

Ann Acad Med Singapore 2014;43:267-74

Key words: Child, Early goal-directed therapy, Emergency, Sepsis

¹Department of Emergency Medicine, KK Women’s and Children’s Hospital, Singapore

²Department of Emergency Medicine, Singapore General Hospital, Singapore

³Department of Paediatric Subspecialties, KK Women’s and Children’s Hospital, Singapore

Address for Correspondence: Dr Chong Shu Ling, Department of Emergency Medicine, KK Women’s and Children’s Hospital, 100 Bukit Timah Road, Singapore 229899.

Email: Chong.Shu-Ling@kkh.com.sg

The Golden Hours in Paediatric Septic Shock—Current Updates and Recommendations

Shu Ling Chong,¹ MBBS, MRCPCH (UK), Gene YK Ong,¹ MBBS, MRCPCH (UK), Anantharaman Venkataraman,² MBBS, FRCP (Edin), FRCSEd (A&E), Yoke Hwee Chan,³ MBBS, M Med (Paeds), MRCP (Paeds) (UK)

Abstract

Introduction: Paediatric sepsis is a global health problem. It is the leading cause of mortality in infants and children worldwide. Appropriate and timely initial management in the first hours, often termed as the “golden hours”, has great impact on survival. The aim of this paper is to summarise the current literature and updates on the initial management of paediatric sepsis. **Materials and Methods:** A comprehensive literature search was performed via PubMed using the search terms: ‘sepsis’, ‘septic shock’, ‘paediatric’ and ‘early goal-directed therapy’. Original and review articles were identified and selected based on relevance to this review. **Results:** Early recognition, prompt fluid resuscitation and timely administration of antibiotics remain key in the resuscitation of the septic child. Use of steroids and tight glycaemic control in this setting remain controversial. **Conclusion:** The use of early goal-directed therapy has had significant impact on patient outcomes and protocolised resuscitation of children in septic shock is recommended.

Ann Acad Med Singapore 2014;43:267-74

Key words: Child, Early goal-directed therapy, Emergency, Sepsis

Introduction

Sepsis in children is a global health issue. The Global Health Observatory estimates that 58% of deaths in children under 5 years old are caused by infectious diseases.¹ Mortality increases as sepsis progresses to septic shock. The implementation of childhood vaccination programmes and the advent of vaccines such as *Haemophilus influenza* and pneumococcal vaccines have resulted in a change in the types of microbial agents responsible for sepsis. Previously common causes of septic shock such as *Haemophilus influenza* type b, *Neisseria meningitides* and *Streptococcus pneumoniae*, are now less commonly seen in countries with widespread immunisation programmes.²⁻⁴ Changing trends in pneumococcal serotypes have also been reported.⁵ Despite that, the incidence of sepsis in children has not declined and constitutes a significant economic burden.⁶ The World Federation of Pediatric Intensive Care and Critical Care Societies (WFPICCS) has recently launched the Global

Sepsis Initiative, a quality improvement programme at an attempt to improve sepsis outcome in children, targeting countries with different level of resources.⁷

The early recognition of septic shock and aggressive, goal-directed treatment is associated with improved outcomes for paediatric patients.^{8,9} The objective of this article is to review the latest evidence in treatment strategies during the first hours of management, often referred to as the “golden hours”.

Materials and Methods

A comprehensive literature search was performed via PubMed using the search terms: ‘sepsis’, ‘septic shock’, ‘paediatric’ and ‘early goal-directed therapy’. Original and review articles were identified and selected based on relevance to this review. Articles that were not written in English were excluded.

¹Department of Emergency Medicine, KK Women’s and Children’s Hospital, Singapore

²Department of Emergency Medicine, Singapore General Hospital, Singapore

³Department of Paediatric Subspecialties, KK Women’s and Children’s Hospital, Singapore

Address for Correspondence: Dr Chong Shu Ling, Department of Emergency Medicine, KK Women’s and Children’s Hospital, 100 Bukit Timah Road, Singapore 229899.

Email: Chong.Shu-Ling@kkh.com.sg

Results

Definitions

The International Paediatric Sepsis Consensus Conference published consensus definitions of various organ dysfunction categories, systemic inflammatory response syndrome (SIRS), severe sepsis, and septic shock specifically for children (Table 1).¹⁰

Clinical Manifestations of Sepsis

Early recognition of shock and prompt treatment is pivotal in improving patient outcome. In the early phase of shock, the paediatric patient usually mounts a robust tachycardia. There is a compensatory increase in systemic vascular resistance. Both these factors aid in maintaining the blood pressure. Changes in pulse pressure precede a decrease in systolic blood pressure, and the latter is known to be a late sign of shock. Hence, hypotension is not required for the diagnosis of shock.

A child who is in septic shock typically presents with altered sensorium. This may present as inconsolable crying, agitation, or increased drowsiness. The peripheries are cool and mottled, and the capillary refill time is more than

2 seconds. Conversely, in warm shock, the peripheries are warm and flushed, and there is flash capillary refill time. There is decreased urine output of less than 1 mL/kg/hour. The signs of shock should be integrated because no single sign confirms the diagnosis of shock.¹¹

Differences Between Children and Adults

The adult patient responds to the shock state by increasing the heart rate and reducing the systemic vascular resistance (SVR), giving rise to the classical warm shock state. SVR is diminished due to decreased vascular response to catecholamines and alterations in alpha-adrenergic receptor signal transduction.¹² This hyperdynamic state is displayed in almost 90% of adults. Vasomotor paralysis is the main cause of death in adults with septic shock.

In contrast to adults who typically present with high cardiac output vasodilatory shock, the physiological response to sepsis varies in children. In children, the ability to increase the heart rate is limited. Doubling the heart rate in an infant would result in a tachycardic response that cannot be sustained, because the diastolic phase would be too short to allow for adequate cardiac refill. The variability in the physiological response was shown in a small case series of 50 children with fluid-refractory, dopamine-resistant shock.¹² Fifty-eight percent of them showed a low cardiac index and high systemic vascular resistance state, 20% had a high cardiac index and low systemic vascular resistance, 22% had a low cardiac index and low systemic vascular resistance. This difference has a direct impact on the choice and timeliness of fluid resuscitation and the use of inotropes.¹³ Children with sepsis often have absolute or relative hypovolaemia and respond well to aggressive fluid resuscitation.¹⁴

First Hour Management

The role of early fluid resuscitation has been demonstrated to improve outcomes in paediatric septic shock.¹⁴ The landmark randomised controlled study by Rivers et al¹⁵ further highlighted the significance of early goal-directed therapy of septic shock in adults.

Airway Management

Oxygen should be given to any patient who is in shock. A child with a Glasgow coma scale (GCS) of less than 8, or one that is rapidly decreasing, should be intubated. In a patient who is able to maintain his or her own airway but requires large amount of fluid resuscitation (60 mL/kg or more), elective intubation should be considered. Up to 40% of the cardiac output supports the work of respiratory muscles.¹³ By taking over the work of breathing through

Table 1. Definitions for Systemic Inflammatory Response Syndrome, Sepsis and Septic Shock¹⁰

Condition	Symptoms
Systemic Inflammatory Response Syndrome (SIRS)	The presence of at least 2 of the following 4, one of which must be abnormal temperature or leukocyte count: Core temperature >38.5°C or <36°C, tachycardia (as defined as mean heart rate >2 SD above normal for age) or children <1 year with bradycardia (as defined by mean heart rate <10th percentile for age), mean respiratory rate >2 SD above normal for age or leukocyte count elevated or depressed for age.
Sepsis	SIRS in the presence of or as a result of suspected or proven infection.
Septic Shock	Sepsis and cardiovascular organ dysfunction: (despite administration of isotonic IV fluid bolus >40 mL/kg in 1 hour) Hypotension <5th percentile for age or systolic BP <2 SD below normal for age, or need for vasoactive drugs to maintain blood pressure (BP) in normal range, or 2 of the following – unexplained metabolic acidosis, increased arterial lactate, oliguria, prolonged capillary refill or raised core to peripheral temperature gap.

assisted ventilation, this amount can be directed to other vital organs. The effect of left ventricular afterload reduction with positive pressure ventilation also improves cardiac output. Early intubation should also be considered for young infants and neonates as they have a lower functional residual capacity.¹⁶

Induction agents before intubation may cause vasodilatation and worsen the shock. Ensuring adequate intravascular volume may ameliorate this effect. Positive pressure ventilation, and particularly excessive ventilation, also decreases the effective preload to the heart. Although etomidate is an induction agent with relatively less side effects on the haemodynamic state, it should be avoided in the septic child, as adrenal suppression has been demonstrated after the use of etomidate and is associated with a higher mortality rate.^{17,18}

Intravenous (IV) Access

Vascular access is of critical importance in the resuscitation of shock. Intravenous (IV) access may be more challenging in children compared to adults. However, fluid resuscitation and inotropic infusion should not be delayed in cases of difficult IV access. Depending on available expertise, the emergency physician should institute resuscitation via intraosseous access if vascular access is not readily secured. The intraosseous route is safe and can be used to administer all medications that would otherwise have been administered intravenously.^{11,19-23} It has been recommended that no more than 3 attempts or 90 seconds be taken to obtain IV access before considering the intraosseous route.²⁴

Fluid Resuscitation

Fluid resuscitation is indicated early, in the presence of tachycardia and changes in pulse pressure, or with physical examination findings consistent with septic shock, as stated above.

Children with septic shock have traditionally been believed to have severe hypovolaemia and aggressive fluid resuscitation has been recommended.¹⁴ In an earlier landmark study, there was clear survival benefit for those with septic shock and given fluid resuscitation in excess of 40 mL/kg.¹⁴ Fluids should be given in aliquots of 20 mL/kg over 5 to 10 mins,²⁵ and commonly up to 60 mL/kg in the first hour in the emergency department, as per ACCM/PALS guidelines.¹³ Concerns for large volumes of resuscitation fluid include the development of cerebral oedema or acute respiratory distress. It has been recommended that in the absence of clinical signs of fluid overload (such as increased work of breathing, lung crepitations, gallop rhythm or hepatomegaly), fluid boluses can be administered to as much as 200 mL/kg.¹³ Early involvement of community

paediatricians with rapid fluid resuscitation has also been shown to reduce mortality.⁸ Every hour that passes without restoring appropriate circulatory volume is associated with a 2-fold increase in mortality.⁸

Worldwide, the priority has moved to improve access to facilities capable of time-critical IV fluid resuscitation.¹⁴ Four randomised controlled studies involving children with dengue and WHO classification stage 3 and stage 4 shock have shown that isotonic fluid resuscitation in the emergency department attains nearly 100% survival.²⁶⁻²⁹ Mortality from diseases associated with hypovolaemic shock has also been shown to decrease by more than 10-fold with the availability and rapid administration of IV fluids,³⁰ including in children with meningococcaemia.³¹ The World Sepsis Initiative has included early IV fluid administration in the clinical bundle for non-industrialised countries.⁷

More recently, the FEAST trial³² showed, however, that fluid boluses increased 48-hour mortality in critically ill children with impaired perfusion. This study was a multicentre trial performed in resource-limited settings with a high prevalence of malarial disease and anaemia. In their population, routine fluid challenge could worsen severe anaemia, cause fluid overload and worsen hypoxaemia.³³ Reperfusion injury caused by rapid increase in plasma volumes, and exacerbation of capillary leak from the transient hypervolemia or hyperosmolality in susceptible patients may also account for the adverse effects of the fluid boluses.³⁴ Murthy et al also commented that the late presentation may result in decreased fluid-responsiveness in the cohort studied by the FEAST trial, and cautioned against a “one-size-fits-all” approach, because the pathophysiological mechanisms differ significantly between different causative agents and infections.³⁵

In children with meningitis and pneumonia, levels of antidiuretic hormone (ADH) are raised^{36,37} and aggressive fluid resuscitation may result in cerebral oedema. Standard recommendations still support timely and aggressive fluid resuscitation, in children with septic shock, while awaiting more specific research directing specific therapies for different aetiologies.

Type of Resuscitation Fluids

While evidence supports timely fluid resuscitation, there is insufficient evidence to support the use of either crystalloid or colloid. The initial study that showed a significantly improved outcome with aggressive fluid resuscitation used a combination of crystalloids and colloids.¹⁴ Previous meta-analysis showed the use of human albumin solution or 0.9% saline resulted in similar survival outcomes.³⁸ This meta-analysis included a large Australian study (SAFE) reflecting the same outcomes.³⁹ The general trend has been

a decline in the use of albumin in paediatric intensive care units in the UK.⁴⁰

A more recent systematic review published in 2010 showed few trials that specifically examined fluid resuscitation strategies in children.⁴¹ The objective of the review was to include sepsis and sepsis-like conditions, in which there may be a theoretical benefit for the use of colloids. The inclusion criteria resulted in the studies mainly centred on those with malaria and dengue, with only one studying sepsis.^{26,27,29,42-47} The trials for dengue shock showed a superior efficacy of colloids for restoring circulation in severe dengue shock. One randomised controlled trial comparing the use of colloid with crystalloid in children with dengue shock showed that those who received Ringer's lactate took the longest time to recover from shock.²⁶ One study for malaria showed a significant overall reduction in mortality in the albumin group compared to the saline group, specifically in the subgroup where acidosis and shock was complicated by coma.⁴³

The single trial in children with sepsis showed no difference in the risk of mortality between saline and gelatin polymer.⁴⁷ The study was too small to detect differences, but did show that a larger volume of crystalloid was required to achieve the same resuscitation endpoint as colloid. Specifically, meningococcal sepsis is associated with microvascular injury, increased vascular permeability and capillary leak syndrome.⁴⁸ It has been recommended that in children with suspected or confirmed meningococcal septicaemia, if signs of shock persist after the first fluid bolus of 20 mL/kg of sodium chloride 0.9%, human albumin can be considered in subsequent aliquots of fluid resuscitation.⁴⁹

Caution has to be exercised with the use of colloids, as they are known to be associated with allergic reactions, coagulation abnormalities and renal toxicity (the latter more so if used in large doses).⁵⁰⁻⁵² The use of hydroxyethyl starch (HES) has been reported to be associated with increased risks of acute kidney injury, need for renal replacement therapy and increased mortality.⁵³⁻⁵⁶ Colloids are also more costly and are not uniformly available, especially in resource-limited countries.

