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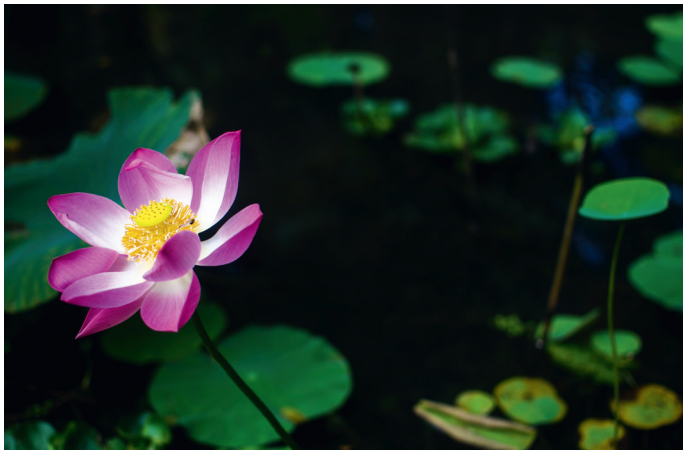

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"All the flowers of all the tomorrows are in the seeds of today."

Indian proverb

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Editorial

High-Sensitivity Troponin Assays: Boon or Bane for the Cardiologist?

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The Troponin Era

The advent of the "troponin era" has its roots in the redefinition of acute myocardial infarction (AMI) by the joint committee of European and American cardiologists in 2000.[1] Troponin was identified as the preferred serologic biomarker for acute coronary syndrome (ACS). Since then, troponin assays have continued to evolve with improved sensitivity and reproducibility, leading to a renewal of guidelines in 2007 and 2012.[2]

With increasing sensitivity of troponin assays, cutoff levels were lowered. A 99th percentile upper reference limit (URL) refers to the troponin concentration at the 99th percentile of a reference population. The use of the 99th percentile URL increases the ability of these assays to detect both early AMI and structural cardiac abnormalities. The first-generation troponin assays were not sufficiently sensitive to detect troponins in reference to "healthy" individuals and thus the cutoffs were set at levels at which the assays coefficient of variation (CV) were 10%. These early assays were thus not sensitive for early myocardial necrosis but highly specific, resulting in its use as a dichotomy tool for ACS rule-in. However, this should not be confused with newer generation high-sensitivity troponin (hsTn) assays, which are assays that have a CV of 10% or less at the 99th percentile URL and are able to detect cardiac troponin levels in at least 50% of the reference normal population.[3]

hsTn assays have only been available since 2010, with commercial availability still limited to a small number of hsTn assays. They are now able to measure tenfold lower concentrations with higher precision as compared to first generation assays.[3] Is the increased sensitivity afforded by hsTn a boon for the cardiologist, or a bane that could result in greater confusion for the physician interpreting these assays?

Role of Troponins in Clinical Practice

The universal definition of myocardial infarction (MI) is the detection of a rise and/or fall of cardiac troponins with at least one value above the 99th percentile URL in addition to at least one of the following: 1) symptoms of ischaemia; 2) new electrocardiogram (ECG) changes of ST-T segments, new left bundle branch block or development of pathological Q waves; 3) imaging evidence of new regional wall motion abnormality or loss of viable myocardium; and/or 4) identification of an intracoronary thrombus by angiography or autopsy.[2] They are separated into 5 types of MI according to aetiology (Table 1). The only aetiology of interest to a cardiologist in the emergency department (ED) is type 1 AMI due to spontaneous plaque rupture. The need to ascertain the type of MI has been, in part, due to the hsTn assays' ability to detect even the smallest amount of ongoing myocardial necrosis, leading to further confusion as a physician attempts to diagnose "troponinitis". Forty-three percent of all troponin assays ordered for inpatients will flag positive. However, only 28% will ultimately be labelled as AMI.[4] A positive test now demands greater physician discretion.

There is, however, an upside to the advent of hsTn. The optimum sensitivity of older standard troponin assays for AMI occurs 10 to 12 hours after the onset of symptoms. This results in the need for hospital admission and observation while serial testing is completed. hsTn assays are able to overcome this because they can detect much lower levels

Table 1. Types of Myocardial Infarction

Type 1	Spontaneous MI
Type 2	MI secondary to ischaemic imbalance
Type 3	MI resulting in death without biomarkers
Type 4a	MI related to PCI
Type 4b	MI related to stent thrombosis
Type 5	MI related to CABG

CABG: Coronary artery bypass graft; MI: Myocardial infarction; PCI: Percutaneous coronary intervention

Source: Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined–a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000;36:959-69.

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of troponin, allowing for earlier recognition of AMI. They are precise, and have small CV levels even at 99th percentile in reference populations, and are specific for myocardial necrosis. Increased values and changes in values over time also correlate well with risk of future adverse cardiac events.[5] In landmark studies, non-ST-elevation myocardial infarction (NSTEMI) can be ruled out as early as 4 hours after symptom onset, allowing shorter inpatient stay for patients without raised levels of troponin and earlier intervention for those with a confirmed AMI.[6] The historically conservative approach to avoid missing a potential ACS has led clinicians to admit many more patients than are subsequently found to have an MI. This further compounds the crowding in the ED, which is associated with adverse outcomes for both patients with and without AMI.[7] Follow-on studies with hsTn demonstrate low-level troponin elevations within 60 to 180 minutes of the AMI, allowing for earlier diagnosis and faster rule-out of AMI.[8,9] Two large prospective ED trials showed that hsTn assays are more accurate than standard troponin assays in the successful diagnosis of AMI within 3 hours of symptom onset.[10] This potentially reduces the duration of stay at the ED and should increase the number of patients successfully discharged from the ED. A modelling study found that early hsTn testing was financially beneficial in almost all cases.[11]

Chest pain is the second most common symptom and leading cost of malpractice dollars spent in the ED. The European Society of Cardiology (ESC) and National Institute for Health and Care Excellence (NICE) guidelines from 2014 have acknowledged the use of hsTn assays and made recommendations on the use of a fast track protocol. The guidelines state that hsTn assays have a NPV of greater than 95% for AMI on admission. Adding on a second repeat test at 3 hours can increase this to 100%.[12]

hsTn assays are strong prognostic markers for cardiovascular death and recurrent ischaemic events in AMI, with studies showing their superiority over standard assays in predicting cardiovascular death at 1-year follow-up.[13] Elevated troponin levels also correlate with an adverse prognosis in several stable chronic disease states.[14] Examples include heart failure, atrial fibrillation, renal failure, pulmonary embolism and sepsis.

Limitations of High-Sensitivity Troponins

Lack of an Industry Standard

The variability in hsTn characteristics between manufacturers prevents comparisons between assays and clinical centres.[5] The appropriate hsTn cutoff for clinical use is far from settled, with no consensus yet as to the population from which to derive this value, preventing consistent interpretation.[15]

Lower Specificity of hsTn for AMI

The main counterpoint to the increased sensitivity of hsTn assays is a lower specificity to rule-in AMI. Reported specificity for hsTn assays is 80% to 85%, compared to 97% for standard troponin assays.[16] Serial sampling to detect assay level changes (delta value) is required to improve assay specificity. ESC guidelines recommend a greater than 20% relative change in patients with an initially elevated hsTn level to diagnose AMI. However, the delta of 20% is based on older generation assays. The situation with hsTn assays is more complex, as both biological variation and assay dependent imprecision can result in wide ranging relative changes.[16] Further studies are required before the use of delta values, relative or absolute, can be adopted. Applying the existing definition of a 20% increase from baseline to hsTn assays may under-detect AMI.

Non-specific as to Aetiology of Myocardial Necrosis

Troponins are highly specific for myocardial necrosis, but are not so with regards to the aetiology. Cardiologists are primarily concerned with elevations due to plaque rupture as to the aetiology, since this has implications on the decision for and timing of coronary intervention. Whilst HsTn is a useful tool with increased sensitivity for the detection of type 1 MIs, this comes at the cost of over-diagnosis.[17]

Future Directions

Outcome data will steadily come from centres adopting the "early rule-out protocols" with hsTn assays. This will allow the analysis of optimal timing of samples to be taken after presentation to ED and the optimal cutoffs for both ruling out and ruling in of AMI. A comparison between clinical effectiveness of different protocols will advance the continuing refinement of workflows at the ED to exclude AMI. It has yet to be demonstrated prospectively whether patients discharged under the hsTn early rule-out protocols have longer term safety comparable to those receiving conventional screening. A key issue is that a miss rate will remain regardless of the assay's sensitivity—what is an acceptable percentage miss rate? This underscores the dilemma a triaging physician constantly faces.

Further research is needed to determine the 99th percentile value for hsTn assays, the influence of variables such as age and gender on these thresholds, and appropriate delta values for the definition of MI.

Conclusion

hsTn assays hold the promise of earlier diagnosis and improved clinical outcomes for patients presenting with chest pain and possible AMI. Its value lies in the potential

for use in the ED, thereby cutting costs and reducing waiting time in already overcrowded hospitals. However, the question is now a matter of specificity. HsTn assays do not differentiate myocardial necrosis due to plaque rupture from other causes. The assumption that all elevated hsTn implies a type 1 MI can lead to confusion and frustration in both the ED and inpatient settings.

In conclusion, the diagnosis of type 1 MI is not made solely on biochemical investigations, and must also involve ECG changes, symptoms and pretest probability. Hence, the usage of hsTn assays should be in tandem with clinical parameters. An emphasis on concurrent clinical assessment would allow the clinician to use and interpret these assays appropriately. This, together with a consensus on testing and assessment strategies, will go a long way to moderate the current variations with the use of hsTn in clinical practice.

Acknowledgment

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REFERENCES

1. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined–a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000;36:959-69.
2. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Eur Heart J 2012;33:2551-67.
3. Apple FS, Collinson PO. Analytical characteristics of high-sensitivity cardiac troponin assays. Clin Chem 2012;58:54-61.
4. Saaby L, Poulsen TS, Hosbond S, Larsen TB, Pyndt Diederichsen AC, Hallas J, et al. Classification of myocardial infarction: frequency and features of type 2 myocardial infarction. Am J Med 2013;126:789-97.
5. Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. Circulation 2011;123:1367-76.
6. Aldous SJ, Richards MA, Cullen L, Troughton R, Than M. A new improved accelerated diagnostic protocol safely identifies low-risk patients with chest pain in the emergency department. Acad Emerg Med 2012;19:510-6.
7. Pines JM, Pollack CV Jr, Diercks DB, Chang AM, Shofer FS, Hollander JE. The association between emergency department crowding and adverse cardiovascular outcomes in patients with chest pain. Acad Emerg Med 2009;16:617-25.
8. Than M, Cullen L, Aldous S, Parsonage WA, Reid CM, Greenslade J, et al. 2-Hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker: the ADAPT trial. J Am Coll Cardiol 2012;59:2091-8.
9. Meller B, Cullen L, Parsonage WA, Greenslade JH, Aldous S, Reichlin T, et al. Accelerated diagnostic protocol using high-sensitivity cardiac troponin T in acute chest pain patients. Int J Cardiol 2015;184:208-15.
10. Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med 2009;361:858-67.
11. Thokala P, Goodacre SW, Collinson PO, Stevens JW, Mills NL, Newby DE, et al. Cost-effectiveness of presentation versus delayed troponin testing for acute myocardial infarction. Heart 2012;98:1498-503.
12. Thygesen K, Mair J, Giannitsis E, Mueller C, Lindahl B, Blankenberg S, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. Eur Heart J 2012;33:2252-7.
13. Aldous SJ, Richards M, Cullen L, Troughton R, Than M. Diagnostic and prognostic utility of early measurement with high-sensitivity troponin T assay in patients presenting with chest pain. CMAJ 2012;184:E260-8.
14. Melki D, Lugnegard J, Alfredsson J, Lind S, Eggers KM, Lindahl B, et al. Implications of Introducing High-Sensitivity Cardiac Troponin T Into Clinical Practice: Data From the SWEDEHEART Registry. J Am Coll Cardiol 2015;65:1655-64.
15. Koerbin G, Abhayaratna WP, Potter JM, Apple FS, Jaffe AS, Ravalico TH, et al. Effect of population selection on 99th percentile values for a high sensitivity cardiac troponin I and T assays. Clin Biochem 2013;46:1636-43.
16. Wu AH, Lu QA, Todd J, Moecks J, Wians F. Short- and long-term biological variation in cardiac troponin I measured with a high-sensitivity assay: implications for clinical practice. Clin Chem 2009;55:52-8.
17. Januzzi JL Jr. What to expect when measuring high-sensitivity troponin: practical advice for clinicians. J Am Coll Cardiol 2015;65:1665-7.

Original Article

Validity of a Revised Short Form-12 Health Survey Version 2 in Different Ethnic Populations

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Abstract

Introduction: The Short Form-12 version 2 (SF-12v2) is a shorter version of the Short Form-36 version 2 (SF-36v2) for assessing health-related quality of life. As the SF-12v2 could not be resolved into the physical- and mental-component summary score (PCS and MCS, respectively) in the general population of Singapore, this study aims to determine and validate the Singapore SF-12 version 2 (SG-12v2). Materials and Methods: The SG-12v2 was generated using the same methodology as the SF-12v2. Bootstrap analysis was used to determine if the SG-12v2 were significantly different from the SF-12v2. Content validity was assessed using percentage of variance (R^2) of the Singapore version of SF-36v2 PCS and MCS explained by the SG-12v2 items. Agreement between the SF-36v2 and the SG-12v2 was assessed using Bland-Altman diagrams. Criterion validity was demonstrated if effect size differences between SF-36v2 and SG-12v2 were small (Cohen's criteria). Known-group validity of SG-12v2 was reported for participants with and without chronic diseases. Results: Five items differed between the SG-12v2 and SF-12v2. Bootstrap analysis confirmed that SG-12v2 and SF-12v2 were significantly different. The SG12v2 explained 94% and 79% of the R^2 of the SF-36v2 PCS and MCS, respectively. Agreement was good and effect size differences were small (<0.3). Participants with chronic diseases reported lower SG-12v2 scores compared to participants without chronic diseases. Conclusion: The SG-12v2 offers advantage over the SF-12v2 for use in the general population of Singapore. The SG-12v2 is a valid measure and will be particularly useful for large population health surveys in Singapore.

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Key words: Health-related quality of life, Singapore, Bland-Altman, Bootstrap

Introduction

The Short Form-36 version 2 (SF-36v2) health-related quality of life (HRQoL) survey is a well established 36-item instrument that had been used in many clinical and epidemiologic studies to assess the quality of life of subjects all around the world. Even though it consists of only 36 items which can be completed within 5 to 10 minutes, in certain studies, it might be considered too lengthy.[1] The SF-12 version 2 (SF-12v2) health survey was developed in the United States as a shorter alternative to the SF-36v2.[1] It represents a subset of items from the SF-36v2 that adequately captures the variance in the HRQoL as measured by the SF-36v2 and can be used in large scale studies where researchers are interested in health states that may have different effects on overall physical and mental health outcomes.

With longer life expectancy, HRQoL increasingly becomes an important topic of study among researchers worldwide. Between 2006 and 2015, 8 studies in Singapore were published using the SF-12v2 to measure HRQoL in specific populations[2-9] and we believe that the number of studies using the SF-12v2 will continue to increase as the

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SF-12v2 reduces the burden of completion compared to the SF-36v2. However, when we analysed the SF-12v2 in the Singapore general population, it was observed that the SF-12v2 could not be resolved into the expected physical- and mental-component summary score (PCS and MCS respectively) unlike the SF-36v2. Thus, the aim of this study was to identify the most suitable items to contribute to the Singapore SF-12v2 (SG-12v2) and to determine its validity and reliability for the multi-ethnic population of Singapore. The SG-12v2 should: 1) be representative and adequate in explaining the SF-36v2 PCS and MCS scores (content validity); 2) give similar PCS and MCS scores as the SF-36v2 instrument (criterion validity); and 3) detect differences in PCS and MCS between individuals with and without chronic medical conditions (i.e. known group validity).

Materials and Methods

Study Design and Participants

A total of 10,747 participants from 4 previous cross-sectional surveys (from 1982 to 1998) were contacted between 2004 and 2007. Of these, 7188 participants were included in the analysis. The description of the demographics can be seen in Table 1. Detailed sample selection methods for the original studies have been described elsewhere.[10-13] Briefly, all studies were a random sample of participants from the Singapore population, with disproportionate sampling stratified by ethnicity to increase the numbers from the minority ethnic groups (Malays and Asian Indians). Questionnaires were administered at the subjects' homes and all interviewed participants were invited to attend a clinical examination for additional tests and collection of biological specimens, shortly after the home visit. Ethics approval was obtained from 2 institutional review boards before study commencement. Informed consent was obtained before conducting the study.

Data Collection

Data on demographic factors and medical history were collected using interviewer-administered questionnaires. Ethnic group was self-reported and participants were classified as being Chinese, Malay or Asian Indian. Marital status was classified as 'never married', 'currently married' or 'separated/divorced/widowed'. Education level was determined through the number of years of schooling and was divided into 3 categories: <7 years, 7 to 10 years and >10 years. Working status was classified as 'working' or 'not working'. Participants were categorised as 'current smoker' or 'current drinker' if they answered 'yes' to the question, 'Do you smoke now?' or 'Have you consumed alcohol within the past three (03) months?', respectively.

Table 1. Characteristics of 7188 Subjects who Completed Either English or Chinese SF-36v2 in the Study

	English n = 6026	**Chinese n = 1162**
Age in years, mean (SD)	48.2 (12.5)	55.4 (11.2)
Sex, no. (%)		
Men	2917 (48.4)	492 (42.3)
Women	3109 (51.6)	670 (57.7)
Race, no. (%)		
Chinese	3704 (61.5)	1162 (100)
Malay	1166 (19.4)	
Indian	1156 (19.2)	
Marital status, no. (%)		
Never married	887 (14.7)	94 (8.1)
Currently married	4656 (77.3)	979 (84.3)
Separated/divorced/widowed	483 (8.0)	89 (7.7)
Years of education, no. (%)		
<7 years	1320 (21.9)	618 (53.2)
7 to 10 years	2165 (35.9)	400 (34.4)
>10 years	2541 (42.2)	144 (12.4)
Employed, no. (%)	4246 (70.5)	641 (55.2)
Housing type, no. (%)		
1 to 3 room flat	984 (16.3)	283 (24.4)
4 to 5 room flat	4019 (66.7)	771 (66.4)
Private condo/landed property	1023 (17.0)	108 (9.3)
Smoke, no. (%)	777 (12.9)	139 (12.0)
Drink, no. (%)	1400 (23.2)	226 (19.5)
Presence of disease, no. (%)	3344 (55.5)	746 (64.2)
Family functioning measure, mean (SD)	59.2 (18.2)	56.0 (16.7)

History of chronic diseases was captured through self-report data. Participants were asked whether they had ever been told that they had hypertension, diabetes mellitus or high cholesterol. History of coronary heart disease was defined as a positive response to any of the 3 questions, 'Has your doctor ever told you that you have blockage of the arteries to your heart?' or 'Have you had ever had a heart attack?' or 'Have you ever had angioplasty-ballooning or heart bypass operation procedures?' Participants were also asked whether they had ever been told by a physician that they had a cerebrovascular accident (stroke). Information on other chronic diseases (lung disease, cancer, musculoskeletal illness and mental illness) was also captured. For the health examination, participants were examined in the morning after a 10-hour overnight fast. Details of health examination, blood draw, sample preparation and biochemical analyses were previously published.[14]

Short Form-36 Version 2 (SF-36v2)

The Singapore version of the SF-36v2 was available in English, Chinese, Malay and Tamil. In this study, we analysed the data only for English and Chinese language SF-36v2 due to the small number of participants who completed the survey in Malay and Tamil. Data was pooled for the English and Chinese language surveys because it had been shown previously that the 2 languages were equivalent in our population.[15]

Construction of Singapore 12 Version 2

Individual items were recoded, summed and transformed as recommended in the SF-12v2 user manual.[16] In particular, the General Health (GH) item needed to be recalibrated to satisfy the assumption of a linear relationship between item scores and the latent trait defined by their scales. Participants with missing item scores, sociodemographic and clinical data were excluded listwise from the analysis.

We identified the 12 items that would optimally be used as the SG-12v2 questionnaire in 2 steps using the methodology described in the SF-12v2 manual:[16] First, we used forward stepwise regressions of the SF-36v2 items on Singapore SF-36v2 PCS and MCS to select items with the largest variance explained (R^2) on the 2 summary scales. By definition, 2 items each from physical functioning (PF) and mental health (MH) scales were selected and 1 item each from role-physical (RP), bodily pain (BP), social functioning (SF), and role-emotional (RE) scales was selected. Second, forward stepwise regressions were conducted by adding general health item, 'In general, would you say your health was: (GH1)' and the items from the first forward regression. The combination of items from RP, RE and vitality (VT) that explained the greatest variation on the Singapore SF-36v2 PCS and MCS scores would determine the makeup of the SG-12v2. It is an international quality of life assessment (IQOLA) criterion that GH1 be included in all country-specific questionnaires because of its use as a single-item overall health measure in many HRQoL instruments.[1] We then compared the items selected against items selected in various other countries derived from the published literature.[1,17]

Non-parametric bootstrapping was conducted, after the SG12v2 items were identified, to determine if there was a real difference between the SG-12v2 and SF-12v2 in their ability to explain variation (R^2) in PCS and MCS scores. Since the SG-12v2 items were selected using the same data used to calculate the R^2, an over-fitting factor was calculated to adjust the 95% confidence intervals (CI) of the difference in R^2 between the SG-12v2 and SF-12v2 items. The bootstrap and over-fitting factor procedures are described in Appendix 1. Upon adjustment of the 95% CI, should the 95% CI contain the value 0, it would mean that there was no difference between the 2 sets of instruments and that the SF-12v2 might be applicable to the multi-ethnic Asian Singapore population.[18]

Statistical Analyses

The bootstrap procedure was conducted using R version 2.14.2 (R Development Core Team, 2012)[19] whilst the rest of the data analyses were performed using Stata version 10 (StataCorp LP).