Red Cell Transfusion

There is no known optimal haemoglobin target in children with septic shock. A randomised controlled trial of stabilised critically ill children comparing a haemoglobin target of >7 g/dL and >9.5 g/dL did not show a difference in rate of new or progression of organ dysfunction.⁵⁷ In the acutely ill septic child, it is imperative to optimise oxygen delivery by optimising cardiac output and blood oxygen content. A randomised controlled trial of early goal-directed therapy was conducted in paediatric patients with septic shock, with

the multimodal intervention arm targeting a central venous oxygen saturation ($S_{cv}O_2$) of more than 70%.⁵⁸ One of the interventions included transfusing red cells to achieve a haemoglobin level of ≥ 10 g/dL when the $S_{cv}O_2$ was $\leq 70\%$. This study showed a reduced 28-day mortality in the intervention arm. The current recommendation is to target a haemoglobin level of >10 g/dL during active resuscitation. In children with invasive monitoring, this can be guided by the $S_{cv}O_2$. After stabilisation with recovery from shock and hypoxaemia, a more conservative haemoglobin goal of >7 g/dL can be considered.^{25,59}

Use of Inotropes and Vasopressors

Physiological response in septic shock varies in children. Inotropes (and vasopressors or vasodilators) should be individualised to the type of response. The physician must remember that septic shock is a dynamic process and the choice of agents have varying effects on systemic vascular resistance, cardiac contractility and heart rate. The septic child may have a combination of low cardiac output and high systemic vascular resistance, high cardiac output with low systemic vascular resistance or low cardiac output with low vascular resistance.¹² Inotropic support should not be delayed due to the absence of central venous access, and can be administered peripherally. As recommended, dopamine is the first choice of support in a child who is in fluid-refractory shock, up to 10 mcg/kg/min.²⁵ In dopamine-refractory shock, adrenaline may be used. The use of adrenaline may result in hyperglycaemia from gluconeogenesis, increased lactate, and gut injury from decreasing intestinal mucosal pH. Noradrenaline is particularly useful in cases of warm shock.¹² A small series published showed that the use of peripheral noradrenaline (IV or IO) was safe without significant side effects.⁶⁰ Dobutamine should be considered in cases with low cardiac output states. In cases with persistently low cardiac output and raised vascular resistance, phosphodiesterase inhibitors should be considered.^{61,62}

Early Antimicrobial Therapy

Administration of effective antibiotics within the first hour of recognition of septic shock or severe sepsis is strongly recommended.²⁵ Broad spectrum antibiotics should be given as early as possible. In the event that blood cultures are difficult to obtain, this should not delay the first dose of antibiotics. The initial choice of antibiotic should take into account the initial source of the infection, local bacteriology trends and patient's immunity status. With the isolation of the causative organism and known sensitivities, the antibiotics should then be quickly scaled down to target the detected organism specifically. In an adult septic shock study, effective antimicrobial administration within the

first hour of documented hypotension was associated with increased survival to hospital discharge.⁶³ An observational study demonstrated a reduced odds of death for patients who received antimicrobial agents within 60 minutes of emergency department triage time.⁶⁴

Glycaemic Control

Hypoglycaemia must be avoided and treated at all costs in children. However, optimal glycaemic control in sepsis is still widely debated. Much interest was drawn to glycaemic control in critically ill patients when an adult randomised controlled trial in a cardiac surgical unit demonstrated a reduction in intensive care unit (ICU) mortality with intensive IV insulin therapy targeting blood glucose of 4.4 to 6.1 mmol/L.⁶⁵ However, subsequent adult studies in mixed populations of ICU patients, including patients with sepsis, did not show consistent reductions in mortality and in fact demonstrated increased incidence of hypoglycaemia with intensive insulin therapy.^{51,66-70} The NICE-SUGAR trial, a multicentre randomised controlled trial, showed an increase in 90-day mortality and an increased incidence of hypoglycaemia in those who received intensive insulin therapy (blood glucose range, 4.5 to 6 mmol/L) compared to those with target blood glucose of less than 10 mmol/L.⁷¹ In a post hoc analysis of this trial, moderate and severe hypoglycaemia was associated with increased risk of death.⁷²

One randomised controlled trial of critically ill children showed an improvement in inflammatory markers and reduced length of ICU stay in patients with tight glycaemic control but also an increased risk of hypoglycaemia.⁷³ The most recent randomised trial in young children post cardiac surgery did not show benefit in terms of infection rate with intensive therapy.⁷⁴ Current evidence does not support tight glycaemic control but hyperglycaemia (blood glucose >10 mmol/L) should be avoided.

Use of Steroids

There is a strong controversy on the use of steroids in sepsis. While data suggest that sepsis causes a state of relative adrenal insufficiency,⁷⁵⁻⁸⁴ there is no consensus on the exact definition of this insufficiency state. The administration of low dose steroids may hasten the reversal of shock and reduce inotropic-vasopressor requirement in adults.^{18,85-87} One study in children similarly reported earlier shock reversal when low dose hydrocortisone was used for septic shock.⁸⁸ However, steroid therapy has not been conclusively shown to reduce mortality.^{89,90} The CORTICUS trial, a multicentre randomised controlled trial involving adults with septic shock, did not show a difference in 28-day mortality with low dose hydrocortisone treatment compared to placebo.⁹¹ Although earlier reversal of shock was observed in the

treatment arm, there was no difference in the total number of patients with reversal of shock between the groups. A recent study reviewing the use of low dose steroids in the Surviving Sepsis Campaign showed a higher adjusted odds of hospital mortality in those who received steroids for fluid refractory shock.⁹² A retrospective cohort analysis of a large paediatric sepsis trial showed no reduction in mortality attributable to use of adjunctive steroids.⁹³ Presently, the evidence for the use of steroids in children with septic shock is scarce and hence, does not provide a good basis to guide treatment. Steroids may be recommended for use in children with catecholamine-resistant shock and suspected or proven adrenal insufficiency.²⁵ These include children who are on exogenous steroids for chronic illnesses, those with known pituitary or adrenal insults, or children with severe shock and purpura.^{84,88}

Parameters for Improvement

The therapeutic endpoint is the reversal of shock. Clinical parameters include normalisation of heart rate and respiratory rates, restoration of normal conscious level, normal volume pulses with no difference between peripheral and central pulses, capillary refill time of less than 2 seconds and a urine output of more than 1 mL/kg/hour.

Early goal-directed therapy¹⁵ has been shown to have a significant impact on improved organ function in the adult population, and protocolised resuscitation of patients with septic shock is recommended.²⁵ In the paediatric population, the implementation of a goal-directed protocol resulted in earlier recognition of suspected sepsis and reduction in time to interventions and decreased treatment variation.⁹⁴ With the development of an emergency department (ED) septic shock protocol,⁹⁵ it has been shown to decrease the median hospital length of stay. The authors noted more complete recording of triage vital signs, timely fluid resuscitation and antibiotic administration, and serum lactate determination.

Biochemical markers include decreasing lactate levels, improving base deficit and superior vena cava or mixed venous oxygen saturation of >70%.^{15,58} Improvements in lactate and central venous saturations have demonstrated stabilisation of haemodynamic status leading to improved clinical outcomes.⁵⁸

Conclusion

Recommendations for Direction of Future Research

Many of the current recommendations are still consensus-based. In which septic shock child would aggressive fluid resuscitation be beneficial? Better stratification by different specific causative agents and biologically-derived mechanisms³⁵ would allow for more specific and appropriate

protocol application. The development of biomarkers of sepsis to allow early detection and risk stratification is another important area of research to help in early diagnosis and target appropriate treatment. More specific strategies should be explored in order to derive clearer guidelines on glycaemic control and the use of steroids during the golden hours in paediatric septic shock.

REFERENCES

- World Health Organization: Global Health Observatory (GHO). Available at: http://www.who.int/gho/child_health/en/index.html. Accessed 14 March 2013.
- Jacobs RF, Sowell MK, Moss MM, Fiser DH. Septic shock in children: bacterial etiologies and temporal relationships. *Pediatr Infect Dis J* 1990;3:196-200.
- Vadheim CM, Greenberg DP, Eriksen E, Hemenway L, Bendana N, Mascola L, et al. Eradication of Haemophilus influenza B disease in Southern California Kaiser-UCLA vaccine study group. *Arch Pediatr Adolesc Med* 1994;148:51-6.
- Lieu TA, Ray GT, Black SB, Butler JC, Klein JO, Breiman RF, et al. Projected cost effectiveness of pneumococcal conjugate vaccination of healthy infants and children. *JAMA* 2000;283:1460-8.
- Yildirim I, Stevenson A, Hsu KK, Pelton SI. Evolving picture of invasive pneumococcal disease in Massachusetts children: a comparison of disease in 2007-2009 with earlier periods. *Pediatr Infect Dis J* 2012;31:1016-21.
- Watson RS, Carcillo JA. Scope and epidemiology of pediatric sepsis. *Pediatr Crit Care Med* 2005;6:S3-5.
- Kissoon N, Carcillo JA, Espinosa V, Argent A, Devictor D, Madden M, et al. The Global Sepsis Initiative Vanguard Center Contributors. World Federation of Pediatric Intensive Care and Critical Care Societies. *Pediatr Crit Care Med* 2011;12:494-503.
- Han YY, Carcillo JA, Dragotta MA, Bills DM, Watson RS, Westerman ME, et al. Early reversal of pediatric-neonatal septic shock by community physicians is associated with improved outcome. *Pediatrics* 2003;112:793-9.
- Inwald DP, Tasker RC, Peters MJ, Nadel S; Paediatric Intensive Care Society Study Group (PICS-SG). Emergency management of children with severe sepsis in the United Kingdom: the results of the Paediatric Intensive Care Society sepsis audit. *Arch Dis Child* 2009;94:348-53.
- Goldstein B, Giroir B, Randolph A, International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005;6:2-8.
- Kleinman ME, Chameides L, Schexnayder SM, Samson RA, Hazinski MF, Atkins DL, et al. Part 14: Pediatric Advanced Life Support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010;122:S876-908.
- Ceneviva G, Paschall JA, Maffei F, Carcillo JA. Hemodynamic support in fluid refractory pediatric septic shock. *Pediatrics* 1998;102:e19.
- Brierley J, Carcillo JA, Choong K, Cornell T, Decaen A, Deymann A, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. *Crit Care Med* 2009;37:666-88.
- Carcillo JA, Davis AL, Zaritsky A. Role of early fluid resuscitation in pediatric septic shock. *JAMA* 1991;266:1242-5.
- Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368-77.
- Parker MM, Hazelzet JA, Carcillo JA. Pediatric considerations. *Crit Care Med* 2004;32:S591-4.
- den Brinker M, Hokken-Koelega AC, Hazelzet JA, de Jong FH, Hop WC, Joosten KF. One single dose of etomidate negatively influences adrenocortical performance for at least 24h in children with meningococcal sepsis. *Intensive Care Med* 2008;34:163-8.
- den Brinker M, Joosten KF, Liem O, de Jong FH, Hop WC, Hazelzet JA, et al. Adrenal insufficiency in meningococcal sepsis: bioavailable cortisol levels and impact of interleukin-6 levels and intubation with etomidate on adrenal function and mortality. *J Clin Endocrinol Metab* 2005;90:5110-7.
- Rosetti VA, Thompson BM, Miller J, Mateer JR, Aprahamian C. Intraosseous infusion: an alternative route of pediatric intravascular access. *Ann Emerg Med* 1985;14:885-88.
- Glaeser PW, Hellmich TR, Szwecuga D, Losek JD, Smith DS. Five-year experience in prehospital intraosseous infusions in children and adults. *Ann Emerg Med* 1993;22:1119-24.
- Horton MA, Beamer C. Powered intraosseous insertion provides safe and effective vascular access for pediatric emergency patients. *Pediatr Emerg Care* 2008;24:347-50.
- Banerjee S, Singhi SC, Singh S, Singh M. The intraosseous route is a suitable alternative to intravenous route for fluid resuscitation in severely dehydrated children. *Indian Pediatr* 1994;31:1511-20.
- Fiser DH. Intraosseous infusion. *N Engl J Med* 1990;322:1579-81.
- Chameides L, Hazinski MF, eds. Pediatric advanced life support. Dallas: American Heart Association, 1997.
- Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012. *Intensive Care Med* 2013;39:165-228.
- Ngo NT, Cao XT, Kneen R, Wills B, Nguyen VM, Nguyen TQ, et al. Acute management of dengue shock syndrome: A randomized double-blind comparison of 4 intravenous fluid regimens in the first hour. *Clin Infect Dis* 2001;32:204-13.
- Dung NM, Day NP, Tam DT, Loan HT, Chau HT, Minh LN, et al. Fluid replacement in dengue shock syndrome: a randomized, double-blind comparison of four intravenous fluid regimens. *Clin Infect Dis* 1999;29:787-94.
- Ranjit S, Kissoon N, Jayakumar I. Aggressive management of dengue shock syndrome may decrease mortality rate: a suggested protocol. *Pediatr Crit Care Med* 2005;6:412-9.
- Wills BA, Nguyen MD, Ha TL, Dong TH, Tran TN, Le TT, et al. Comparison of three fluid solutions for resuscitation in dengue shock syndrome. *N Engl J Med* 2005;353:877-89.
- Thomas NJ, Carcillo JA. Hypovolemic shock in pediatric patients. *New Horiz* 1998;6:120-9.
- Booy R, Habibi P, Nadel S, de Munter C, Britto J, Morrison A, et al. Meningococcal Research Group. Reduction in case fatality rate from meningococcal disease associated with improved healthcare delivery. *Arch Dis Child* 2001;85:386-90.
- Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, et al; the FEAST Trial Group. Mortality after fluid bolus in African children with severe infection. *N Engl J Med* 2011;364:2483-95.
- Southall DP, Samuels MP. Treating the wrong children with fluids will cause harm: response to 'mortality after fluid bolus in African children with severe infection'. *Arch Dis Child* 2011;96:905-6.
- JA Myburgh. Fluid resuscitation in acute illness – time to reappraise the basics. *N Engl J Med* 2011;364:2543-4.
- S Murthy, Kissoon N. After the FEAST – fluid resuscitation in pediatric sepsis. *Indian J Pediatr* 2013;80:151-4.
- Duke T, Mokela D, Frank D, Michael A, Paulo T, Mgone J, et al. Management of meningitis in children with oral fluid restriction or intravenous fluid at maintenance volumes: a randomized trial. *Ann Trop Paediatr* 2002;22:145-57.

37. Dhawan A, Narang A, Singhi S. Hyponatremia and the inappropriate ADH syndrome in pneumonia. *Ann Trop Paediatr* 1992;12:455-62.
38. Alderson P, Bunn F, Li Wan Po A, Li L, Blackhall K, Roberts I, et al. Human albumin solution for resuscitation and volume expansion in critically ill patients. *Cochrane Database Syst Rev* 2011;10:CD001208
39. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R; SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004;350:2247-56.
40. Sparrow A, Hedderley T, Nadel S. Choice of fluid for resuscitation of septic shock. *Emerg Med J* 2002;19:114-6.
41. Akech S, Lederhann H, Maitland K. Choice of fluids for resuscitation in children with severe infection and shock: systematic review. *BMJ* 2010;341:c4416.
42. Maitland K, Pamba A, Newton CR, Levin M. Response to volume resuscitation in children with severe malaria. *Pediatr Crit Care Med* 2003;4:426-31.
43. Maitland K, Pamba A, English M, Peshu N, Marsh K, Newton C, et al. Randomized trial of volume expansion with albumin or saline in children with severe malaria: preliminary evidence of albumin benefit. *Clin Infect Dis* 2005;40:538-45.
44. Maitland K, Pamba A, English M, Peshu N, Levin M, Marsh K, et al. Pre-transfusion management of children with severe malarial anemia: a randomized controlled trial of intravascular volume expansion. *Br J Haematol* 2005;128:393-400.
45. Akech S, Gwer S, Indro R, Fegan G, Eziefula AC, Newton CR, et al. Volume expansion with albumin compared to gelofusine in children with severe malaria: results of a controlled trial. *PLoS Clin Trials* 2006;1:e21.
46. Cifra HL, Velasco JN. A comparative study of the efficacy of 6% Haes-Steril and Ringer's lactate in the management of dengue shock syndrome 555. *Crit Care & Shock* 2003;6:95-100.
47. Upadhyay M, Singhi S, Murlidharan J, Kaur N, Majumdar S. Randomized evaluation of fluid resuscitation with crystalloid (saline) and colloid (polymer from degraded gelatin in saline) in pediatric septic shock. *Indian Pediatr* 2005;42:223-31.
48. Pathan N, Faust SN, Levin M. Pathophysiology of meningococcal meningitis and septicaemia. *Arch Dis Child* 2003;88:601-7.
49. Visintin C, Mugglestone MA, Fields EJ, Jacklin P, Murphy MS, Pollard AJ, et al. Management of bacterial meningitis and meningococcal septicaemia in children and young people: summary of NICE guidance. *BMJ* 2010;340:c3209.
50. Roberts JS, Bratton SL. Colloid volume expanders. Problems, pitfalls and possibilities. *Drugs* 1998;55:621-30.
51. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008;358:125-39.
52. Wiedermann CJ. Systematic review of randomized clinical trials on the use of hydroxyethyl starch for fluid management in sepsis. *BMC Emerg Med* 2008;8:1.
53. Haase N, Perner A, Hennings LI, Siegemund M, Lauridsen B, Wetterslev M, et al. Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. *BMJ* 2013;346:f839.
54. Zarychanski R, Abou-Setta AM, Turgeon AF, Houston BL, McIntyre L, Marshall JC, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. *JAMA* 2013;309:678-88. Erratum in: *JAMA* 2013;309:1229.
55. Mutter TC, Ruth CA, Dart AB. Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. *Cochrane Database Syst Rev* 2013;7:CD007594.
56. Estrada CA, Murugan R. Hydroxyethyl starch in severe sepsis: end of starch era? *Crit Care* 2013;17:310.
57. Lacroix J, Hebert PC, Hutchison JS, Hume HA, Tucci M, Ducruet T, et al. Transfusion strategies for patients in pediatric intensive care units. *N Engl J Med* 2007;256:1609-19.
58. de Oliveira CF, de Oliveira DS, Gottschald AF, Moura JD, Costa GA, Ventura AC, et al. ACCM/PALS haemodynamic support guidelines for paediatric septic shock: an outcomes comparison with and without monitoring central venous oxygen saturation. *Intensive Care Med* 2008;34:1065-75.
59. Karam O, Tucci M, Ducruet T, Hume HA, Lacroix J, Gauvin F, et al. Red blood cell transfusion thresholds in pediatric patients with sepsis. *Pediatr Crit Care Med* 2011;12:512-8.
60. Lampin ME, Rousseaux J, Botte A, Sadik A, Cremer R, Leclerc F. Noradrenaline use for septic shock in children: doses, routes of administration and complications. *Acta Paediatr* 2012;101:e426-30.
61. Lindsay CA, Barton P, Lawless S, Kitchen L, Zorka A, Garcia J, et al. Pharmacokinetics and pharmacodynamics of milrinone lactate in pediatric patients with septic shock. *J Pediatr* 1998;132:329-34.
62. Irazuzta JE, Pretzlaff RK, Rowin ME. Amrinone in pediatric refractory septic shock: An open-label pharmacodynamic study. *Pediatr Crit Care Med* 2001;2:24-8.
63. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006;34:1589-96.
64. Gaieski DF, Mikkelsen ME, Band RA, Pines JM, Massone R, Furia FF, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. *Crit Care Med* 2010;38:1045-53.
65. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001;345:1359-67.
66. van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006;354:449-61.
67. Arabi YM, Dabbagh OC, Tamim HM, Al-Shimeri AA, Memish ZA, Haddad SH, et al. Intensive versus conventional insulin therapy: A randomized controlled trial in medical and surgical critically ill patients. *Crit Care Med* 2008;36:3190-7.
68. De La Rosa Gdel C, Donado JH, Restrepo AH, Quintero AM, Gonzalez LG, Saldarriaga NE, et al. Strict glycaemic control in patients hospitalised in a mixed medical and surgical intensive care unit: a randomised clinical trial. *Crit Care* 2008;12:R120.
69. Annane D, Cariou A, Maxime V, Azoulay E, D'honneur G, Timsit JF, et al. COITSS Study Investigators. Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. *JAMA* 2010;303:341-8.
70. Preiser JC, Devos P, Ruiz-Santana S, Melot C, Annane D, Groeneveld J, et al. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. *Intensive Care Med* 2009; 35:1738-48.
71. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009;360:1283-97.
72. NICE-SUGAR Investigators, Finfer S, Liu B, Chittock DR, Norton R, Myburgh JA, McArthur C, et al. Hypoglycemia and risk of death in critically ill patients. *N Engl J Med* 2012;367:1108-18.
73. Vlasselaers D, Milants I, Desmet L, Wouters PJ, Vanhorebeek I, van den Heuvel I, et al. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. *Lancet* 2009;373:547-56.

74. Agus MS, Steil GM, Wypij D, Costello JM, Laussen PC, Langer M, et al. Tight glycemic control versus standard care after pediatric cardiac surgery. *N Engl J Med* 2012;367:1208-19.
75. Bouachour G, Tirot P, Gouello JP, Mathieu E, Vincent JF, Alquier P. Adrenocortical function during septic shock. *Intensive Care Med* 1995;21:57-62.
76. Annane D, Sebille V, Troche G, Raphael JC, Gajdos P, Bellissant E. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. *JAMA* 2000;283:1038-45.
77. Schroeder S, Wichers M, Klingmuller D, Hofer M, Lehmann LE, von Spiegel T, et al. The hypothalamic-pituitary-adrenal axis of patients with severe sepsis: altered response to corticotropin-releasing hormone. *Crit Care Med* 2001;29:310-6.
78. Marik PE, Zaloga GP. Adrenal insufficiency during septic shock. *Crit Care Med* 2003;31:141-5.
79. Riordan FA, Thomson AP, Ratcliffe JM, Sills JA, Diver MJ, Hart CA. Admission cortisol and adrenocorticotrophic hormone levels in children with meningococcal disease: Evidence of adrenal insufficiency? *Crit Care Med* 1999;27:2257-61.
80. Hatherill M, Tibby SM, Hilliard T, Turner C, Murdoch IA. Adrenal insufficiency in septic shock. *Arch Dis Child* 1999;80:51-5.
81. Bone M, Diver M, Selby A, Sharples A, Addison M, Clayton P. Assessment of adrenal function in the initial phase of meningococcal disease. *Pediatrics* 2002;110:563-9.
82. Menon K, Clarson C. Adrenal function in pediatric critical illness. *Pediatr Crit Care Med* 2002;3:112-6.
83. Pizarro CF, Troster EJ, Damiani D, Carcillo JA. Absolute and relative adrenal insufficiency in children with septic shock. *Crit Care Med* 2005;33:855-9.
84. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis. *BMJ* 2004;329:485-4.
85. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for treating severe sepsis and septic shock. *Cochrane Database Sys Rev* 2004;1:CD002243.
86. Annane D, Sebille V, Charpentier C, Bollaert PE, Francois B, Korach JM, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002;288:862-71.
87. Oppert M, Schindler R, Husung C, Offermann K, Graf KJ, Boenisch O, et al. Low-dose hydrocortisone improves shock reversal and reduces cytokine levels in early hyperdynamic septic shock. *Crit Care Med* 2005;33:2457-64.
88. Valoor HT, Singhi S, Jayashree M. Low-dose hydrocortisone in pediatric septic shock: an exploratory study in a third world setting. *Pediatr Crit Care Med* 2009;10:121-5.
89. Slusher T, Gbadero D, Howard C, Lewison L, Giroir B, Toro L, et al. Randomized, placebo-controlled, double blinded trial of dexamethasone in African children with sepsis. *Pediatr Infect Dis J* 1996;15:579-83.
90. Markovitz BP, Goodman DM, Watson RS, Bertoch D, Zimmerman J. A retrospective cohort study of prognostic factors associated with outcome in pediatric severe sepsis: what is the role of steroids? *Pediatr Crit Care Med* 2005;6:270-4.
91. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008;358:111-24.
92. Casserly B, Gerlach H, Phillips GS, Lemeshow S, Marshall JC, Osborn TM, et al. Low-dose steroids in adult septic shock: results of the Surviving Sepsis Campaign. *Intensive Care Med* 2012;38:1946-54.
93. Zimmerman JJ, Williams MD. Adjunctive corticosteroid therapy in pediatric severe sepsis: observations from the RESOLVE study. *Pediatr Crit Care Med* 2011;12:2-8.
94. Cruz AT, Perry AM, Williams EA, Graf JM, Wuestner ER, Patel B. Implementation of goal-directed therapy for children with suspected sepsis in the emergency department. *Pediatrics* 2011;127:e758-66.
95. Larsen GY, Mecham N, Greenberg R. An emergency department septic shock protocol and care guidelines for children initiated at triage. *Pediatrics* 2011;127:e1585-92.

Anticoagulation Needs in Asians with Atrial Fibrillation: A Mythbuster

Zeenathnisa M [Aribou](#),¹, Adrian [Mondry](#),¹ *MD PhD*

Abstract

Atrial fibrillation (AF) has long been known to increase the risk of stroke. As a result, relevant international guidelines recommend that measures to reduce the risk of thrombus formation should be considered in all patients presenting with AF. Based on risk assessment scores, patients would then receive either thrombocyte aggregation inhibitors or oral anticoagulants. Despite this advice, compliance rates with the recommendations are poor across all countries surveyed. Evidence from the Global Anticoagulant Registry in the Field (GARFIELD) registry shows that major deviation from guidelines is due in large part to physicians' decision-making. In this brief narrative review, we address some of the frequent reasons cited by physicians why the guidelines are disregarded for Asian patients.

Ann Acad Med Singapore 2014;43:275-8

Key words: Bleed, Elderly, Falls, Patient preference, Stroke prevention

¹Department of Medicine, National University Hospital, Singapore

Address for Correspondence: Dr Adrian Mondry, Department of Medicine, Division of General Medicine, National University Hospital, NUHS Tower Block, Level 10, 1E Kent Ridge Road, Singapore 119228.

Email: mondry@hotmail.com

Anticoagulation Needs in Asians with Atrial Fibrillation: A Mythbuster

Zeenathnisa M [Aribou](#),¹, Adrian [Mondry](#),¹ MD PhD

Abstract

Atrial fibrillation (AF) has long been known to increase the risk of stroke. As a result, relevant international guidelines recommend that measures to reduce the risk of thrombus formation should be considered in all patients presenting with AF. Based on risk assessment scores, patients would then receive either thrombocyte aggregation inhibitors or oral anticoagulants. Despite this advice, compliance rates with the recommendations are poor across all countries surveyed. Evidence from the Global Anticoagulant Registry in the Field (GARFIELD) registry shows that major deviation from guidelines is due in large part to physicians' decision-making. In this brief narrative review, we address some of the frequent reasons cited by physicians why the guidelines are disregarded for Asian patients.