Assessment of Content, Criterion and Known-Group Validity of the SG12v2

We assessed content validity in 2 ways: First, by the percentage of variance (R^2) of the SF-36v2 PCS and MCS scores explained by the SG-12v2 items. The expected standard was ≥ 0.9;[1,16] Second, Pearson correlations between the SG-12v2 and the SF-36v2 PCS and MCS are expected to achieve ≥ 0.9.[1,16] Bland-Altman plots were used to enable us to visually assess the agreement between the SG-12v2 and the SF-36v2 PCS and MCS values. Criterion validity was determined using effect size differences between the SF-36v2 and SG-12v2. Effect size difference was calculated by dividing the differences in the mean scores by the standard deviation (SD) of the SF-36v2 summary score.[20] The SG-12v2 is considered to give similar results as the SF-36v2 if the effect size difference is smaller than the minimum important difference (MID; i.e., Cohen's effect size of 0.3-0.5).[17,21,22] We extended the evaluation of effect size difference to patients with and without a specific disease to determine how the instrument performed for the various groups. This would also provide evidence for known-group validity of the SG-12v2, where we expect participants without chronic diseases to have higher PCS and MCS compared to participants with any chronic diseases.

Comparison of the Singapore and the United States' (US) Instrument

Items from the 2 instruments were compared to determine the differences. Exploratory factor analyses was also conducted, for each of the instrument, and compared. The 8 domains of the SF-36v2 were expected to resolve into 2 factors, with PF and MH expected to have positive and strong association with their respective summary measures and negative association with the other summary measure.

Results

Content, Criterion and Known-Group Validity of SG12v2

The SG-12v2 explained 94% and 79% of the total variance of the SF-36v2 PCS and MCS, respectively (Table 2). The

Table 2. Items Comparison between the Singapore 12 Version 2 and the SF-12 Version 2

Singapore			**SF-12v2**		
Domain Item No.	SF-36 Item No.	Item Wording	Domain Item No.	SF-36 Item No.	Item Wording
PF3*	3c	Lifting/carrying groceries	PF2	3b	Moderate activities
PF8*	3h	Walking several hundred metres	PF4	3d	Climbing several flights
RP2	4b	Accomplished less	RP2	4b	Accomplished less
RP3	4c	Limited in kind of work	RP3	4c	Limited in kind of work
BP2	8	Extent pain interfered with work	BP2	8	Extent pain interfered with work
GH1	1	Your health is excellent…poor	GH1	1	Your health is excellent…poor
VT4*	9i	Feel tired	VT2	9e	Have a lot of energy
SF1*	6	Extent social activities interfered	SF2	10	Frequency social activities interfered
RE2	5b	Accomplish less	RE2	5b	Accomplish less
RE3	5c	Didn't do work as carefully	RE3	5c	Didn't do work as carefully
MH3	9d	Felt calm and peaceful	MH3	9d	Felt calm and peaceful
MH5*	9h	Been a happy person	MH4	9f	Felt downhearted and low
PCS R^2	MCS R^2				
0.938	0.788				

MCS: Mental-component summary; PCS: Physical-component summary
*Item differs from the SF-12v2.

Pearson correlations between SG-12v2 and the SF-36v2 PCS and MCS achieved the expected standard of 0.9 (PCS: 0.96; MCS: 0.88). In addition, we plotted Bland-Altman diagrams to assess the agreement between the SG-12v2 and SF-36v2 PCS and MCS (Figs. 1 and 2). The plots showed that a majority of the data spread for both PCS and MCS was within the 95% confidence interval (CI) band, indicating good agreement between the 2 instruments.

Effect size difference between the SG-12v2 and the SF-36v2 scores were conducted across several chronic disease groups in Table 3. The SG-12v2 and SF-36v2 detected similar significant differences between each of the chronic disease group as well as the 'no chronic disease' group. The largest effect size between the SG-12v2 and SF-36v2 scoring algorithms was the MCS score for subjects reporting psychological diseases, with a value

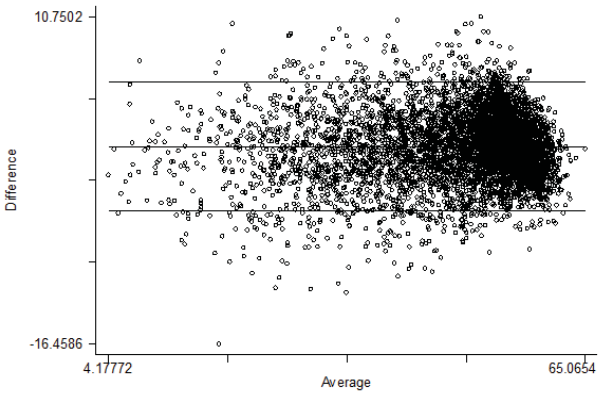

Fig. 1. Bland-Altman diagram shows the measure of agreement between Singapore SF-12v2 and SF-36v2 physical-component summary (PCS). Majority of the data lies within 95% confidence band indicating good agreement between the 2 instruments. Pitman's test of difference in variance: r = 0.063, indicating concordance between the 2 instruments.

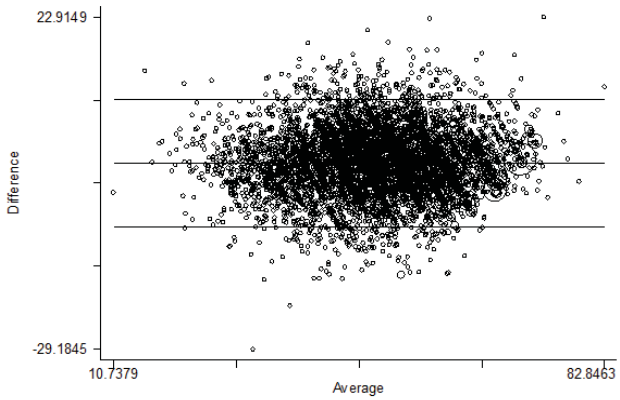

Fig. 2. Bland-Altman diagram shows the measure of agreement between Singapore SF-12v2 and SF-36v2 mental-component summary (MCS). Majority of the data lies within 95% confidence band indicating good agreement between the 2 instruments. Pitman's test of difference in variance: r = 0.004, indicating concordance between the 2 instruments.

Table 3. Effect Size Comparison between Singapore SF-12v2 and SF-36v2 Scores across Chronic Disease Groups

	PCS		MCS	
	Mean	**SD**	**Mean**	**SD**
All subjects (n = 7188)				
SF-36	50.1	9.8	50.0	10.0
SF-12	50.0	9.9	50.0	10.0
Effect size*	0.01		0.00	
No chronic disease (n = 3098)				
SF-36	52.2	8.1	50.6	9.6
SF-12	51.9	8.3	50.9	9.4
Effect size*	0.04		0.03	
Any chronic disease (n = 4090)				
SF-36	48. 5	10.6	49.5	10.2
SF-12	48.6	10.8	49.3	10.4
Effect size*	0.01		0.02	
Cardiovascular disease (n = 3276)				
SF-36	48.7	10.6	50.0	10.3
SF-12	48.9	10.8	49.8	10.4
Effect size*	0.02		0.02	
Stroke (n = 111)				
SF-36	40.0	14.0	46.8	13.0
SF-12	40.3	14.3	46.3	11.9
Effect size*	0.02		0.04	
Diabetes mellitus (n = 754)				
SF-36	46.6	12.4	48.0	11.0
SF-12	46.9	12.8	47.5	11.1
Effect size*	0.02		0.04	
Psychological diseases (n = 74)				
SF-36	38.1	14.3	42.3	11.7
SF-12	37.0	15.0	43.8	12.2
Effect size*	0.08		0.13	
Pulmonary disease (n = 336)				
SF-36	46.7	11.8	48.5	10.5
SF-12	47.0	11.9	48.2	10.7
Effect size*	0.03		0.03	
Joint disease (n = 1535)				
SF-36	45.7	11.5	47.7	9.8
SF-12	45.7	12.0	47.6	9.9
Effect size*	0.01		0.01	

MCS: Mental-component summary; PCS: Physical-component summary
*Calculated by taking the difference between the mean SF-36v2 and SF-12v2 and dividing by the standard deviation (SD) of the SF-36v2.

of 0.13, which nonetheless was smaller than the definition of MID. In terms of known-group validity, as expected, subjects who reported as having some form of disease had lower PCS and MCS scores as compared to the subjects who indicated 'no chronic disease'.

Comparison of the Singapore and US Instruments

The composition of SG-12v2 and SF-12v2 items can be found in Table 2. Five items (in asterisk) from the SG-12v2 differed from the SF-12v2. Results from bootstrap analysis confirmed that the items from SG-12v2 were indeed different

Table 4. Factor Score Coefficients‡ for the Singapore SF-12v2, the original SF-12v2 and the SF-36v2 PCS and MCS

Scales†	Factor Score Coefficients					
	SF-36v2		SG-12v2		SF-12v2	
	PCS	MCS	PCS	MCS	PCS	MCS
Physical functioning	0.251*	-0.0618	0.273*	-0.121	0.0314	0.250*
RP	0.349*	-0.147	0.305*	-0.101	0.341*	-0.107
BP	0.251*	-0.0609	0.245*	-0.0258	0.294*	-0.0859
GH	-0.187	0.464*	-0.143	0.528*	-0.179	0.471*
Vitality	-0.146	0.457*	-0.0473	0.413*	-0.124	0.451*
Social functioning	0.221*	0.0204	0.215*	0.0316	0.241*	0.0128
RE	0.323*	-0.124	0.298*	-0.101	0.373*	-0.172
Mental health	-0.093	0.389*	-0.105	0.507*	0.0269	0.260*

BP: Bodily pain; GH: General health; MCS: Mental-component summary; PCS: Physical-component summary; RE: Role-emotional; RP: Role-physical

*Indicate the higher weightage placed on the respective summary score.

†8 Domains of the SF-36v2.

‡Obtained from exploratory principal component factor analysis with Varimax rotation and used to compute the Physical- and Mental-component scores.

from the SF-12v2, since the 95% CI did not contain the value 0 for both PCS and MCS.

Table 4 shows the results of the factor weights obtained from the exploratory principal component factor analysis for the 2 countries. Only the 12 items from Singapore were able to converge into the PCS and MCS. When we selected the same items as the SF-12v2 and subjected them to exploratory principal component factor analysis, 2 factors were derived but could not be meaningfully labelled as PCS and MCS because both PF and MH load on to the same factor.

Discussion

Our study showed that the 12 items selected to optimally represent the PCS and MCS of the SF-36v2 differed by 5 items from those in the US. This was confirmed through the bootstrap analysis. The SG-12v2 showed good content, criterion and known-group validity and attained good agreement with the SF-36v2 with no evidence of a systematic bias.

In trying to understand why the SF-12v2 could not converge into the summary component scores, we replaced 1 of the 2 original SF-12v2 PF items with items from the SF-36v2 PF scale. We found that as long as the following items were not simultaneously selected, the modified SF-12v2 would resolve into PCS and MCS (results available on request): 'Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports' (vigorous activities), 'Moderate activities, such as moving table, pushing a vacuum cleaner, bowling, or playing golf' (moderate activities) and 'Climbing several flights of stairs' (climbing stairs). Two possible explanations could help explain our findings. First, although these 3 items measure physical activities, these activities require a certain level of mental toughness. Gerber et al, had previously showed a significant association between higher levels of physical activities and increased mental toughness scores.[23] Second, Singaporeans were found to be generally inactive, with activity levels below the recommended levels of physical activity (Fig. 3).[24] Hence, these 3 items might be more difficult for respondents in the Singapore context.

In the mental health scale, we found that 1 of the 2 mental health items differed between Singapore and the original instrument. We suspect that the reason why the item 'During the past 4 weeks, have you felt downhearted and depressed' was not appropriate in determining the mental health status of our local population was because Singaporeans, being Asians, still hold strongly to their culture and roots (depending on their ethnic background). As such, mental health issues are regarded as taboo topics for fear of facing discriminations by others.[25,26]

An important strength of this study lies in the bootstrap analyses. To our knowledge, this is the first study to use a 1000 bootstrap with replacement analysis to measure the difference in R^2 between a localised version of SF-12v2 and the original instrument. Furthermore, to ensure that the data was not over-fitted, we adjusted the 95% CI with an over-fitting factor. The fact that the results still showed that the SG-12v2 and the SF-12v2 were significantly different accentuated the need for a local version of the SF-12v2. Our findings are important for researchers and clinicians

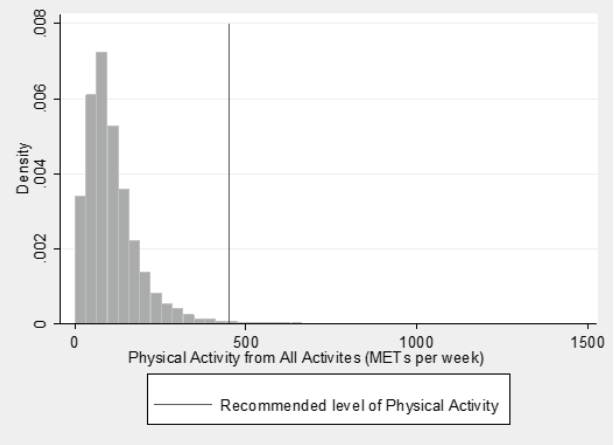

Fig. 3. Graph showing the levels of physical activity engaged by the 7188 Singaporean respondents. All activities: includes Transportation, Household, Leisure and Occupation activities. Recommended level of Physical Activity = 450 METs per week (Source: Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc 2007;39:1423-34). MET: Metabolic equivalent of task.

who are interested in studying HRQoL in Singapore and around Southeast Asia.

This study is not without limitations. First, we restricted the item selection methodology to match what was used to develop the original SF-12. An alternative method might have been to use item response theory to customise the instrument to the population studied.[27] Nonetheless, we chose to follow the same method as the original SF-12 to ensure that we did not deviate too much from the original intent of the developers.

Conclusion

In this multi-ethnic Asian population, the SG-12v2 had been showed to be as good a measure when compared to the SF-36v2. In addition, it is a necessary replacement of the SF-12v2 since the SF-12v2 cannot be resolved into PCS and MCS. Thus, in local clinical trials and large population-based studies, should the SF-36v2 be deemed too long an instrument to be used, researchers can consider using the SG-12v2 as a substitute instrument.

Acknowledgement

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REFERENCES

1. Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. J Clin Epidemiol 1998;51:1171-8.
2. Griva K, Goh CS, Kang WC, Yu ZL, Chan MC, Wu SY, et al. Quality of life and emotional distress in patients and burden in caregivers: a comparison between assisted peritoneal dialysis and self-care peritoneal dialysis. Qual Life Res 2016;25:373-84.
3. Yang F, Wang VW, Joshi VD, Lau TW, Luo N. Validation of the English version of the Kidney Disease Quality of Life questionnaire (KDQOL-36) in haemodialysis patients in Singapore. Patient 2013;6:135-41.
4. Ho RC, Fu EH, Chua AN, Cheak AA, Mak A. Clinical and psychosocial factors associated with depression and anxiety in Singaporean patients with rheumatoid arthritis. Int J Rheum Dis 2011;14:37-47.
5. Lim L, Jin AZ, Ng TP. Anxiety and depression, chronic physical conditions, and quality of life in an urban population sample study. Soc Psychiatry Psychiatr Epidemiol 2012;47:1047-53.
6. Yap KB, Niti M, Ng TP. Nutrition screening among community-dwelling older adults in Singapore. Singapore Med J 2007;48:911-6.
7. Luo N, Wang P, Fu AZ, Johnson JA, Coons SJ. Preference-based SF-6D scores derived from the SF-36 and SF-12 have different discriminative power in a population health survey. Med Care 2012;50:627-32.
8. Ho RC, Giam YC, Ng TP, Mak A, Goh D, Zhang MW, et al. The influence of childhood atopic dermatitis on health of mothers, and its impact on Asian families. Pediatr Allergy Immunol 2010;21:501-7.
9. Ng TP, Feng L, Chiam PC, Kua EH. Psychiatric morbidity and acute hospitalization in elderly people. Int Psychogeriatr 2006;18:701-11.
10. Cutter J, Tan BY, Chew SK. Levels of cardiovascular disease risk factors in Singapore following a national intervention programme. Bull World Health Organ 2001;79:908-15.
11. Hughes K, Aw TC, Kuperan P, Choo M. Central obesity, insulin resistance, syndrome X, lipoprotein(a), and cardiovascular risk in Indians, Malays, and Chinese in Singapore. J Epidemiol Community Health 1997;51:394-9.
12. Hughes K, Yeo PP, Lun KC, Thai AC, Sothy SP, Wang KW, et al. Cardiovascular diseases in Chinese, Malays, and Indians in Singapore. II. Differences in risk factor levels. J Epidemiol Community Health 1990;44:29-35.
13. Tan CE, Emmanuel SC, Tan BY, Jacob E. Prevalence of diabetes and ethnic differences in cardiovascular risk factors. The 1992 Singapore National Health Survey. Diabetes Care 1999;22:241-7.
14. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-421.
15. Tan ML, Wee HL, Lee J, Ma S, Heng D, Tai ES, et al. The Short Form 36 English and Chinese versions were equivalent in a multiethnic Asian population. J Clin Epidemiol 2013;66:759-67.

16. Ware JE KM, Keller SD. SF-12: How to Score the SF-12 Physical and Mental Health Summary Scales. 2nd ed. Boston, MA: The Health Institute, New England Medical Center; 1995.
17. Lam CL, Tse EY, Gandek B. Is the standard SF-12 health survey valid and equivalent for a Chinese population? Qual Life Res 2005;14:539-47.
18. Julious S. Using confidence intervals around individual means to assess statistical significance between two means. Pharm Stat 2004:217-22.
19. R Development Core Team (2011). R: A Language and Environment for Statistical Computing. Vienna, Austria: the R Foundation for Statistical Computing; 2012.
20. Kazis LE, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health status. Med Care 1989;27:S178-89.
21. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, New Jersey: Lawrence Erlbaum Associates; 1988.
22. Wyrwich KW, Nienaber NA, Tierney WM, Wolinsky FD. Linking clinical relevance and statistical significance in evaluating intra-individual changes in health-related quality of life. Med Care 1999;37:469-78.
23. Gerbera M, Kalakb N, Lemolac S, Cloughd P, Pühsea U, Elliota C, et al. Adolescents' exercise and physical activity are associated with mental toughness. Ment Health Phys Act 2012;5:35-42.
24. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc 2007;39:1423-34.
25. Peng T. Mental Illness May Go Untreated in Asian-Americans. Newsweek. Available at: www.newsweek.com/mental-illness-may-go-untreated-asian-americans-87613. Accessed on 7 January 2016.
26. Yang K. Chinese personality and its change. In: Bond MH, editor. The psychology of the Chinese people. Hong Kong: Oxford University Press; 1986.
27. Lai JS, Cella D, Chang CH, Bode RK, Heinemann AW. Item banking to improve, shorten and computerize self-reported fatigue: an illustration of steps to create a core item bank from the FACIT-Fatigue Scale Qual Life Res 2003;12:485-501.

Appendix 1

The bootstrap procedure is as follows:	
0.	Start with K = 1.
1.	Generate a bootstrap sample with replacement from observed data.
2.	Fit to the bootstrap sample, the Singapore PCS and MCS models using regression coefficients that have been optimised from the observed data. Call the R^2 from these fits $r^{2(K)*}_{PCS}$ and $r^{2(K)*}_{MCS}$.
3.	Using the bootstrap sample, refit the Singapore PCS and MCS models. Call the R^2 from these fits $r^{2(K)}_{PCS}$ and $r^{2(K)}_{MCS}$.
4.	Fit the models obtained in step 3 onto the observed data. Call the R^2 from these fits $r^{2(K)PRED}_{PCS}$ and $r^{2(K)PRED}_{MCS}$.
5.	Calculate $\Delta r^{2(K)*}_{PCS} = r^{2(K)*}_{PCS} - r^2_{PCS,US}$ and $\Delta r^{2(K)*}_{MCS} = r^{2(K)*}_{MCS} - r^2_{MCS,US}$ where $r^2_{PCS,US}$ and $r^2_{MCS,US}$ are r-sq for US models from the observed data.
6.	Calculate the over-fitting factor for PCS as $\eta^{(K)}_{PCS} = r^{2(K)}_{PCS} - r^{2(K)PRED}_{PCS}$. Do similarly for MCS model.
7.	Redo steps 1 to 7 for K = 2,3…1000.

MCS: Mental-component summary score; PCS: Physical-component summary score; US: United States

Calculate the average over-fitting factor for PCS model as $\eta PCS = ave(\eta^{(K)}_{PCS})$ and calculate the bootstrap estimate of 95% confidence intervals for Δr^2_{PCS} using the percentile method and call the lower and upper bounds as $\Delta r^{2,LB}_{PCS}$ and $\Delta r^{2,UB}_{PCS}$. The over-fitting-corrected 95% confidence intervals for Δr^2_{PCS} is then calculated as ($\Delta r^{2,LB}_{PCS} - \eta_{PCS}$; $\Delta r^{2,UB}_{PCS} - \eta_{PCS}$). Procedure for calculating the over-fitting-corrected confidence intervals for the MCS model follows similarly.

Original Article

The Use of Parenteral Nutrition Support in an Acute Care Hospital and the Cost Implications of Short-term Parenteral Nutrition

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Abstract

Introduction: Parenteral nutrition (PN) is indicated for patients who are unable to progress to oral or enteral nutrition. There are no local studies done on estimating the cost of PN in acute settings. The aims of this study are to describe the demographics, costs of PN and manpower required; and to determine the avoidable PN costs for patients and hospital on short-term PN. Materials and Methods: Patient data between October 2011 and December 2013 were reviewed. Data collected include demographics, length of stay (LOS), and the indication/duration of PN. PN administration cost was based on the cost of the PN bags, blood tests and miscellaneous items, adjusted to subsidy levels. Manpower costs were based on the average hourly rate. Results: Costs for PN and manpower were approximately S$1.2 million for 2791 PN days. Thirty-six cases (18.8%) of 140 PN days were short-term and considered to be avoidable where patients progressed to oral/enteral diet within 5 days. These short-term cases totalled $59,154.42, where $42,183.15 was payable by the patients. The daily costs for PN is also significantly higher for patients on short-term PN (*P* <0.001). Conclusion: In our acute hospital, 90% of patients referred for PN were surgical patients. Majority of the cost comes from the direct daily cost of the bag and blood tests, while extensive manpower cost was borne by the hospital; 18.8% of our cohort had short-term avoidable PN. Daily PN may cost up to 60% more in patients receiving short-term PN. Clinicians should assess patient's suitability for oral/enteral feeding to limit the use of short-term PN.