Ann Acad Med Singapore 2014;43:275-8

Key words: Bleed, Elderly, Falls, Patient preference, Stroke prevention

Introduction

Atrial fibrillation (AF) increases the risk of stroke 5-fold in Caucasians. While the relative risk for stroke is somewhat lower in Asia, estimated at 3.6% in Singapore,¹ total AF and stroke-associated mortality rates are reported to be similar.

The pathophysiology of stroke in patients with AF is usually multifactorial. However, cardiogenic embolism due to the lack of organised atrial contraction is ultimately the root cause. AF-associated stroke carries a heavy disease burden as more such patients become bedridden than patients whose stroke has a different underlying cause.²

Anticoagulation in AF has been known to reduce the incidence of stroke events since the early 1990s. The most recent international guidelines are those of the American College of Chest Physicians (ACCP, published in 2012), European Society of Cardiology (ESC, published in 2010 and updated in 2012), Canadian Cardiovascular Society (CCV, published in 2012) and by the American Academy of Neurology (AAN, 2014). Table 1 shows an overview

of current guidelines.

In Eastern Asia, the overall guidance follows that of Western societies. In fact, Chinese guidelines are translated from the American Heart Association guidance. Only the Japanese guidelines, which are not evidence- but consensus-based, give mildly different advice in that they recommend lower international normalised ratio (INR) targets of 1.6 to 2.6 in patients over 70 years of age.

To aid decision-making in the prescription of anticoagulation, several scoring tools have been developed. Of these, CHA₂DS₂-VASc³ and HAS-BLED⁴ are the currently recommended tools. There is no clear numerical evidence for balancing bleeding risk against the risk of stroke. The most recent ACCP guidelines have assessed evidence related to patients' preferences and recommend that a ratio of stroke versus gastrointestinal (GI) bleeding risk in the range of 2:1 to 3:1 should prompt the physician to recommend oral anticoagulation.

¹Department of Medicine, National University Hospital, Singapore

Address for Correspondence: Dr Adrian Mondry, Department of Medicine, Division of General Medicine, National University Hospital, NUHS Tower Block, Level 10, 1E Kent Ridge Road, Singapore 119228.

Email: mondry@hotmail.com

Table 1. Current Guidelines on Anticoagulation in AF from America, Europe, and the Far East

Organisation	Year	Country	Reference
ACCP	2012	USA	Guyatt et al. <i>Chest</i> 2012;141:48S-52S
AHA	2011	USA	Goldstein et al. <i>Stroke</i> 2011;42:517-584
AAN	2014	USA	Culebras et al. <i>Neurology</i> 2014;82:716-724
CCVS	2012	Canada	Skane et al. <i>Can J Cardiol</i> 2012;28:125-136
ESC/ESH	2012	EU	Camm et al. <i>Eur Heart J</i> 2012;33:2719-2747
China	2011	PRC	Anon. <i>Chinese J Neurol</i> 2011;44:282-286
JCS	2010	Japan	Group JCSJW. <i>Circ J</i> 2010;74:2479-2500
CRCS	2013	Korea	http://www.stroke-crc.or.kr

ACCP: American College of Chest Physicians; AHA: American Heart Association; AAN: American Academy of Neurology; CCVS: Canadian Cardiovascular Society; ESC: European Society of Cardiology; ESH: European Society of Hypertension; JCS: Japanese Cardiology Society; CRCS: Clinical Research Centre for Stroke; AF: Atrial Fibrillation; USA: United States of America; EU: European Union; PRC: People's Republic of China

Until very recently, oral long-term anticoagulation was exclusively done using dicoumarol derivatives. Although the dicoumarol derivative warfarin reduces stroke risk by 65% in patients with non-valvular AF, its complex dose-response relationship, manifold food and drug interactions, regular blood monitoring requirements and risk of haemorrhage are serious disadvantages which may have contributed to the low rate of effective anticoagulation in patients with AF. With the recent approval of several new drugs, often referred to as the novel oral anticoagulants (NOACs), therapeutic options have increased. As of January 2014, 3 such drugs have been licensed in Singapore: dabigatran, rivaroxaban and apixaban.

In Singapore, anticoagulation use in AF is “strongly recommended in most circumstances without reservations”, according to the Ministry of Health Clinical Pharmacy Guideline on Anticoagulation published in 2006. Regardless of this recommendation, a recent local study⁵ showed that 40.7% of the study population (n = 1826) were discharged without any anticoagulation despite high thromboembolic risk. This is an international phenomenon, evident both in Western countries, and in the Far East.

The reasons for this are multifactorial. Physician's decision, patient's refusal, previous bleeding history are some of the common reasons stated for not choosing the appropriate anticoagulation therapy. However, it is striking that in a recent analysis of data from the GARFIELD registry, Kakkar et al noted that ineffective anticoagulation in 48% of the cases could be attributed to decisions made by physicians.⁶

This paper addresses some of the objections to anticoagulation therapy frequently voiced by physicians. The topical subheadings quote these as we typically encounter them in daily practice when we try to establish why our patients' anticoagulation is not in line with the available guidance. For each topic, we first reviewed the evidence provided in the guidelines cited above. We then submitted suitable search terms to PubMed and Google Scholar to look for relevant newer studies addressing these questions, as well as specifically looking for studies in patients with an Asian background. We present the information in the form of a narrative literature review.

“This Patient is too Old for Anticoagulation”: Anticoagulation in Elderly Patients

“Old age” is often cited as a reason why physicians opt not to anticoagulate. In fact, however, the risk of stroke increases from 1.5% in patients aged 50 to 59 years to 23.5% in patients aged 80 to 89 years and is inversely correlated to the prognosis.⁷

Wolf et al, analysing data from the Framingham study, saw an incremental rise of AF as a main contributor to stroke in patients with increasing age.⁸ Wolf's reports on the link between AF and stroke led to studies suggesting the use of warfarin to reduce stroke risk in patients with AF. While these early studies on the link between AF and stroke were conducted in Caucasian patients, the situation appears to be similar in Asian populations. In a prospective cohort of 302 stroke patients older than 80 years of age, Wang et al found the risk factors for stroke in very elderly Chinese to be similar to those reported in Western countries.⁹ Similar prevalence is reported in Japan and Korea.

A recent meta-analysis showed that physicians are less likely to opt for anticoagulation therapy in patients over 70.¹⁰ Several possible reasons for this decision have been cited.

Physicians often fear that elderly patients, who are frequently on poly-pharmacological treatments, cannot maintain therapeutic INR due to various interactions of medications and compliance issues. Yet the patients (mean age 83.9 years) studied in The Warfarin versus Aspirin for Stroke Prevention in Octogenarians with Atrial Fibrillation study (WASPO) achieved the therapeutic INR range in 69%, expressed as a percentage of time patients spent in the target INR range from 2.0 to 3.0.¹¹ Even taking into account the closer monitoring of study patients, WASPO emphasises that good quality anticoagulation control can be achieved in elderly patients receiving poly-pharmacological treatment and hence, age alone should not be the deciding factor as to whether effective anticoagulation control can be achieved.

Since the early 2000s, several studies have specifically looked at the safety of anticoagulation in the very elderly.

For instance,

- The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA)¹² study assessed the annual risk of primary events of 973 elderly patients (mean age 81.5 years). The risk of primary events, which included ischaemic stroke, systemic embolus or intracranial haemorrhage, was lower for patients on warfarin as opposed to those on aspirin (1.8% of patients vs 3.8%). Warfarin efficacy was similar in elderly patients (aged ≥ 85 years) and younger patients.
- WASPO¹¹ showed that elderly patients (mean age 83.9 years) taking aspirin had more incidents of adverse events when compared to patients taking warfarin (33% of patients vs 6%, $P = 0.002$).
- A large Italian study¹³ specifically looked at bleeding risk in very old patients on vitamin K antagonists. In their population of 4093 patients with a median age of 84 years (range, 80 to 102 years) at the start of the study, major bleeding events were rare at 1.87 events per 100 patient years.

Physicians treating elderly patients tend to use anti-platelet agents such as aspirin, because of the perceived increased risk of bleeding associated with anticoagulation therapy. Contrary to this common perception, however, the risk of significant bleeding in patients receiving warfarin and aspirin is similar (1.5% vs 1.4%),¹⁴ so that elderly patients would benefit most from anticoagulation.

Average life expectancy is predicted to increase over the next few years. But with an ageing population, the incidence of stroke too will increase and elderly patients, particular those with AF will eventually form the majority of stroke patients. This calls for urgent action as the prevalence of AF has been estimated to triple by the year 2050.¹⁵

“My Patient is Likely to Bleed on Anticoagulation”: Risk of Haemorrhage

Perhaps the most feared complication of anticoagulation therapy is intracranial haemorrhage. The absolute risk of warfarin-associated intracranial haemorrhage in AF patients is relatively low at 0.2% per year. A recent meta-analysis of 39 studies looked at major bleeding events as a function of indication for anticoagulation.¹⁶ It concluded that no significant difference in bleeding rates could be found between contemporary indications AF, ischaemic heart disease, venous thromboembolism and prosthetic heart valves. The meta-analysis also showed that the rate of ICH increases by 9% every year of age ($P = 0.0001$) in the patient population ($n = 22,415$) but is increased by 72% with each 1.0-point increase in target INR. This emphasises the importance of anticoagulation within the target range.

A number of bleeding risk scoring tools exists, but they are often not pragmatic in clinical settings as they require access to a laboratory, money and time. Without taking recourse to established scoring systems, physicians tend to underestimate stroke risk by 22%, while they overestimate the bleeding risk by as much as 670%.¹⁷

The most readily available scoring tool is HAS-BLED.⁴ It takes into account presence of hypertension, abnormal renal or liver function, history of stroke, history of bleeds in the past, labile INR, age (aged ≥ 65 years), drug history and alcohol use. A score of ≥ 3 would alert the physician to closely monitor patients. It is however not an absolute exclusion criterion from anticoagulation therapy.¹⁸ Rather, physicians must ensure that the patients with HAS-BLED ≥ 3 are regularly monitored and that the target INR range is reached.

While intracranial haemorrhage is potentially fatal, both patients and physicians usually primarily think of GI haemorrhage when considering the risks of anticoagulation therapy. A recent meta-analysis looking at the increase of bleeding rates comparing aspirin with placebo showed an absolute increase of 0.12% per year. Use of warfarin along with other drugs does not further increase the bleeding risk. Direct comparison of monotherapy with warfarin versus aspirin showed no significant differences.¹⁹

“My Patient Falls too Often to be Safely Put on Anticoagulation Therapy”: Anticoagulation and Falls

Elderly patients who are thought to be likely to fall are often not started on anticoagulative therapy because of perceived risk of bleeding complications. The risk for anticoagulation related bleeds in falling patients cannot be measured in a controlled study. Hence, all published data are estimates. Based on a Markov decision analytic model to determine the ideal treatment for elderly patients with AF who are at increased risk of falling, a patient with an average risk of 5% of AF-associated stroke would be required to fall about 300 times per year for the risks of anticoagulation (intracranial bleeding) to outweigh the benefits. The most current available guidance by the AAN, published in 2014, thus advises not to withhold anticoagulation because of perceived risk of falls.

“My Patient Does not Want Anticoagulation”: The Role of Adequate Education

A study which investigated the impact of patient preference for anticoagulation treatment in AF showed that 47% of the 97 randomly selected AF patients (age range, 70 to 85 years) were not being prescribed warfarin by the physicians although they wanted to be on warfarin treatment.²⁰ It is important that physicians educate patients on the various

anticoagulant agents and explain the importance, the risks and the benefits of being on anticlot therapy.¹⁷ Preliminary data from an ongoing study shows that 49% of the patients were unaware of the reasons why they were treated with either aspirin or anticoagulants.

The most recent ACCP guidelines have specifically addressed the issue of patient preferences. They found that most patients would regard a stroke versus bleeding risk ratio ranging from 3:1 to 2:1 as an argument to sway them towards anticoagulation, and recommends that physicians should take the same approach.

Conclusion

The perceived risks of anticoagulation are barriers, which hinder physicians from prescribing appropriate treatment to local patients. Table 2 lists the raised concerns and evidence refuting them. Anticoagulation therapy has proven to be beneficial to all patients with AF, and the benefit of adequate anticoagulation typically outweighs the risk. Anticoagulation is especially important in the elderly population as they have an increased risk of stroke due to AF. This would ultimately ensure that AF-associated strokes can be reduced with appropriate and effective use of anticoagulation.