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Key words: Hospitalised, Avoidable, Nutrition support team

Introduction

Parenteral nutrition (PN) is indicated for patients who are unable to progress to oral or enteral nutrition. The European Society for Clinical Nutrition and Metabolism (ESPEN) and the American Society for Parenteral and Enteral Nutrition (ASPEN) both recommend PN if a patient is unable to progress to oral or enteral nutrition within 7 days postoperatively.[1,2] The ASPEN guidelines[2] further recommend that "PN provided for duration of <5 to 7 days would be expected to have no outcome effect and may result in increased risk to the patient".

In a paper by the Nutrition Support Team (NST) in Singapore General Hospital,[3] it was found that 14.9% of patients had PN durations less than 7 days. Approximately one-third of these patients were also found to have started on PN inappropriately, based on the ASPEN 2002 guidelines on the indication for nutrition support therapy.[4] Inappropriate PN use is associated with medical complications and incurs additional costs for both patients and hospital.[2,5,6] Delegge et al[7] reported an additional US$80,000 PN hospital cost within 6 months for inappropriate PN use, while another study reported annual costs of US$81,000.[8]

The cost of PN varies across different parts of the world, due to the differences in healthcare subsidies and insurance coverage. PN can be in the form of premixed multichamber bags or pharmacy compounded all-in-one

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bags, with the former at a lower price. The average costs for 1 day of PN therapy (inclusive of additives and service fees) in the United States is US$186.92 (S$244.87) for premixed multichamber bags and US$272.40 (S$356.84) for compounded PN.[9] In Europe, premixed bags without additives may cost between €39.69 and €72.87 (S$63.90 to S$117.32), while compounded bags cost between €46.04 and €82.02 (S$74.12 to S$132.05), depending on whether it is compounded within the hospitals or by subcontractors.[10-12] The cost range for compounded PN in neighbouring Malaysia is reported to be between MYR 235 to MYR 398[13,14] (S$89.30 to S$151.24). However, majority of the authors only included manpower for preparing and administering the bags, and not the overall manpower required by NST that includes assessment, reviewing, nursing and phlebotomy.

PN cost varies locally; depending on the negotiated price individual hospitals have with the compounding laboratory. A few hospitals have in-house laboratories to compound PN bags. Some hospitals also provide extra subsidies for patients while others do not. Hence, costs of compounded PN can range from S$150 to S$230. The variety of premixed bags available in each hospital also varies greatly, and costs can range anywhere from S$50 to S$130, based on the negotiated price between the hospital and the pharmaceutical companies. In our hospital, costs of premixed bags range from S$73 to S$127, and compounded bags from S$174 to S$214, depending on the bag composition and volume.

Singapore has a complex system for medical bills, where the government/Ministry of Health (MOH) provides subsidies of up to 80% for the total bill in acute public hospital wards. This is the first-tier of healthcare protection where the government-run hospitals will apply means testing to determine the level of subsidy for the patients. However, PN does not come at a subsidised cost in majority of the hospitals, as it is not classified as a standard medication. As such, the second tier of protection, also known as Medisave, a compulsory individual medical savings account scheme, will pay for the cost of PN. The MOH reported an average Medisave balance of S$16,900 in the year 2010.[15] However, the current Medisave withdrawal limit is S$ 450 per day, and patients have to pay the remaining daily hospital expenses that exceed this amount. Patients may be covered from the additional expenses through Medishield Life activation, which is the third tier protective insurance scheme, by the end of 2015.

There is currently no national policy or guidelines on the use of PN. Each hospital has its own set of PN policy and protocol; hence the types, frequencies and costs of blood tests and miscellaneous items (intravenous [IV] drip sets, IV pumps etc.) may differ as well. Manpower hours allocated to the administering of PN may also be different, with some hospitals having a NST to look after the patients on PN. The NST's role in our hospital is to provide support and monitoring of patients on PN, and to assist in the transitioning of PN to enteral or oral nutrition.

Many studies pertaining to cost of PN generally were done on home PN, where patients require long-term nutritional support. There are no known local studies done on estimating the cost of PN support in acute settings, or for short durations of less than 5 days, regardless of intentional or unintentional short-term prescription. There are no known studies on manpower-related hours and costs involved in administering PN in the local healthcare settings.

The aims of this study are to: a) describe the demographics, costs of PN, associated blood tests, manpower as well as manpower hours required for patients on short-term PN less than 5 days; b) compare the average daily bill size of patients on short-term PN to patients who required PN on extended periods while warded; and c) determine the costs for patients and hospital on short-term PN that are avoidable.

Materials and Methods

Patients admitted to our hospital who received PN between October 2011 and December 2013 were eligible for analysis. The hospital started electronic ordering of PN since October 2011. Data collected include patient demographics, admission diagnoses, intensive care unit (ICU) admissions, hospital length of stay (LOS), indication and duration of PN, reasons for stopping PN, central line insertions, types of central lines and number of line changes.

Patients were considered to be in the short-term avoidable PN group if they were started on PN and terminated within 5 days. Patients were excluded from analysis for PN≤ 5 days if they died within 5 days of commencing PN, multiple short periods (≤5 days) of PN in the same admission because of medical complications, refused PN after referral was made to the NST or transferred to another hospital within 5 days.

Patients were considered to be in the unavoidable PN group if the number of PN days was >5 days and unable to progress to oral/enteral nutrition. Those started on PN for more than once in the same admission was considered as a single patient for cost and mortality analysis. Those who had PN support during the different admissions were considered as repeated patients for cost analysis.

Manpower hours and costs were calculated based on time spent by the NST (gastroenterology consultant, pharmacist and dietitian), additional nursing hours and phlebotomist hours. The NST does not charge patient per consult and hence manpower costs are fully borne by the hospital. Costs were obtained from the hospital's human resources department, based on the average hourly rate in the year 2014 that the hospital was paying for each professional service.

Table 1. Costs* and Frequencies of Blood Tests Required for PN Monitoring in Changi General Hospital

Blood Tests	Baseline	Week 1	Week 2	Subsequent Weeks	Cost† Per Test (S$)
Urea	Compulsory	Daily	Alternate day	Alternate day	0.08 – 7.00
Creatinine					0.08 – 7.00
Sodium					0.08 – 7.00
Potassium					0.08 – 7.00
Magnesium					0.08 – 12.00
Chloride					0.08 – 8.00
Bicarbonate					0.08 – 7.00
Glucose					0.08 – 6.50
Calcium	Compulsory	Daily	Once	Once	0.08 – 7.00
Phosphate					0.08 – 8.00
LFTs	Compulsory	Once	Once	Once	0.48 – 54.00
Lipid profile					0.24 – 28.60
Pre-albumin					0.08 – 25.00
Prothrombin & partial thromboplastin time					0.16 – 29.10
Full blood count					0.08 – 14.52
Zinc					0.16 – 58.00
C-reactive protein	As required	As required	As required	As required	0.08 – 12.00
Finger prick hypocount		Every 6 hourly	Reduced frequency		2.32 – 24.00

LFT: Liver function test

*Costs are dependent on the subsidy levels that patients received.

†Where the lower range of cost indicates cost for subsidised patients and the higher range for private full fee-paying patients.

PN cost was based on the cost of the bags to patients and adjusted according to the patient's paying class (subsidised or private rates). Majority of the patients are provided with compounded PN in our hospital. Patients may start on premixed PN in the intensive care units over the weekend if the NST is not available to review the patient, and subsequently switched to compounded PN.

Costs for blood biochemistry were also calculated based on level of subsidies the patient receives, which can be up to 90% of usual costs. Only blood tests specifically ordered for PN monitoring were included (Table 1). Additional tests not in the PN protocol are not included in the final bill size calculations. Daily blood glucose monitoring by finger prick test was also added to the costs of PN as they are charged to patients.

Peripherally inserted central catheter (PICC) line insertion was calculated and added to total costs if it was specifically inserted for nutrition support (Table 2). Additional line costs were included if the patient had received line changes during the PN period specifically for PN use. Central venous catheters were not factored into the cost as they were required for critically ill patients and not solely inserted for PN. However, changes from central to PICC lines were added into the final cost if it was solely for PN use. Manpower costs for PICC line insertion were factored into total line costs. Miscellaneous items required for administration of PN were also included in the final costing. These include the intravenous administration and dressing sets required.

Table 2. Costs* of PICC Line Insertion and Other Miscellaneous Items Required for the Provision of PN

Central Lines and Other Equipment Required	Cost (S$)
PICC line inclusive of procedural costs	400.00 – 950.00
Intravenous administration set	0.58 – 6.25 daily
Basic dressing set	0.58 – 6.00 daily
Sterile gloves Alcohol wipes Disinfecting agents e.g. chlorhexidine	Not applicable as it is included in standard daily treatment fee in the ward
IV pump	Not applicable as pumps are provided for free by pharmaceutical companies as per agreement with the hospital
IV drip pole	Not applicable as it is not charged to patients

PICC: Peripherally inserted central catheter; IV: Intravenous

*Costs are dependent on the subsidy levels that patients received.

Manpower hours were estimated by observation and recording of time taken for nursing staff to set up a new PN bag, the administrative work in preparing the tubes for blood collection, and handing over of information to staff for the next shift. Phlebotomy hours were estimated through observing and recording the time taken to obtain blood samples from patients. NST discussion and ward round timings for each patient was estimated at 10 minutes per patient. Time taken by the pharmacist in reviewing patients, ordering of bags and liaising with compounding pharmacy were also included. Dietitian review per patient was estimated for initial patient assessment, regular reviews and extra time required in weaning patient off PN.

Statistical Analysis

All data were entered into SPSS Version 19.0 (IBM, Chicago, IL). Tests were run at a two-tailed significance level of 0.05. Normally distributed data was presented as median or mean ± SD. Independent t-test was used to detect any differences between continuous variables.

Results

A total of 192 patients were placed on PN between October 2011 and December 2013. The demographics for the total patient population are as described in Table 3. The median LOS was 34 days with median PN administration of 9 days. Majority of the patients were surgical patients (90.1%) and 30-day mortality rate was at 21.4%. Twenty-eight patients were excluded from the cost analyses and comparison analyses, of which 10 patients had multiple short periods (≤5 days) of PN in the same admission and 18 patients died within 5 days of commencing PN. The patients were started on PN for reasons as indicated in Table 4.