Table 2. Summary of the Myths on Anticoagulation in Asians and Evidence Disputing such Myths

Myth	Evidence
“Patient is too old for anticoagulation.”	WASPO trial reports that 69% of patients (mean age, 83.9 years) achieved therapeutic INR range of 2.0 to 3.011. BAFTA trial reports that similar efficacy of warfarin was seen in elderly (aged > 85 years) and younger patients. ¹² Poli et al showed bleeding events amongst elderly patients (with a median age of 84 years) were rare at 1.87 events per 100 patient years. ¹³
“Patient is likely to bleed on anticoagulation.”	Hansen et al showed no significant differences in bleeding rates between warfarin monotherapy and aspirin monotherapy thus perhaps implying that warfarin is not more likely to cause bleeding. ¹⁹ Hansen et al also showed that incidence rate of GI bleeding on monotherapy is lower than for aspirin monotherapy. ¹⁹
“My patient falls too often to be safely put on anticoagulation therapy.”	Markov decision model showed that with an average risk of 5% of AF-associated stroke, patients would be required to fall about 300 times a year for the risks of anticoagulation (i.e intracranial haemorrhage) to outweigh the benefits (AAN guideline 2014).
“My patient does not want anticoagulation.”	Protheroe et al showed that 47% of the 97 randomly selected AF patients (age range, 70 to 85 years) were not being prescribed warfarin by the physicians although they wanted to be on warfarin treatment. ²⁰

WASPO: Warfarin versus Aspirin for Stroke Prevention in Octogenarians with AF; BAFTA: Birmingham Atrial Fibrillation Treatment of the Aged; AAN: American Academy of Neurology; AF: Atrial fibrillation

REFERENCES

- Yap KB, Ng TP, Ong HY. Low prevalence of atrial fibrillation in community-dwelling Chinese aged 55 years or older in Singapore: a population-based study. *J Electrocardiol* 2008;41:94-8.
- Rasekh A. Anticoagulants and atrial fibrillation. *Tex Heart Inst J* 2005;32:218-9.
- Lip GY, Nieuwlaet R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010;137:263-72.
- Pisters R, Lane DA, Nieuwlaet R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;138:1093-100.
- GS K, M MT, TW L. Adherence to anticoagulation guidelines in non-valvular atrial fibrillation patients remains poor despite admission to a tertiary cardiology unit. *Europace* 2013. p. ii122-ii67.
- Kakkar AK, Mueller I, Bassand JP, Fitzmaurice DA, Goldhaber SZ, Goto S, et al. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry. *PLoS One* 2013;8:e63479.
- Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol* 1998;82:2N-9N.
- Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. *Arch Intern Med* 1987;147:1561-4.
- Wang D, Hao Z, Tao W, Kong F, Zhang S, Wu B, et al. Acute ischemic stroke in the very elderly Chinese: risk factors, hospital management and one-year outcome. *Clin Neurol Neurosurg* 2011;113:442-6.
- Pugh D, Pugh J, Mead GE. Attitudes of physicians regarding anticoagulation for atrial fibrillation: a systematic review. *Age Ageing* 2011;40:675-83.
- Rash A, Downes T, Portner R, Yeo WW, Morgan N, Channer KS. A randomised controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO). *Age Ageing* 2007;36:151-6.
- Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007;370:493-503.
- Poli D, Antonucci E, Testa S, Toso A, Ageno W, Palareti G, et al. Bleeding risk in very old patients on vitamin K antagonist treatment: results of a prospective collaborative study on elderly patients followed by Italian Centres for Anticoagulation. *Circulation* 2011;124:824-9.
- Stroke Prevention in Atrial Fibrillation Study. Final results. *Circulation* 1991;84:527-39.
- Zeevi N, Chhabra J, Silverman IE, Lee NS, McCullough LD. Acute stroke management in the elderly. *Cerebrovasc Dis* 2007;23:304-8.
- Linkins L, O'Donnell M, Julian JA, Kearon C. Intracranial and fatal bleeding according to indication for long-term oral anticoagulant therapy. *J Thromb Haemost* 2010;8:2201-7.
- Bungard TJ, Ghali WA, McAlister FA, Buchan AM, Cave AJ, Hamilton PG, et al. Physicians' perceptions of the benefits and risks of warfarin for patients with nonvalvular atrial fibrillation. *CMAJ* 2001;165:301-2.
- Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet* 1994;343:687-91.
- Hansen ML, Sorensen R, Clausen MT, Fog-Petersen ML, Raunso J, Gadsboll N, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch Intern Med* 2010;170:1433-41.
- Protheroe J, Fahey T, Montgomery AA, Peters TJ. The impact of patients' preferences on the treatment of atrial fibrillation: observational study of patient based decision analysis. *BMJ* 2000;320:1380-4.

Combined Transcatheter Therapy of Aortic Stenosis and Thoracic Aortic Aneurysm

Dear Editor,

Transcatheter aortic valve implantation (TAVI) and thoracic endovascular aortic repair (TEVAR) are independently well established techniques for treating aortic valve stenosis and thoracic aortic aneurysms. The co-existence of both lesions in patients occurs as they share similar risk factors but the treatment of patients with these combined lesions and high surgical risk remains unclear. The presence of a thoracic aneurysm was an exclusion criterion in the landmark PARTNER trial.^{1,2} The presence of such a lesion increases the risks of aortic rupture and significant device interaction may occur during the procedure. There have thus been no prior reports of the feasibility of treating such patients with combined TAVI and TEVAR.

Case Report

An 87-year-old male with hypertension, renal impairment and multiple laparotomies (gastrectomy and cholecystectomy) presented with New York Heart Association Class III heart failure at our centre. The logistic euroscore and Society of Thoracic Surgeons score was 23.9% and 4.7% respectively. Besides these surgical scores, the patient was very frail, thus TAVI was considered. Transthoracic echocardiogram revealed severe aortic valve stenosis with an aortic valve area of 0.68 cm² and mean transthoracic gradient of 76 mmHg with a preserved left ventricular ejection fraction of 70%. His coronary angiogram showed a 60% tubular stenosis of the mid right coronary artery and his iliofemoral angiogram confirmed a minimal luminal diameter of 7.8 mm.

The annulus was measured to be 24 mm on transesophageal echocardiogram. During this study, a complex aortic lesion consisting of severe atherosclerosis, ulceration and localised dissection and aneurysm was detected in the descending aorta (Fig. 1). This was confirmed to be a saccular aneurysm located on the inner curve at the inferolateral aspect of the aorta just distal to the left subclavian artery on computed tomography (Fig. 2). These findings were discussed with the vascular surgeon and alternative modes of therapy including open surgery with aortic repair and valve replacement were offered. The risks of combined TAVI and TEVAR were also discussed. The decision for TAVI and TEVAR was subsequently made. The concern was the risk of aortic

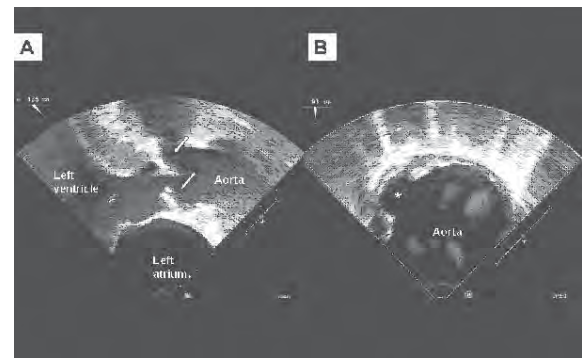


Fig. 1. Transesophageal echocardiogram showing severe aortic valve stenosis (A) and the aortic lesion (B). The arrows demarcate the severely calcified aortic valves and the asterisk marks the aneurysm.



Fig. 2. Computed tomography of the aortic saccular aneurysm (marked by arrows) seen in the lateral projection (A) and the anterior posterior projection (B).

dissection if TAVI were to be done first as the SAPIEN XT valve (Edwards Lifesciences, Irving, California) would be delivered via a relatively short sheath and exits would be uncovered at the level of the abdominal aorta. Conversely, the risk of having TEVAR first would be stent graft migration due to interaction with the TAVI delivery system.

The heart valve team decided to proceed with a femoral cutdown to facilitate the advancement of the 19 Fr Edwards sheath. A JR4 diagnostic catheter was positioned carefully over a J-tipped 0.035 wire and then exchanged for an Amplatz Extra-Stiff Wire (Cook medical Inc, Bloomington, IN). Sequential dilations were performed using the Edwards dilators and the 19 Fr Edwards sheath was then placed in

situ. Balloon aortic valvuloplasty with a 20-mm NuMED Nucleus™ balloon (NuMED, Inc.) was performed with rapid ventricular pacing. The Edwards Novaflex delivery system (Edwards Lifesciences, Irving, California) was loaded in the usual way and then delivered over the stiff wire.³ The flexion of the sheath was performed later than usual (at the take-off of the left subclavian artery) to avoid trauma to the aneurysmal site. The valve was uneventfully deployed under rapid ventricular pacing at a rate of 180 per min in the standard manner.⁴ The final result was good with the mean transaortic gradient reduced to 13 mmHg with only trivial paravalvular regurgitation and no endoleak seen. Following this, the Novaflex sheath was gradually antilexed across the aortic arch, avoiding the aneurysmal section. While keeping the stiff wire in situ (in the left ventricle), the 19 Fr Edwards sheath was exchanged for a 22 Fr Cook sheath. The wire was intentionally kept in the left ventricle to avoid having to pass the stiff wire again across the Edward SAPIEN XT valve and risk dislodging it. A 34 mm x 150 mm Zenith® Proform TX2® graft was then delivered and deployed over the stiff wire successfully (Fig. 3). The sheath was subsequently removed and the access site was closed surgically. The repeat transthoracic echocardiogram showed normal aortic prosthetic function at 6 months with mean gradient of 10 mmHg and aortic valve area of 2.5 cm². The patient remained well at 23 months of follow-up and remained in NYHA class I.

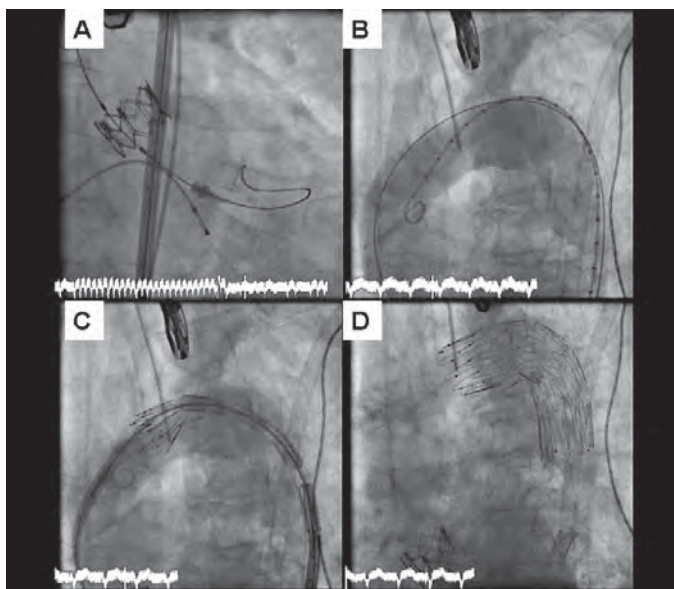


Fig. 3. Fluoroscopic images of the Edwards SAPIEN XT valve and the Zenith® Proform TX2® graft. (A) Deployment of the SAPIEN XT valve. (B) Assessing dimensions with a marker pigtail catheter. (C) Deployment of the stent graft. (D) Fluoroscopic image of both the stent graft and the SAPIEN XT valve.

Discussion

Aortic aneurysms can be associated with severe aortic valve stenosis. This could be in the setting of bicuspid aortic valve stenosis with ascending aortic aneurysms or dissection. A large proportion of patients with aortic valve stenosis share similar risk factors and pathology as atherosclerotic lesions and the co-existence of these lesions are likely. Due to the potential risks of an aortic dissection, the presence of significant aortic diseases has been excluded in clinical trials of TAVI.^{1,2} To our knowledge, this is the first reported case of a combined TAVI and TEVAR and highlights the challenges of such a procedure.

Firstly, the choice of access is important. The sheaths required in TEVAR are often larger than those of TAVI; so, the selection of an adequate femoral size is crucial. The choice of TAVI first, followed by TEVAR next, is favoured by the anatomy in this patient as we were confident that the stiff delivery system and wire were more likely to contact the outer curve of the aorta in this patient and avoid the aortic lesion. This may not always be the optimal sequence especially if the lesion is situated on the outer curve.

There was also a consideration of staging the procedure (i.e. performing TAVI first and then TEVAR on another date). This also has the benefit of reduced contrast load. In the end, this was not done as we felt that we could avoid 2 separate large arteriotomies. Moreover, the stent graft was needed for standby should a dissection occur during TAVI.

There was also a concern that the acutely increased cardiac output and blood pressure following TAVI may predispose to progression of the aneurysm or dissection. If TEVAR were to be performed before TAVI, the chief concern would be device interaction as the long stent graft is likely to interact with the stiff Edwards Novaflex delivery system, resulting in dislocation of the stent graft. The use of contrast could be significant in this group of patients. We mitigated this by obtaining the optimal valve plane for TAVI during the initial workup rather than during the procedure. The presence of calcium landmarks also enabled us to minimise contrast injection during valve deployment.

Finally, it is important to keep the wire in the left ventricle after a successful TAVI as rewiring and positioning of a stiff wire near the newly deployed Edward SAPIEN valve for the purposes of TEVAR may predispose to valve migration or even embolisation.

Conclusion

Combined TAVI and TEVAR may be feasible in selected patients. Preprocedural planning is crucial to the choice of access, the sequence of the procedure and the prevention of complications.

REFERENCES

1. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;364:2187-98.
2. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597-1607.
3. Webb JG, Altwegg L, Masson JB, Al Bugami S, Al Ali A, Boone RA. A new transcatheter aortic valve and percutaneous valve delivery system. *J Am Coll Cardiol* 2009;53:1855-8.
4. Webb JG, Chandavimol M, Thompson CR, Ricci DR, Carere RG, Munt BI, et al. Percutaneous aortic valve implantation retrograde from the femoral artery. *Circulation* 2006;113:842-50.

Edgar LW Tay, ¹*MBBS, MRCP, FAMS*, Jimmy KF Hon, ¹*MB ChB, MRCEd, FRCS(C-Th)(Eng)*, James WL Yip, ¹*MBBS, MRCP, FAMS, Kristine LK Teoh, ¹MBBChir (Cantab), MS (Lon), FRCS (C-Th)(Eng), Kian Keong Poh, ¹FAMS, FRCP, FACC, Sophia BL Ang, ¹MBBS, MMed (Anesthesia), Lenny KA Tan, ¹MBBS, FRCP, FRCPE, Peter Robless, ¹MBChB, FRCS, MD*

¹National University Heart Centre, National University Health System, Singapore

Address for Correspondence: Dr Edgar Tay, National University Heart Centre, National University Health System, NUHS Tower Block Level 9, 1E Kent Ridge Road, Singapore 119228.
Email: Edgar_Tay@nuhs.edu.sg

Obstructed Hemivagina and Ipsilateral Renal Anomaly—A Reproductive Surgical Unit's Experience

Dear Editor,

Uterus didelphys with an imperforate hemivagina is an embryonic malformation of the genitourinary system of the female that occurs between the 12th and 16th weeks of pregnancy. This defect may manifest itself as a duplication of all or part of the female reproductive system. The obstruction of one hemivagina will block outflow, resulting in complications such as haematocolpos and haematometra. The persistence of this situation may also be complicated by the occurrence of endometriosis as a result of blood reflux into the abdominal cavity. These anomalies are frequently accompanied by kidney and urinary tract malformations (i.e. kidney agenesis and dysplasia, double collecting system, ectopic ureter) on the same side as the defect.¹

Materials and Methods

A retrospective case review revealed 4 patients being diagnosed with uterine didelphys with obstructed hemivagina from August 2010 to May 2012. All patients underwent examination under anesthesia, hysteroscopic resection of the obstructing vaginal septum with therapeutic laparoscopy.²

Results

Please refer to Table 1. The mean age at diagnosis was 15 years (range, 12 to 22 years). Menarche ranged from 12 to 13 years of age, with a mean of 12.5 years. All patients had a history of regular menses with cyclic pelvic pain. Two patients had suspected uterine didelphys discovered through the presence of other developmental anomalies that prompted earlier workup. All patients had the diagnosis made after radiological investigations. Three of our patients, in their teenage years, presented with compressive symptoms such as backache and acute retention of urine to the paediatrics department. All had obstructed hemivagina, ipsilateral renal anomaly and 1 had bilateral renal anomaly.