Thirty-six patients (18.8%) were placed on short-term PN. These patients were admitted for the following reasons: perforated gastric or intestinal ulcer requiring surgical intervention (n = 10); suspected ileus/postoperative ileus (n = 7); small bowel obstruction requiring resections (n = 3) or conservative management (n = 3); bleeding gastrointestinal

Table 3. Demographics of Patients on PN Support in the Hospital

Baseline Demographics	
No. of patients	192
Patient paying class type (%)	
Private	33 (17.2)
Subsidised	159 (82.8)
Age (years)	65.6 ± 15.7
Median length of stay (days)	34 (min 6 – max 290)
Median length of PN days (days)	9 (min 2 – max 267)
Total PN days (days)	2791
Sex (%)	
Male	113 (58.9)
Female	79 (41.1)
Patient type (%)	
Surgical	173 (90.1)
Medical	19 (9.9)
Mortality (%)	
Died while on PN	18 (9.4)
30-day	41 (21.4)

PN: Parenteral nutrition

Table 4. Comparison between Patients on Short-term Avoidable and Unavoidable PN

	Short-term (n = 36)	**Unavoidable (n = 128)**
Reasons for PN		
Bowel ischaemia	0	3
Conservative management (NBM ≥7 days)	14	30
Ileus	7	24
Intestinal/gastric obstruction	6	15
Poor nutritional status (pre- and post-operation)	5	23
Short bowel syndrome	0	3
Postoperative complications (e.g. anastamotic leak)	2	23
Unable to progress to EN or oral diet	2	7
Patient type		
Surgical	30	119
Medical	6	9
Gender		
Male	22	77
Female	14	51
Age	61.3 ± 15.5	67.0 ± 15.4*
PN days		
Total	140	2268
Median	4	11
Reasons for termination of PN		
Progressed to oral diet	26	83
Progressed to enteral feeding	10	32
Line infection requiring removal of PICC line	-	5
Death†/palliation	-	4
Others (refusing PN therapy, transfer to other facilities)	-	4

EN: Enteral nutrition; NBM: Nil by mouth; PICC: Peripherally inserted central catheter; PN: Parenteral nutrition
*Nil significant difference between the 2 groups.
†Excluding patients who died within 5 days after commencing PN.

Table 5. Total Administrative and Manpower Costs Related to PN for All 192 Patients

PN Cost Components	Full Fee Paying Patients (Private Class) (S$) n = 33	Subsidised Patients Before Subsidy (S$) n = 159	Subsidised Patients After Subsidy (S$) n = 159	Total Costs Before Subsidy (S$) n = 192
Total costs for PN administration	182,108.87	840,587.64	407,452.49	1,022,696.51
Central line insertion	31,350.00	140,600.00	59,600.00	171,950.00
Parenteral nutrition	96,816.95	449,344.66	340,732.40	546,161.61
Blood tests	43,345.92	199,018.98	2,129.77	242,364.90
Miscellaneous items*	10,596.00	51,624.00	4,990.32	62,220.00
Manpower costs not charged to patients	42,446.17	193,148.00	NA	235,594.17
Pharmacist	30,168.67	136,777.33	-	166,946.00
Dietitian	4430.00	20,266.67	-	24,696.67
Physician	3820.00	17,575.00	-	21,395.00
Nursing	2722.50	12,661.00	-	15,383.50
Phlebotomy	1305.00	5868.00	-	7173.00

NA: Not applicable; PN: Parenteral nutrition
*Include daily dressing and IV drip set.

tract (n = 3); bowel ischaemia (n = 2); gastric outlet obstruction requiring stenting (n = 2); pancreatitis (n = 1); pancolitis (n = 1); esophageal varices (n = 1); advanced rectal cancer requiring resection (n = 1); ruptured liver cyst (n = 1); and colon cancer with suspected anastamotic leak postoperation (n = 1). All of these 36 patients progressed to oral/enteral nutrition within 5 days of commencing PN.

Total PN and manpower costs for all 192 patients add up to S$1,258,290.68 for the 2791 PN days (S$450.84 per PN day) (Table 5). Of the total costs, S$589,561.36 (46.9% of total costs) was payable by the patients through their Medisave account/cash/insurance, with S$433,135.15 subsidised by the hospital or MOH based on the prevailing subsidy rates. Total manpower costs not charged to patients amounted to S$235,594.17.

Thirty-six cases (18.8%) with a total of 140 PN days were considered to be short-term PN as they had less than 5 days of PN (range of 2 to 5 days) and were progressed to oral diet (n = 26) or enteral feeding (n = 10) within 5 days of commencing PN. These short-term PN cases totalled S$59,154.42, of which S$42,183.15 was payable by the patients after MOH and hospital subsidies were applied on the blood tests and PN formulations.

The mean daily PN cost for private class patients was higher for those on short-term avoidable PN compared to those of unavoidable PN, which may be up to 60% more (Table 6). The total costs were affected mainly by the cost of PICC line insertion, daily blood analyses for the

Table 6. Itemised Daily Parenteral Nutrition Costs for Private and Subsidised Class Patients

Itemised Daily Costs	Avoidable (PN Days ≤5) (S$)	Unavoidable (PN Days >5) (S$)	*P* Value
Private class patients	n = 10	n = 22	
Total PN costs without PICC line	367.96 ± 26.13	312.39 ± 24.39	<0.001
Total PN costs with PICC line	603.88 ± 183.54	376.73 ± 57.22	0.003
PN bag	195.13 ± 9.06	194.94 ± 12.50	NS
Blood analyses	136.83 ± 24.88	93.59 ± 17.65	<0.001
Miscellaneous items*	36.00 ± 0.00	23.86 ± 6.73	<0.001
Subsidised class patients	n = 26	n = 106	
Total PN costs without PICC line costs	138.27 ± 29.24	151.76 ± 9.10	0.028
Total PN costs with PICC line costs	206.47 ± 79.65	185.67 ± 29.28	NS
PN bag	133.42 ± 29.24	147.92 ± 9.26	0.019
Blood analyses	1.32 ± 0.41	1.20 ± 0.50	NS
Miscellaneous items	3.52 ±0.23	2.66 ± 0.65	<0.001

NS: Not significant; PICC: Peripherally inserted central catheter; PN: Parenteral nutrition
*Include IV drip set and wound dressing set.

Table 7. Comparison of Average Daily Manpower Hours Required for Patients with Avoidable Versus Unavoidable PN

Manpower	Avoidable PN n = 36	Unavoidable PN n = 128	*P* Value
Pharmacist (hours)	1.28 ± 0.24	1.17 ± 0.49	<0.001
Dietitian (hours)	0.41 ± 0.02	0.25 ± 0.05	<0.001
Nutrition support physician (hours)	0.17 ± 0.00	0.13 ±0.01	<0.001
Nursing (hours)	0.25 ± 0.00	0.25 ±0.01	NS
Phlebotomy (hours)	0.25 ± 0.00	0.16 ± 0.03	<0.001
Total			
Daily manpower (hours)	2.35 ± 0.02	1.96 ± 0.11	<0.001
Daily manpower cost (S$)	102.83 ± 1.09	87.61 ± 3.79	<0.001

NS: Not significant; PN: Parenteral nutrition

first 5 days of PN, and the miscellaneous items required for administration. For long-term PN patients, the cost of initial PICC line insertion was averaged out and less blood analyses were required, which significantly reduced daily average cost. This was not replicated in the subsidised patient group. This is likely due to the large subsidies provided for PICC line insertions and blood analyses, which may be as high as 80%. Total PN-related costs for a private class patient is approximately 2.5 times higher than a subsidised class patient.

In addition, 326.67 manpower hours were incurred for these 36 patients, which is an additional manpower cost of S$14,400.33. The average daily manpower hours for pharmacist, dietitian, nutrition support physician and phlebotomy were significantly higher in these patients as well (Table 7), due to higher manpower needs during the initial assessment and monitoring phases for PN initiation. As a result, average daily manpower cost is also higher in these patients (Table 7). Nursing manpower hours was similar between the 2 groups, as the similar nursing procedures or needs are required for each PN day.

Discussion

This is the first local study that reported the total costs related to PN. Majority of the patients referred for PN in our institution are surgical patients, where patients with postoperative complications and ileus accounting for one-third of the referrals. The median length of PN days is 9 days, similar to other local studies.[3,16] The total costs inclusive of manpower for 2791 PN days was approximately S$1.2 million (S$450.84 per PN day). The main cost components are from blood tests and PN formulations, which accounted for three-quarters of the total costs. While it is not a huge component of healthcare cost in Singapore, it should be treated with importance as the patients paid for nearly half of the PN-related bills, as PN does not qualify for major subsidies. Majority of the PN patients were receiving subsidised medical care and the amount of subsidies provided amounted to approximately S$433,000, with the patients paying the remnant S$590,000 (46.9% of total costs). Manpower costs amounted to S$235,000 for the 2791 PN days and this was not included in the bill.

In our PN population, majority of patients on PN can progress safely to oral or enteral nutrition. Of the 36 patients with short-term PN, all of them progressed safely to oral and enteral nutrition without any complications and may have avoided the need for PN. A total of 140 PN days (S$ 525.39 per PN day) could have been saved if patients were transitioned to oral/enteral nutrition earlier. This would have also saved approximately S$74,000 (PN-related and manpower costs), of which S$43,000 (57.3%) were payable by the patients. While PN is indicated for patients who are unable to progress to enteral or oral diet within 5 to 7 days, it could have been avoided in these 36 patients if they were trialled on oral/enteral feeds before referring for PN support.

Similar conclusions encouraging the trial of oral or enteral feeding have been reported by other authors.[3,6-8,16] A large number of studies have shown that enteral nutrition can be started for patients postgastrointestinal surgery without problems.[17-20] Surgical teams should assess patient suitability for insertion of a feeding jejunostomy during the time of operation. This will help reduce the need for postoperative PN support. In our patient group, majority of the patients did not require insertion of feeding tubes and could have progressed to oral trials easily.

In the Singapore healthcare model where maximum daily Medisave withdrawal is only S$450, this has implications on the daily medical bills. For example, a subsidised patient would have spent half of the daily permissible Medisave withdrawal on paying the PN associated bills. Any excess payments would have to be paid in cash if the patient has

no other healthcare insurance. This will deplete Medisave funds, which may be required in future hospital admissions or other medical payments.

Additionally, the provision of PN requires intensive manpower to assess patient, monitor progress, preparation and administration of PN bags. Approximately 327 hours, translating to S$14,400 was invested on patients with short-term PN that were avoidable. Better manpower could have been spent on other aspects of patient care, should the patient have been initiated with enteral nutrition or oral diet. Initiating enteral or oral nutrition will result in 10 to 15 fold decreases in hospitalisation costs based on a 1500 to 2000 kcal daily requirement.