Discussion

Ultrasound and magnetic resonance imaging (MRI) were the most frequently used modalities for initial imaging. MRI, the most sensitive imaging modality for congenital anomalies, was used in only 2 cases. In previous studies,

MRI was found to be 100% sensitive and 83% to 100% specific.³

Because of the interesting clinical picture, didelphys uterus with unilateral obstruction is often published in the literature. This anomaly usually presents with acute or chronic pelvic pain following menarche. There is a large variation in time to accurate diagnosis. This may be due to several factors. Since only one uterine horn is obstructed, the patient menstruates regularly from the other horn delaying the diagnosis of outflow obstruction that would more readily be made had she presented with amenorrhea and cyclic pain. As it is rare, it is not on the list of differential diagnosis that is considered. When these patients present to doctors with abdominal pain, they may be given analgesics e.g. nonsteroidal anti-inflammatory drugs (NSAIDs). This may inadvertently cause a delay in diagnosis because they diminish or eliminate menses.⁴ In this report, we have observed that this method fails. That patient was sent to the orthopaedic surgeon who was not conversant in congenital anomalies, and subsequently, failed to make the correct diagnosis. It is common for these patients to have cyclic pelvic pain which in the presence of menstrual outflow obstruction results in retrograde flow, haematometra, haematosalpinx, and endometriosis.

The review of the literature in the management of such cases have revealed several approaches. Traditionally, it has been under examination under anaesthesia with scapel and blade for resection of the vaginal septum, resulting in hymenectomy.⁵ In some cases, because of the abdominal symptoms, laparotomy has been done inadvertently, with a hysterectomy in one case.⁴

The aims of the management is to confirm the diagnosis, treat symptoms, improve reproductive potential and preserve hymen (important in some cultures).

Resection of the vaginal septum can be done with hysteroscopy with ultrasound guidance or with additional laparoscopy. Under hysteroscopic resection, a resectoscope is used. The benefits include resection under direct visualisation, preservation of the hymen and the ability to resect a high small haematocolpus. Patient 1 was a challenging case. She had a high small haematocolpus with a small button hole opening which was picked up under magnification by hysteroscopy.

Table 1. Summary of the Results from Imaging Modalities Compared with Intra-operative Findings and Follow-up.

Patient*	Imaging Modality	Scan Findings	Operative Findings	Follow-up
1	U/S	Bicornuate uterus, possible haematocolpus and absent left kidney.	Vaginoscopy/hysteroscopy—Right cervix seen, small button hole in mid point of septum with possible pus drainage. Laparoscopy—Uterine didelphys, both tubes normal with slight left peritubal adhesions. Cystoscopy—Right ureter orifice seen, left ureteric orifice not seen.	29 months: well
	MRI	Uterine didelphys with left haematometrocolpus, hypoplastic ectopic left kidney. Possible ectopic left ureter insertion in vagina.		
2	U/S	Uterine didelphys, obstruction of right vagina by septum.	Vaginoscopy/hysteroscopy—Low haematocolpus (obstructed), complete septum. Laparoscopy—Uterine didelphys, right mildly dilated haematosalpinx.	50 months: well
3	U/S	Uterine didelphys with obstruction of the right vagina, left uterine horn appears unaffected, possible vaginal septum obstructing the right side. Haematocolpus with bicornuate uterus, absent right kidney.	Vaginoscopy/hysteroscopy—Left 13 cm haematocolpus (obstructed). Laparoscopy—Bicornuate uterus, both tubes and ovaries normal (Figs. 1 and 2).	20 months: well
	CT	Haematocolpus with bicornuate uterus, absent right kidney.		
4	MRI	Complete septate uterus with left haematometrocolpos and left haematosalpinx, left renal agenesis and lumbar scoliosis (Fig. 3).	Vaginoscopy/hysteroscopy—10 cm left haematocolpus, complete septum. Laparoscopy—Bicornuate uterus with left blocked haematosalpinx- neosalpingostomy done, endometriosis on posterior uterine surface and left ovarian fossa.	29 months: well

U/S: Ultrasound; MRI: Magnetic resonance imaging; CT: Computed tomography
*In all cases, hymen was preserved.

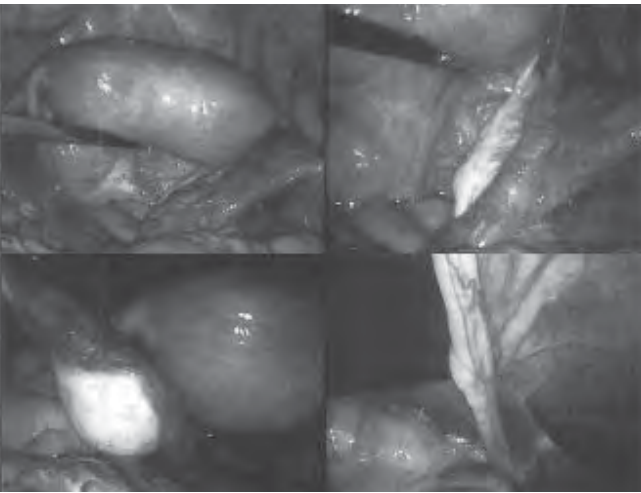


Fig. 1. Bicornuate uterus as seen laparoscopically during surgery.

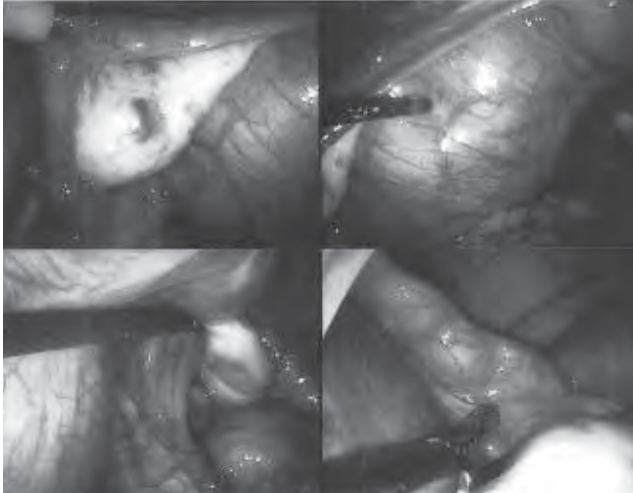


Fig. 2. Obstructed hemivagina as seen laparoscopically during surgery.

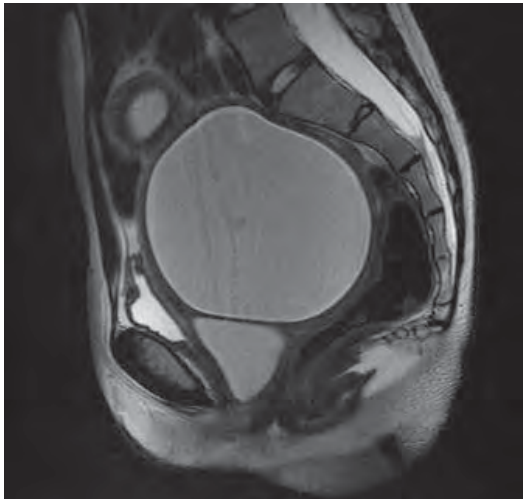


Fig. 3. MRI of left haematometocolpos.

The other issue is the discordance between ultrasound findings and operative findings. In Patient 1, besides bicornuate uterus and possible haematocolpos, there was nothing else reported on the ultrasound. Laparoscopically, there was slight peritubal adhesions which were resected. In Patient 2, the tubes were reported to be normal but laparoscopically, there was mild right haematosalpinx. We advocate the addition of routine laparoscopy as part of the surgical procedure because it allows the diagnosis of Mullerian abnormalities and treatment of conditions such as endometriosis and pelvic adhesions. The presence of hydrosalpinx on ultrasound would strongly support the inclusion of laparoscopy. It also allows maximising the fertility potential with measures such as tubal surgery and endometriotic ablation (possibly from retrograde menses).

One interesting case that we have in our series is Patient 1, a 22-year-old female who presented past 14, which is the usual age of presentation. She presented with decreased menstrual flow. She presented late because she had a button-hole defect in the vaginal septum which allowed limited flow of menses and hence no overt symptoms. The limitation faced during surgery was that there was no obvious bulge on hysteroscopy. We used the button hole⁵ that was extruding pus-like material as a guide for resection. We made a 4-cm incision originating from the button hole. Hysteroscopy allowed us a magnified vision to identify the button hole which the naked eye would have missed. On resection during surgery, there was pus in the hemivagina which was probably the result of an ascending infection.

Conclusion

In view of current evidence, hysteroscopic resection should be the modality of choice. We advocate the use of hysteroscopic resection because it allows a magnification of

visual field for surgical procedure and better identification of the anatomy with allowing the preservation of hymen. We advocate laparoscopy because it allows the confirmation of the diagnosis, allows the diagnosis and treatment of conditions e.g. endometriosis not seen on ultrasound, allows the maximisation of reproductive potential e.g. neosalpingostomy (since this will not unblock on its own, and early intervention prevents chronic damage to tubes) and preservation of the hymen.

REFERENCES

1. Heinonen PK. Clinical implications of the didelphic uterus: long-term follow-up of 49 cases. *Eur J Obstet Gynecol Reprod Biol* 2000;91:183-90.
2. Kim TE, Lee GH, Choi YM, Jee BC, Ku SY, Suh CS, et al. Hysteroscopic resection of the vaginal septum in uterus didelphys with obstructed hemivagina: A case report. *J Korean Med Sci* 2007;22:766-9.
3. Letterie GS, Haggerty M, Lindee G. A comparison of pelvic ultrasound and magnetic resonance imaging as diagnostic studies for Mullerian tract abnormalities. *Int J Fertil Menopausal Stud* 1995;40:34-8.
4. Cicinelli E, Romano F, Didonna T, Schonauer LM, Galantino P, Di Naro E. Resectoscopic treatment of uterus didelphys with unilateral imperforate vagina complicated by hematocolpos and hematometra: case report. *Fertil Steril* 1999;72:553-5.
5. Lee CL, Wang CJ, Swee LD, Yen CF, Soong YK. Laparoscopic hemihysterectomy in the treatment of a didelphic uterus with a hypoplastic cervix and obstructed hemivagina. *Hum Reprod* 1999;14:1741-3.

Kai Lit Tan, ¹MRCOG, Edwin WH Thia, ¹MRCOG, Matthew SK Lau, ¹MRCOG, Steven BL Teo, ¹MRCOG, Jerry KY Chan, ¹PhD, Sadhana Nadarajah, ¹MRCOG, Seong Fei Loh, ²FRCOG, Veronique Viardot-Foucault, ¹MD, Heng Hao Tan, ¹MRCOG

¹Department of Reproductive Medicine, KK Women's and Children's Hospital, Singapore

²Thomson Fertility Centre, Singapore

Address for Correspondence: Dr Heng Hao Tan, Department of Reproductive Medicine, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899.

Email: tan.heng.hao@kkh.com.sg

Prostate Carcinoma Presenting with Symptoms Mimicking Rectal Cancer

Dear Editor,

Prostate carcinoma (PC) usually presents asymptotically with raised prostate specific antigen (PSA) or abnormal digital rectal examination (DRE).¹ Rarely, PC infiltrates the rectum and presents with symptoms mimicking rectal cancer (RC).² It is difficult to differentiate between the 2 clinically. We hereby report our experience in managing 2 such cases of PC that presented to our colorectal department.

Case Reports

Patient 1: A 72-year-old man presented with a few months of faecal incontinence and change in bowel habits and a circumferential rectal mass felt on DRE. Serum carcinoembryonic antigen (CEA) was 5 and a computed tomography (CT) scan of his abdomen and pelvis showed a large rectal tumour from anal verge to rectosigmoid junction with extensive nodal disease (Fig. 1). Colonoscopy showed a circumferential narrowing of the rectum and the working diagnosis was RC. However, biopsies of the rectal mucosa showed a poorly differentiated infiltrative carcinoma and immunohistochemical (IHC) stains were positive for PSA and alpha-methylacyl coenzyme A racemase (AMACR) suggestive of a prostatic adenocarcinoma. Serum PSA was then ordered and it was raised at 99.95. Magnetic resonance imaging (MRI) of the rectum showed extensive infiltration

of the prostate, seminal vesicles, rectum and the whole anal canal (spanning 11 cm) and intervening rectoprostatic spaces (Fig. 2). Bone scan was negative. A laparoscopic diverting sigmoid colostomy was performed in view of faecal incontinence likely from involvement of the anal sphincters from the extensive tumour. The consensus at our department's tumour board meeting for the origin of the tumour was a primary PC. He was referred to the urology department and a prostate biopsy was not performed in view of the raised PSA, positive prostate specific stains on biopsy and MRI findings. He received androgen deprivation (hormonal) and radiation therapy. Three months later, there was a good response with his PSA level dropping to 0.19. However, he passed away 7 months later from pneumonia and posterior circulation stroke.

Patient 2: A 75-year-old man presented with constipation and change in bowel habits and a circumferential, stenosing rectal mass was felt on DRE. Colonoscopy showed a raw ulcerated rectal mucosa suspicious for RC (Fig. 3) and biopsies showed a poorly differentiated carcinoma with features of adenocarcinoma. A CT scan of his abdomen and pelvis was normal except for an ill-defined prostate. The working diagnosis was RC but in view of the CT scan findings and prior clinical experience in Patient 1, serum PSA and prostate specific IHC stains were ordered to exclude

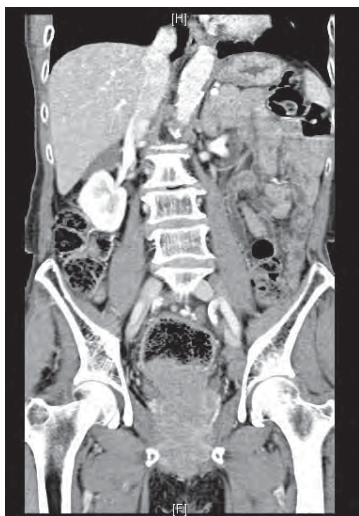


Fig. 1. CT scan of Patient 1, showing extensive tumour in rectum.

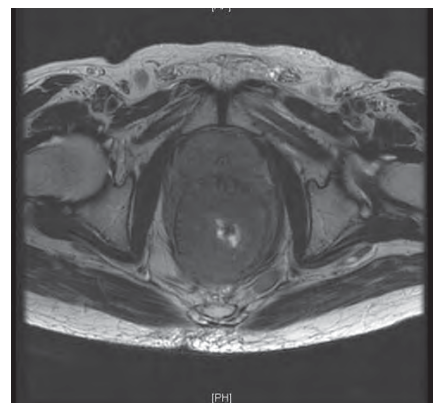


Fig. 2. T2 axial MRI rectum of Patient 1 showing prostate tumour invading around the walls of rectum and narrowing the lumen.

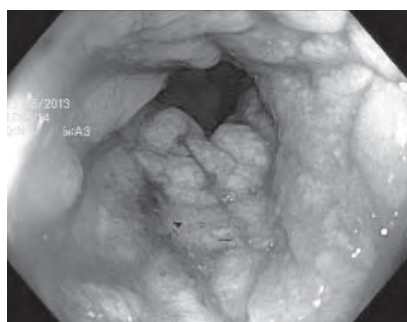


Fig. 3. Colonoscopy of Patient 2 showing raw ulcerated mucosa suspicious for RC.

PC. PSA was raised at 38.62 and the stains from the biopsies were positive for PSA, AMACR and prostatic specific acid phosphatase (PSAP). Bone scan was positive for multiple foci of osteoblastic lesions. He was referred to the urology department and PC was confirmed on prostate needle biopsy. Hormonal therapy was initiated for his metastatic PC and his colorectal symptoms improved.

Discussion

PC is the third most common cancer among men in Singapore based on Singapore Cancer Registry, Interim Report (2008 to 2012). They usually present asymptotically with raised PSA or abnormal DRE and with symptoms only when locally advanced or metastatic. Common manifestations of locally advanced PC include urinary symptoms, ureteral obstruction causing renal failure, haematospermia and even impotence. Manifestations of metastatic disease include bone pain, pathologic fractures, anemia, lower extremity edema and less commonly

malignant retroperitoneal fibrosis, paraneoplastic syndromes and disseminated intravascular coagulation.¹ Despite the close proximity of the prostate with the rectum, PC rarely infiltrates the rectum because of Denonvilliers' fascia acting as a barrier. Autopsy studies have found this incidence to be between 1% and 9%.³

In the rare instance when PC does invade the rectum, it can present with symptoms such as constipation, abdominal pain, rectal bleeding and altered bowel habits, mimicking RC.² PC tends to insinuate between the 2 layers of Denonvilliers' fascia, resulting in circumferential involvement around the rectum and ultimately fascial and mucosal penetration hence a circumferential mass or stricture is often felt on DRE.⁴ The first presentation may be to the colorectal department and inappropriate anterior resection and abdomino-perineal resection have been reported in the literature because of the clinical similarities between these two.⁵ In our 2 cases, the presenting symptoms, DRE and colonoscopy findings were all suggestive of RC. The CT scan of Patient 1 was even reported as a large rectal tumour. It is difficult to differentiate between PC infiltrating the rectum and RC based on the clinical features alone but several tests would help the clinician in doing so.

Firstly, prostate specific IHC stains are useful to differentiate between the 2. In Patient 1, the pathologist performed prostate specific stains on the biopsies upon seeing a poorly differentiated, infiltrative carcinoma. They were positive for PSA and AMACR (Fig. 4) and this prompted us to order PSA levels and a MRI rectum which supported the diagnosis of PC infiltrating the rectum rather than RC. In Patient 2, the histology of the rectal biopsy showed a poorly differentiated carcinoma with features suggestive of adenocarcinoma. The pathologist did not

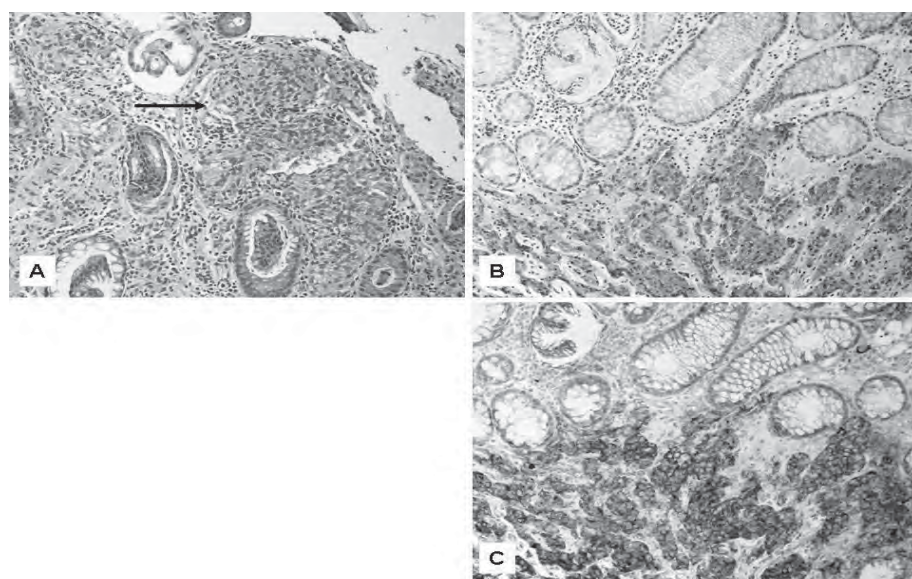


Fig. 4. Immunohistochemical stains of rectal biopsy of Patient 1. (A) Biopsy showing island of tumour cells (arrow) between rectal glands, haematoxylin and eosin stain x200. (B) Tumour cells are positive for prostatic specific antigen, immunoperoxidase stain x200. (C) Tumour cells are positive for racemase, immunoperoxidase stain x200.

perform any prostate specific stains initially but with a CT scan showing ill-defined prostate and previous clinical experience in Patient 1, we requested for prostate specific stains to be added after discussion with the pathologist and they were positive for PSA, AMACR and PSAP. We also then ordered a serum PSA which was raised at 38.62. Subsequently, PC was confirmed on prostate needle biopsy. In a review of the histopathological slides of 20 cases of PC found on colorectal biopsies by Lane et al, it was found that it was difficult to differentiate between the two based on the histology itself. The authors recommended ruling out a prostatic origin when faced with a poorly differentiated carcinoma in a rectal biopsy with the use of prostate specific IHC stains.⁶

Secondly, serum PSA is a simple blood test that can help to differentiate between the two. It is an established way for detecting PC and if raised, a prostate biopsy would then be advised to exclude PC. However, this is not investigation routinely ordered by a colorectal surgeon and is not a mass screening test in Singapore. Both our patients did not have any history of PC, any urinary symptoms, or their PSA tested prior to their presentation to our colorectal department which may have made the diagnosis more apparent. Hence, a high index of suspicion is required to prompt the clinician to order this test when faced with such a clinical scenario. Clinicians should be aware of this clinical entity and its presentation.

Conclusion

In rare instances, PC can infiltrate the rectum and present with symptoms mimicking RC. It is difficult to differentiate between the two based on clinical features alone. A high index of suspicion is required to avoid it being missed, delayed or misdiagnosed especially since the patient may not have any prior history of PC, urinary symptoms or PSA screening tests before. The use of prostate-specific IHC stains in biopsies and serum PSA are useful in differentiating between the two.

REFERENCES

1. Campbell-Walsh Urology, 10th Edition 2012. Chapter 99: Early detection, diagnosis and staging of prostate cancer. Saunders, 2011.
2. Bowrey DJ, Otter MI, Billings PJ. Rectal infiltration by prostatic adenocarcinoma: report on six patients and review of the literature. *Ann R Coll Surg Engl* 2003;85:382-5.
3. Arnheim FK. Carcinoma of the prostate: a study of the postmortem findings in one hundred and seventy-six cases. *J Urol* 1948;50:599-603.
4. Lasser A. Adenocarcinoma of the prostate involving the rectum. *Dis Colon Rectum* 1978;21:23-5.
5. Fry DE, Amin M, Harbrecht PJ. Rectal obstruction secondary to carcinoma of the prostate. *Ann Surg* 1979;189:488-92.
6. Lane Z, Epstein JI, Ayub S, Netto GJ. Prostatic adenocarcinoma in colorectal biopsy: clinical and pathologic features. *Hum Pathol* 2008;39:543-9.

Zhenbang Liu, ¹MBBS, MRCS, Quormeng Leong, ²MBBS, MRCS, FRCS, Hai Yi Teo ³MBBS, FRCPa, Yee Mun Lee, ¹MBBS, MRCS, FRCS

¹Urology Department, Tan Tock Seng Hospital, Singapore

²General Surgery Department, Tan Tock Seng Hospital, Singapore

³Pathology Department, Tan Tock Seng Hospital, Singapore

Address for Correspondence: Dr Zhenbang Liu, Urology Department, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.
Email: Zhenbang.liu@mohh.com.sg

General Surgery (GS) Residency Selection Process: A Comparison Between Singapore (Singhealth) and United States

Tze Tec Chong, ¹MBBS, FACS, Khee Chee Soo, ^{1,2}MD, FRACS, FACS

Completion of medical school training is a milestone in every doctor's career which represents a starting point from which the next phase of medical training begins. Traditionally, this phase starts with the trainee as a houseman, then a medical officer and onwards to go through further training if desired. For those who are surgically inclined, one would apply for Basic Surgical Training (BST) and then after completion of MRCS part 1, go on to Advanced Surgical Training (AST). The total time commitment for BST and AST average 6 years. This system, however, is gradually phased out.

Recently, the Ministry of Health (MOH) has decided to embark our trainees on a different path of surgical training and has adopted the residency system modelled after that in the United States (US). General surgery residency was among the first residencies to roll out live, and as of 2013, this programme is in its 4th year of implementation. The Accreditation Council for Graduate Medical Education -International (ACGME-I) has visited this programme and re-accredited it till 2016. Entry into General Surgery (GS) residency can be attained directly from medical school or as a house officer (HO) / medical officer (MO).

This paper seeks to compare and contrast the differences in the selection processes for general surgery residents in Singapore (Singhealth) and the United States.

Singapore

In Singapore, the GS residency is hosted by 3 Sponsoring Institutions (SIs) which house various hospitals under their umbrellas: (i) Singapore Health Service comprising Singapore General Hospital, Changi General Hospital, KK Women's and Children's Hospital; (ii) National University Health System comprising National University Hospital and Jurong General Hospital; (iii) National Healthcare Group -Alexandra Hospital Pte Ltd (NHG-AHPL) comprising Tan Tock Seng Hospital, Khoo Teck Puat Hospital and Institute of Mental Health. All applications to any of the 3 SI general surgery programmes in Singapore are submitted to MOH to create a portfolio. The application portfolio consists of

personal statement, transcripts, hospital postings (HO/MO), curriculum vitae (CV) and referees (3 for graduating seniors and the dean's letter of recommendation acts as the 4th referee and 4 for HO/MO). The referees are contacted electronically by MOH to enter their comments and scores for the applicant on a standard questionnaire.

Candidates are encouraged to go to the various SI open houses to learn more about their programmes as well as have discussions with the respective programme faculty and advisors. Each programme also has its unique website to convey information to prospective applicants. These programmes individually do not have a formal interview schedule as MOH discourages formal interviews by the SI. However, the equivalent mechanisms are in place to get to know the applicants better as well as assess their fit into these respective SI.

The next step is for the applicants to sit through the formal interview conducted by MOH called the Multiple Mini Interviews (MMI). Candidates are required to complete a circuit of 4 interview stations,¹ each lasting approximately 10 minutes. Candidates will be presented with a short case scenario for each station and allowed 2 minutes of reading time. The actual interview will last for about 8 minutes and the responses assessed on pre-determined domains that include but not limited to:

- (a) Teamwork and collegiality
- (b) Communication skills
- (c) Compassion
- (d) Professional and ethical conduct
- (e) Personal attributes

MOH will then inform the SI of those candidates who have been successful at the MMI, and this list of candidates will be ranked by the SI for matching. If the SI feels that a particular candidate is outstanding but did not make it for the MOH list after the MMI, they can request for him or her to be added back to the list accordingly (WK Wong, December 2013, personal communication).

At Singapore Health Service (Singhealth), the programme

¹Department of Vascular Surgery, Singapore General Hospital, Singapore

²National Cancer Centre, Singapore

Address for Correspondence: Dr Chong Tze Tec, Department of Vascular Surgery, Singapore General Hospital, Outram Rd, Singapore 169608.