Initiation of PN requires extensive blood tests that are costly for the institutions as majority of the blood tests, are provided at a subsidised rate. Central venous line insertion is also required for central PN initiation and PICC line is the main option for patients in our institution. For the short-term PN cases, the insertion of central venous lines increases the medical cost and risk of line infections for these patients. PN is associated with increased central line-associated bloodstream infections in a number of studies.[21-24]

Initiating PN also requires additional blood taking, which may lead to spurious blood work.[25] Although such occurrences are rare and we were unable to identify if any of our patients had spurious blood work for this study, it may possibly lead to unnecessary medical intervention and costs. The initiation of PN in these patients may have inadvertently increased the LOS and the medical bill size because of the extended period of stay. The Enhanced Recovery After Surgery (ERAS®) guidelines for elective colorectal surgery recommend "preoperative fasting should be minimised and postoperatively patients should be encouraged to take normal food as soon as possible after surgery".[26]

One of the limitations in this study is that we estimated the time taken for individual patient review. However, it is likely that we may have underestimated the time taken as patients on PN tend to have more complicated medical conditions, hence requiring much more time during the ward rounds. The other limitation is that we were unable to determine the number of patients who required activating Medishield coverage or financial support assistance from the hospital's social work department. This has implications on the final medical bill size that the patient needs to pay, as well as the amount of financial assistance the hospital needs to provide should the patient have insufficient medical funds coverage.

Conclusion

In this study, 90% of patients in our acute care hospital who were referred for PN had underlying surgical conditions. The total cost of providing PN, including manpower cost, was $450.87 per PN day of which 46.9% of total cost was payable by patients. Majority of the cost for PN administration came from the cost of PN bags and blood tests; 18.8% of our study cohort had short-term PN which could have been avoided. This translated to higher PN cost at $525 per PN day, of which 57.3% was payable by patients. The cost for patients on short-term avoidable PN was up to 60% more compared to those who needed long-term PN. In addition, extensive manpower hours were required to manage this group of patients and manpower costs of S$14,400.33 were fully borne by the hospital. Clinicians should assess patient's suitability for oral/enteral feeding to limit the use of short-term PN. The MOH may also need to look into the possibility of providing subsidy for PN, or include PN to be centrally purchased through the healthcare cluster's Group Procurement Office. This will standardise the price of PN and benefits from bulk purchase will be passed on to the patients.

REFERENCES

1. Braga M, Ljungqvist O, Soeters P, Fearon K, Weimann A, Bozzeti F. ESPEN Guidelines on parenteral nutrition: surgery. Clin Nutr 2009;28:378-86.
2. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr 2009;33:277-316.
3. Chuah SW, Ng DH, Liu P, Liu MH, Ng JL, Ling KL. The use of parenteral nutrition in an acute care hospital. Ann Acad Med Singapore 2013;42:395-400.
4. ASPEN Board of Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. JPEN J Parenter Enteral Nutr 2002;26:1s-138s.
5. Kennedy JF, Nightingale JM. Cost savings of an adult hospital nutrition support team. Nutrition 2005;21:1127-33.
6. Trujillo EB, Young LS, Chertow GM, Randall S, Clemons T, Jacobs DO, et al. Metabolic and monetary costs of avoidable parenteral nutrition use. JPEN J Parenter Enteral Nutr 1999;23:109-13.
7. DeLegge MH, Basel MD, Bannister C, Budak AR. Parenteral nutrition use for adult hospitalized patients: a study of usage in a tertiary medical center. Nutr Clin Pract 2007;22:246-9.
8. Maurer J, Weinbaum F, Turner J, Brady T, Pistone B, D'Addario V, et al. Reducing the inappropriate use of parenteral nutrition in an acute care teaching hospital. JPEN J Parenter Enteral Nutr 1996;20:272-4.

9. Turpin RS, Canada T, Liu FX, Mercaldi CJ, Pontes-Arruda A, Wischmeyer P. Nutrition therapy cost analysis in the us: pre-mixed multi-chamber bag vs compounded parenteral nutrition. Appl Health Econ Health Policy 2011;9:281-92.
10. Achach K, Peroux E, Hebuterne X. [Economic assessment of different administration modes for total parenteral nutrition]. Gastroenterol Clin Biol 2002;26:680-5.
11. Berlana D, Sabin P, Gimeno-Ballester V, Romero-Jiménez R, Zapata-Rojas A, Marquez E, et al. Cost analysis of adult parenteral nutrition systems: three-compartment bag versus customized. Nutr Hosp 2013;28:2135-41.
12. Menne R, Adolph M, Brock E, Schneider H, Senkal M. Cost analysis of parenteral nutrition regimens in the intensive care unit: three-compartment bag system vs multibottle system. JPEN J Parenter Enteral Nutr 2008;32:606-12.
13. Batani RA, Kadir NA, Bahari MB. Evaluation of the parenteral nutrition services in Hospital Pulau Pinang. Malaysian J Pharm Sci 2006;4:25-32. Available at: http://web.usm.my/mjps/mjps04022006/mjps04022006_3.pdf. Accessed on 2 May 2014.
14. Batani RA, Abdullah D, Bahari MB. Evaluation of the total parenteral nutrition service at Universiti Sains Malaysia Hospital. e-SPEN.2007; 2:e111-e5. Available at: http://www.clinicalnutritionespen.com/article/S1751-4991(07)00034-0/fulltext. Accessed on 2 May 2014.
15. Ministry of Health. Costs and Financing 2013. Available at: http://www.moh.gov.sg/content/moh_web/home/costs_and_financing/financing.html. Accessed on 2 May 2014.
16. Chan SL, Luman W. Appropriateness of the use of parenteral nutrition in a local tertiary-care hospital. Ann Acad Med Singapore 2004;33:494-8.
17. Akashi Y, Hiki N, Nunobe S, Jiang XH, Yamaguchi T. Safe management of anastomotic leakage after gastric cancer surgery with enteral nutrition via a nasointestinal tube. Langenbecks Arch Surg 2012;397:737-44.
18. Harvey SE, Parrott F, Harrison DA, Bear DE, Segaran E, Beale R, et al. Trial of the route of early nutritional support in critically ill adults. N Engl J Med 2014;371:1673-84.
19. Gerritsen A, Besselink MG, Cieslak KP, Vriens MR, Steenhagen E, van Hillegersber R, et al. Efficacy and complications of nasojejunal, jejunostomy and parenteral feeding after pancreaticoduodenectomy. J Gastrointest Surg 2012;16:1144-51.
20. Kudsk KA, Croce MA, Fabian TC, Minard G, Tolley EA, Poret A, et al. Enteral versus parenteral feeding. Effects on septic morbidity after blunt and penetrating abdominal trauma. Ann Surg 1992;215:503-11.
21. Beghetto MG, Victorino J, Teixeira L, de Azevedo MJ. Parenteral nutrition as a risk factor for central venous catheter–related infection. JPEN J Parenter Enteral Nutr 2005;29:367-73.
22. Casaer MP, Mesotten D, Hermans G, Schetz M, Meyfroidt G, Van Cromphaut S, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Me 2011;365:506-17.
23. Ippolito P, Larson EL, Furuya EY, Liu JF, Seres DS. Utility of electronic medical records to assess the relationship between parenteral nutrition and central line-associated bloodstream infections in adult hospitalized patients. JPEN J Parenter Enteral Nutr 2015;39:929-34.
24. Yilmaz G, Koksal I, Aydin K, Caylan R, Sucu N, Aksoy F. Risk factors of catheter-related bloodstream infections in parenteral nutrition catheterization. JPEN J Parenter Enteral Nutr 2007;31:284-7.
25. Fairholm L, Saqui O, Baun M, Yeung M, Fernandes G, Allard JP. Monitoring parenteral nutrition in hospitalized patients: issues related to spurious bloodwork. Nutr Clin Pract 2011;26:700-7.
26. Gustafsson UO, Scott MJ, Schwenk W, Demartines N, Roulin D, Francis N, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. Clin Nutr 2012;31:783-800.

Original Article

In Vitro Efficacy of Six Alternative Antibiotics against Multidrug Resistant *Escherichia Coli* and *Klebsiella Pneumoniae* from Urinary Tract Infections

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Abstract

Introduction: Increasing resistance in *Escherichia coli* and *Klebsiella pneumoniae* to firstline antibiotics makes therapeutic options for urinary tract infections (UTIs) challenging. This study investigated the in vitro efficacies of 6 antibiotics against multidrug resistant (MDR) uropathogens. Materials and Methods: Minimum inhibitory concentrations to ceftibuten, cefpodoxime, fosfomycin, mecillinam, temocillin, and trimethoprim were determined against 155 MDR-isolates of *E. coli* and *K. pneumoniae*. The presence of extended-spectrum beta-lactamases (ESBL) and plasmid-borne AmpC enzymes was determined by phenotypic testing with genotyping performed by multiplex polymerase chain reaction. Results: Temocillin demonstrated highest susceptibility rates for both *E. coli* (95%) and *K. pneumoniae* (95%) when breakpoints for uncomplicated UTIs were applied; however, temocillin susceptibility was substantially lower when "systemic infection" breakpoints were used. Fosfomycin demonstrated the best in vitro efficacy of the orally available agents, with 78% and 69% of *E. coli* and *K. pneumoniae* isolates susceptible, respectively. The next most effective antibiotics were ceftibuten (45%) and mecillinam (32%). ESBL and *ampC* genes were present in 47 (30%) and 59 (38%) isolates. Conclusion: This study demonstrated few oral therapeutic options for MDR-uropathogens, with fosfomycin demonstrating the best in vitro activity.

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Key words: Extended-spectrum beta-lactamases, Fosfomycin, Temocillin, Ceftibuten

Introduction

Urinary tract infections (UTIs) are one of the most common bacterial infections worldwide. Enteric Gram-negative organisms account for more than 90% of UTIs, of which *Escherichia coli* remains the predominant uropathogen. UTIs also remain as one of the most common indications for antimicrobial prescription.[1] Current guidelines recommend nitrofurantoin and trimethoprim-sulfamethoxazole as firstline antimicrobials for treatment of acute uncomplicated cystitis, with fluoroquinolones and β-lactams listed as alternative options.[1] However, resistance among uropathogens against these prescribed antibiotics is increasing worldwide. Rising antibiotic resistance poses a serious public health threat and therapeutic challenge. As initial treatment of acute uncomplicated cystitis is typically empirical, likelihood of clinical failure overshadows the benefits of a specific empirical drug therapy as population resistance towards the drug increases.[1] This limits therapeutic options and delays appropriate therapy. Reduced susceptibility to oral antibiotics also results in an increased use of broad-spectrum, intravenous antibiotic therapy for treatment of uncomplicated UTIs. Additional hospitalisation increases both individual and national demands for scarce healthcare resources, which emphasises the need to search for alternative agents in the treatment of multidrug resistant (MDR) UTIs. Regional data suggests that antibiotic resistance in uropathogens to recommended firstline antibiotics is prevalent in the Asia Pacific region,[2] while local data from Singapore indicates that resistance to quinolones, trimethoprim-sulfamethoxazole and cephalothin exceeds

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30%.[3] The worldwide spread of broad-spectrum beta-lactamases such as extended-spectrum beta-lactamases (ESBLs) and plasmid-borne AmpC enzymes represent an additional threat to therapeutic options for UTIs.

Alternative and less commonly used oral antibiotics for the treatment of UTIs include third generation cephalosporins, pivmecillinam (in European countries) and fosfomycin; while temocillin has been suggested as a potential intravenous therapeutic option instead of carbapenems or third-generation cephalosporins. Trimethoprim has been used in the United Kingdom as firstline therapy for UTIs, as the absence of the sulphonamide component may reduce the risk of adverse reactions. However, these alternative antibiotics are not commonly used in Singapore and there is no data on local susceptibility. This study was performed to evaluate the in vitro efficacy of these 6 antibiotics uncommonly used in Singapore against MDR uropathogens.