Email: chong.tze.tec@sgh.com.sg

identifies interested candidates at the open house. After the review of CVs, the programme director sends out invites to prospective residents for a “chit chat” session which is an informal sit down session with 3 faculty members to get to know the candidate better and, at the same time, to allow the candidate to find out more about the programme. Typically, a session lasts 30 minutes. Notes are taken from all these meetings which are used during the final selection process (PC Cheow, December 2013, personal communication).

Aside from the contents of the portfolio submitted to MOH, comments regarding the candidates are sought from all surgical faculties. These may be from interactions as a student, HO or MO. In an effort to get to know how these candidates function as members of a team, comments are also sought from the current residents and registrars as their interaction with the candidates which might differ from that with the consultants.

Finally, all the information from the MMI, portfolio, faculty comments and staff interactions are compiled and presented at the rank meeting. This rank meeting is separate for students and HO/MO at this time since 2 separate rank lists have to be presented to MOH. Members of the rank meeting include programme director, core faculty, representative head of departments and any interested faculty member. The confidential rank list generated from this meeting would be circulated to all the faculty again for comments prior to its final submission to MOH.

Candidates, on the other hand, also have a deadline for the submission of their rank lists. They are allowed to apply for up to 3 different specialties if one of their choices includes the clinician scientist track. Otherwise, a maximum of 2 clinical specialties. A matching process then ensues under the purview of MOH, and the applicants and SI will be notified of the results.

United States

In 2010, a total of 246 accredited general surgery programmes were available throughout in the US. All programmes have their unique characteristics and selection criteria. For this comparison, I will focus on 3 institutions—namely Brown University, Duke University and Washington University. Highly sought after programmes have successful application rates of around 1% i.e. there is one residency position for every hundred applicants. Almost all applications come from the graduating medical school class.

A prescreen is conducted on all the applications. In general, any failures in the United States Medical Licensing Examination (USMLE) scores or courses in medical school will be eliminated. The information is then reviewed once the file is complete through the Electronic Residency Application Service (ERAS).

ERAS is a service that transmits applications, letters of recommendation (LoRs), Medical Student Performance Evaluations (MSPEs), medical school transcripts, USMLE transcripts, Comprehensive Osteopathic Medical Licensing Examination (COMLEX) transcripts, and other supporting credentials from applicants and their designated Dean's Office to the respective programme directors.

Applications are scored objectively based on medical school transcripts, sub-internship grades, dean's recommendations, clerkship grades, class rank, research activities, leadership activities etc. (M Awad, December 2013, personal communication). Every programme has a different weightage to each of these components which add up to a final score.² Based on these, about 100 applicants are invited to participate in the interviews which happen 3 times to allow for schedule clashes with other programmes. Sometimes, programmes in the same geographical area will cluster their interview schedules to minimise travel time and cost for the candidates.

There is no formal open house for the candidates to get to know programmes. In general, since most of these programmes are established, their reputation is already well known in the community, and it is easy to find out by either speaking with current residents of the programmes or graduates of the programmes who may be in the candidate's medical school faculty or clinical faculty. Residents are often connected to others who are in the same “interview trail” and would share programme information with one another.

Candidates would usually select 10 to 15 programmes to attend the interviews for, it is a compromise between cost, risk of interview burn-out and maximising chances of matching into a residency which can be very competitive depending on the discipline of interest and programme.

Typically, residents have a social gathering prior to or immediately after the interview date with the residents e.g. at dinner or drinks. This is to allow the candidates to interact more freely with the residents without faculty oversight, and encourage them to ask questions or voice concerns about the programme. It also gives the residents a chance to get to know the candidates better personally to see if they would be a good fit for the programme.

On the day of interview, each candidate is usually interviewed by the chairman of department or programme director and 2 to 3 other faculty members.³ These sessions may be also attended by a senior resident. The setting of the interview can be one-to-one or multiple faculty present. The interview format is usually left to the discretion of the interviewer(s) but often includes the following themes: presentation, personality, goals, work ethic, verbal skills. A subjective score is given for each interview session and combined to give a final subjective score (D Harrington, December 2013, personal communication).

The total score is then tabulated from the objective and subjective scores using each programme unique algorithm and shown to all faculty involved at ranking meeting. All comments made during the interview sessions are reviewed and resident feedback is welcome. These come from the social event i.e. dinner, informal sessions while waiting during interview day, lunch and during the tour of facilities given by the residents. A final rank list is submitted to the National Resident Matching Program (NRMP) for the match.⁴

On the administrative side, the match is conducted by the NRMP. The NRMP is sponsored by 5 organisations: the American Board of Medical Specialties (ABMS), the American Medical Association (AMA), the Association of American Medical Colleges (AAMC), the American Hospital Association (AHA), and the Council of Medical Specialty Societies (CMSS). Each year, the NRMP conducts a match that is designed to optimise the rank ordered choices of students and programme directors. Registration starts in August with 1 December as the final deadline. From mid January to February, candidates and programmes submit their preference lists. Results of the match will be announced in the third week of March.⁵

Recommendations to Improve on the Singapore Selection Process

Choosing a surgical residency is a big decision for any graduating students, be they HOs or MOs. It entails a period of 5 years for clinical training and comes with it, a certain lifestyle. Ideally, all applicants would have worked at the SI of their choice prior to putting in an application for residency, however this is not practical for most of them. Unlike the BST/AST system where the faculty has close contact with the candidates and knows their personality, work ethic, clinical skills and acumen etc, the new residency system does not allow this luxury. As such, the selection of residents for residency is a crucial task for the faculty. With attrition rates of 17% to 26% in the US, no system or metric is perfect, constant improvements are needed with tweaks taking into account the local context.⁶

As the Singapore system allows entry into residency from different levels i.e. graduating medical students both from graduate and undergraduate medical schools, HO, MO and foreign registrars, the metric to judge these candidates cannot be uniform. Someone with more clinical experience should be expected to have conducted more research and perhaps pass basic examinations like MRCS part 1.

In line with that concept, a prescreen by MOH using the MMI does give some valuable information. We should add to that, a formal interview process by each SI to allow the candidates and faculty to better understand each other. All 3 SIs have their unique characteristics and may suit candidates

differently. An interview session would help bring forth these characteristics. An informal session with existing residents should be encouraged e.g. dinners or interactive games where personality traits not otherwise exposed during interviews can be uncovered. Consideration for overseas graduates must be given to attract the best students in the region and returning students so at least 2 dates should be set aside for interview activities.

While interviews are essentially a subjective assessment of the candidate, thoughts should be given to best add objectivity to the process. Predetermined domains e.g. work ethic, verbal skills, goals, presentation may be utilised for questions to be asked around them. A scoring sheet with comments can then be designed. This comes in handy during rank meetings as the faculty often have met too many candidates and may not remember every detail about them. These sheets will serve a useful reminder to the faculty.

The ranking of candidates should be done on one list where all applicants irrespective of clinical experience are critically looked at together. This would then be more streamlined than putting up a list for HO/MO and another for graduating students. Also, mandating a set quota for one group versus another should not be encouraged. We should instead focus on the strengths and weaknesses of each candidate and rank the person as such and accept a mix of residents by the match results. After all, a diverse vibrant group of backgrounds in the residency programme often is the best mix for a successful one.

There has been a long tradition for the current system of surgical training and we are proud of this heritage. Now we are entering into the next phase of training with the residency programme. The push towards academic medicine in Singapore causes us to strive to push past the current status quo by placing more emphasis on education and research. This should however not detract from our core mission as surgeons to heal patients who have given us their trust to help them in times of sickness and pain. It is with this in mind that we look at our selection process to determine who our next generation of surgeons will be.

REFERENCES

1. Ministry of Health Holdings, Singapore. Available at: www.physician.mohh.com.sg. Accessed 1 December 2013.
2. Washington University. Available at: <http://gsres.wustl.edu/>. Accessed 1 December 2013.
3. Brown University. Available at: <http://med.brown.edu/surgery/education/residency/>. Accessed 1 December 2013.
4. Duke University. Available at: <http://surgery.duke.edu/education-and-training/residency-programs/general-surgery-residency-training-program>. Accessed 1 December 2013.
5. National Resident Matching Program. Available at: <http://www.nrmp.org/>. Accessed 1 December 2013.
6. Dodson TF, Webb AL. Why do residents leave general surgery? The hidden problem in today's programs. *Curr Surg* 2005;62:128-31.

Re: General Surgery (GS) Residency Selection Process: A Comparison Between Singapore (Singhealth) and United States

T'zu Jen Tan, ¹MD (Indiana), Kok Yang Tan, ¹MMed (Gen Surg), FRCS (Edin), FAMS

The paper authored by Chong TT et al¹ details the current state of the local selection process with the comparison to the selection processes used at highly sought after programmes in the United States (US). Several valid improvements to standardise the subjective evaluation process and social fit of the candidates have been suggested. Every system is optimised to some extent, as the product of its own constraints. Some aspects of the US residency interview and matching process are dictated by the sheer number of programmes available, the geographic distance, and the maturity of the residency system. We should be careful to craft our way forward sensibly, sifting the valuable lessons of the past and keeping an awareness of our present while forging our future.

The last 4 years has seen the postgraduate medical education in Singapore embark on a process of rapid transformation with the adoption of structured specialty residency training under the format of the United States Accreditation Council for Graduate Medical Education (ACGME). We have witnessed the legacy system of trial periods with undifferentiated Medical Officer (MO) postings before commitment to a broad specialty area of surgery as a Basic Specialist Trainee (BST) and then entry into an institutionally supported track for a 4-year course of Advanced Specialist Training (AST), move aside for a more rigidly defined 5-year programme for General Surgery residency. There are many benefits to a more structured approach to specialty training with closer monitoring and granularity of the competencies being developed. However, the residency system has also reduced the length and flexibility of training time, along with a different set of indicators for tracking surgical experience and a lower barrier in paper qualifications to entering traineeship.

The ACGME has introduced restricted duty hours for trainees as well as the overall number of traineeship positions. The net effect is there is novel pressure for the graduating medical student with an interest in a specialty

area to apply to residency early on, while in contrast, the residencies are trying to identify mature candidates who will be able to progress rapidly within these constraints. The new graduates are also competing with a backlog of postgraduates for the same positions, which creates a wider disparity in the experiences and portfolios of the applicants. The lack of opportunity for exposure to the specialties has long been an issue with the residency matching system in the US: the cumulative attrition rate for general surgical residents has hovered at about 20%, a figure that has been steady for the past 20 years but is much higher than our local systems have historically been accustomed to. With the phasing in of the residency match system by certain specialties, we have inherited this problem and compounded it by the scarcity of match positions in alternative specialties, although this should improve as our systems achieve steady-state. In addition, the majority of our candidates are from an undergraduate system of medical education and may have less life experience to assess their personal compatibility with the pace and rigours of training.

For the surgical training programmes in Singapore, moving from the 2-step courtship process of dating and then meeting the parents with the BST and AST selections to the “speed-dating” of the residency match selection process, is a venture into uncharted waters. While there are excellent candidates at all levels, being able to recognise the innate qualities and backgrounds that will allow them to thrive in the residency system and successfully develop into the surgeons of tomorrow, through a looking-glass review of portfolios and a few brief interviews, remains a challenge. A consequence of this quest for efficiency is a focus on paper qualifications and perhaps a bias towards those with the charisma to present well at interviews, but sometimes overlooking those who prove their worth through their work and dedication. Perhaps also passed over in this process are those with backgrounds that are less familiar to us, such as international medical graduates, even those

¹Department of General Surgery, Khoo Teck Puat Hospital, Singapore

Address for Correspondence: Dr T'zu Jen Tan, Department of General Surgery, Khoo Teck Puat Hospital, 90 Yishun Central, Singapore 768828.

Email: tan.tzu.jen@alexandrahealth.com.sg

from top medical schools.

Taking a hybrid approach to amalgamate the best of both systems may be what is most suitable for our needs. Allowing new graduates to develop their basic clinical skills through the Transitional Year residency training and adding a national level 1-year MO level surgical posting with rotations through the 3 sponsoring institutions, similar to the preliminary positions available in the US, for those interested in careers in surgery, may allow a better process of match-making.

REFERENCES

1. Chong TT, Soo KC. General Surgery (GS) Residency Selection Process: A Comparison Between Singapore (Singhealth) and United States. *Ann Acad Med Singapore* 2014;43:288-90.

THE ROYAL COLLEGE OF SURGEONS OF EDINBURGH

In 1998 Lady Fraser gifted a sum of money to the Royal College of Surgeons of Edinburgh in order to set up a trust fund in the memory of her late husband, Sir James Fraser. A Travelling Fellowship has been established and is known as

THE SIR JAMES FRASER TRAVELLING FELLOWSHIP

The Fellowship will be awarded to Fellows or Members of the College in good standing working in Singapore, Sabah or Sarawak to enable them to visit the Royal College of Surgeons of Edinburgh, to attend a Surgical Congress in the UK and to enable them to visit medical centres in Scotland by arrangement.

Funding will be £1500 and awarded biennially. This will cover an airfare and some subsistence during the visit. The College will provide accommodation on its campus (up to a maximum of 7days).

The Royal College of Surgeons of Edinburgh collects personal data from you during the application process for Awards and Grants. We will not share this information with any third parties, and your data will be used solely for the purpose of processing and administrating this application.

Applicants must submit a copy of their curriculum vitae no more than 5 pages and two letters of reference, together with a statement of not more than 1000 words as to why they would like to take advantage of the Fellowship, to:

The Awards and Grants Administrator
Secretariat
The Royal College of Surgeons of Edinburgh
Nicolson Street
Edinburgh EH8 9DW
United Kingdom

Tel: ++44 (0)131 527 1618
e-mail: c.mccartney@rcsed.ac.uk

Electronic submissions are acceptable

Closing date for applications is: Friday 27 June 2014