Materials and Methods

This single centre retrospective study consisted of *Escherichia coli* (n=81) and *Klebsiella pneumoniae* (n=74) clinical urinary isolates collected from 2005 to 2013, with routine disc susceptibility testing performed according to guidelines from the Clinical Laboratory Standards Institute (CLSI).[4] Test isolates were selected based solely on the presence of an MDR-phenotype, defined as "resistance to 3 or more antimicrobial classes".[5] Study isolates were nearly all resistant to amoxicillin-clavulanate (87%), ciprofloxacin (97%), cephalexin (95%), cefuroxime (96%) and trimethoprim-sulfamethoxazole (87%), and predominantly resistant to ceftriaxone (52%) and nitrofurantoin (55%). Phenotypic screening for ESBL was performed by the disk approximation method and confirmed by supplemental double-disk testing. Phenotypic screening for AmpC beta-lactamases was performed on cefoxitin-resistant isolates, using a previously described method.[6]

Susceptibility testing to fosfomycin was performed by the reference agar dilution method, as broth dilution methods are not recommended by the CLSI. Doubling dilutions of fosfomycin (testing range, 0.5-256 mg/L) were prepared in Mueller Hinton agar (Becton Dickinson) supplemented with 25 mg/L glucose-6-phosphate (Sigma-Aldrich). Bacterial isolates were inoculated using an inoculum replicator which delivered 104 CFU/10 µl. Susceptibility testing for mecillinam (testing range, 0.06-64 mg/L), ceftibuten (0.06-64 mg/L) and trimethoprim (0.5-32 mg/L) was performed by microbroth dilution according to current CLSI guidelines.[4] Serial dilutions of each antibiotic (Sigma-Aldrich, Singapore) in solution were inoculated into 96-well microtitre trays which were stored at -70°C until required. On the day of testing, a 0.5 McFarland suspension of each isolate was inoculated and trays incubated at 35°C for 18 hours in an ambient air condition. Susceptibility testing for temocillin and cefpodoxime was performed by Etest® (bioMérieux, France), according to manufacturer's guidelines, as the test compounds were not commercially available for preparation of broth dilution. Etest® strips were applied on Mueller Hinton agar inoculated with bacterial suspensions and inhibition endpoints interpreted following 18 hours of incubation at 35°C. Concurrent quality control testing for all test methods was performed according to standard CLSI guidelines. Antibiotic susceptibilities for cefpodoxime, ceftibuten, fosfomycin, mecillinam and trimethoprim were interpreted using current breakpoints from the CLSI.[4] For isolates with detected ESBL or AmpC enzymes, cephalosporin susceptibilities were interpreted as resistant regardless of the tested minimum inhibitory concentration (MIC). In the absence of formal breakpoints for temocillin, susceptibilities were interpreted using MIC breakpoints from the British Society for Antimicrobial Chemotherapy (BSAC),[7] which defines Enterobacteriaceae as susceptible if the MIC is ≤8 mg/L in systemic infections, or ≤32 mg/L in UTIs.

Multiplex polymerase chain reaction (PCR) was performed to characterise *ampC* and ESBL genes. Colonies were emulsified in 100 µl of sterile water, and 5 µl of the suspension was used for PCR. Testing for *bla*SHV, *bla*TEM and *bla*CTX-M and plasmid-borne *ampC* genes was performed by methods previously described.[8,9]

Results

When considering the study isolates as a whole, temocillin and fosfomycin demonstrated the best in vitro efficacy. Temocillin susceptibility was dependent on the breakpoints applied, with 147 (94.9%) isolates susceptible when applying "urinary infection" breakpoints compared with 55 (35.5%) isolates susceptible when "systemic infection" breakpoints were applied. The in vitro efficacy of fosfomycin was lower, with 114 (73.5%) isolates tested as susceptible. Susceptibilities for the 4 other tested antibiotics were less than 50%, with highest resistance to trimethoprim. Of note, resistance to mecillinam was high with only 49 (31.6%) study isolates susceptible.

There were species-specific differences in susceptibility to the tested antibiotics. Most *E. coli* isolates were susceptible to temocillin (n = 77, 95%) based on "urinary infection" breakpoints, but susceptibility was much lower (n = 36, 44.4%) when using "systemic infection" breakpoints (Table 1). The other antibiotics with relatively good in vitro activity against *E. coli* were fosfomycin (n = 63, 77.8%) and ceftibuten (n = 51, 63%), with lower susceptibility to cefpodoxime (n = 38, 46.9%) and mecillinam (n = 40, 49.4%). As seen for *E. coli*, temocillin susceptibilities in *K. pneumoniae* varied depending on the breakpoint chosen, with

Table 1. In Vitro Activities of Tested Antibiotics against *Escherichia coli*

Antibiotic	ESBL/ AmpC*	S (%)	I (%)	MIC 90	MIC Range	Minimum Inhibitory Concentration (mg/L)										
						≤0.25	0.5	1	2	4	8	16	32	64	128	≥256
Temocillin†	+	53 (93%)	n/a	32	4 – 48					3 (5%)	8 (14%)	19 (33%)	23 (40%)	4 (7%)		
	-	17 (100%)	n/a	16	2 – 16				1 (6%)	1 (6%)	6 (35%)	9 (53%)				
Mecillinam	+	6 (11%)	2 (4%)	128	0.25 – 128	1 (2%)		1 (2%)	3 (5%)		3 (5%)	2 (4%)	3 (5%)	9 (16%)	37 (65%)	
	-	3 (18%)	1 (6%)	128	1 – 128			3 (18%)				1 (6%)	1 (6%)		12 (71%)	
Cefpodoxime	+	2 (4%)	0 (%)	>256	0.38 – 512		1 (2%)	1 (2%)			1 (2%)	1 (2%)	1 (2%)	1 (2%)	3 (5%)	1 (2%)
	-	16 (94%)	1 (6%)	2	0.125 – 4	2 (12%)	3 (18%)	5 (29%)	5 (29%)	1 (6%)						
Ceftibuten	+	2 (4%)	4 (7%)	128	0.5 – 128		2 (4%)					4 (7%)	7 (12%)	16 (28%)	28 (49%)	
	-	17 (100%)	0 (%)	1	0.125 – 8	4 (24%)	6 (35%)	1 (6%)			1 (6%)					
Trimethoprim	+	5 (9%)	n/a	64	2 – 64				2 (4%)	3 (5%)		2 (4%)	2 (4%)	48 (84%)		
	-	4 (24%)	n/a	64	0.5 – 64		1 (6%)	1 (6%)	1 (6%)	1 (6%)				13 (76%)		
Fosfomycin	+	38 (67%)	11 (19%)	256	0.5 – 256		1 (2%)		2 (4%)		1 (2%)	4 (7%)	11 (19%)	19 (33%)	11 (19%)	8 (14%)
	-	13 (76%)	1 (6%)	256	2 – 256				1 (6%)			3 (18%)	4 (24%)	5 (29%)	1 (6%)	3 (18%)

I: Intermediate susceptibility; MIC: Minimum inhibitory concentration; S: Susceptible

*+ = present, - = absent.

†Urinary infection breakpoints applied for temocillin.

Table 2. In Vitro Activities of Tested Antibiotics against *Klebsiella pneumoniae*

Antibiotic	ESBL/ AmpC*	S (%)	I (%)	MIC 90	MIC Range	Minimum Inhibitory Concentration (mg/L)										
						≤0.25	0.5	1	2	4	8	16	32	64	128	≥256
Temocillin†	+	53 (93%)	n/a	32	4 – 48					3 (5%)	8 (14%)	19 (33%)	23 (40%)	4 (7%)		
	-	17 (100%)	n/a	16	2 – 16				1 (6%)	1 (6%)	6 (35%)	9 (53%)				
Mecillinam	+	6 (11%)	2 (4%)	128	0.25 – 128	1 (2%)		1 (2%)	3 (5%)		1 (2%)	2 (4%)	3 (5%)	9 (16%)	37 (65%)	
	-	3 (18%)	1 (6%)	128	1 – 128			3 (18%)				1 (6%)	1 (6%)		12 (71%)	
Cefpodoxime	+	2 (4%)	0 (%)	>256	0.38 – 512		1 (2%)	1 (2%)			1 (2%)	1 (2%)	1 (2%)	1 (2%)	3 (5%)	1 (2%)
	-	16 (94%)	1 (6%)	2	0.125 – 4	2 (12%)	3 (18%)	5 (29%)	5 (29%)	1 (6%)						
Ceftibuten	+	2 (4%)	4 (7%)	128	0.5 – 128		2 (4%)					4 (7%)	7 (12%)	16 (28%)	28 (49%)	
	-	17 (100%)	0 (%)	1	0.125 – 8	4 (24%)	6 (35%)	1 (6%)			1 (6%)					
Trimethoprim	+	5 (9%)	n/a	64	2 – 64				2 (4%)	3 (5%)		2 (4%)	2 (4%)	48 (84%)		
	-	4 (24%)	n/a	64	0.5 – 64		1 (6%)	1 (6%)	1 (6%)	1 (6%)				13 (76%)		
Fosfomycin	+	38 (67%)	11 (19%)	256	0.5 – 256		1 (2%)		2 (4%)		1 (2%)	4 (7%)	11 (19%)	19 (33%)	11 (19%)	8 (14%)
	-	13 (76%)	1 (6%)	256	2 – 256				1 (6%)			3 (18%)	4 (24%)	5 (29%)	1 (6%)	3 (18%)

I: Intermediate susceptibility; MIC: Minimum inhibitory concentration; S: Susceptible

*+ = present, - = absent.

†Urinary infection breakpoints applied for temocillin.

94.6% (n = 70) susceptible when using "urinary infection" breakpoints, compared with 25.7% (n = 19) susceptible when using "systemic infection" breakpoints. *K. pneumoniae* isolates were also mostly susceptible to fosfomycin (n = 51, 68.9%), with significantly lower susceptibility to ceftibuten (25.7%), cefpodoxime (24.3%), mecillinam (12.2%) (Table 2). Susceptibility to trimethoprim was equally low for both *E. coli* (n = 64, 13.6%) and *K. pneumoniae* (n = 20, 12.2%).

Fosfomycin MIC testing showed that *E. coli* had very different MIC distributions compared to *K. pneumoniae* (Fig. 1), with the current fosfomycin breakpoint bisecting the normal MIC distribution for *Klebsiella* species. In our study population, current fosfomycin breakpoints would have an increased tendency for intermediate susceptibility results when testing *K. pneumoniae* against this antibiotic. The MIC50 value for temocillin was 12 mg/L for *E. coli* and 16 mg/L for *K. pneumoniae*, which straddles the 8 mg/L and 32 mg/L breakpoints for urinary and systemic infections, respectively. This distribution of temocillin MIC values explains the wide variation of susceptibility depending on whether a "urinary" or "systemic infection" breakpoint was applied.

ESBLs were present in 15 (18.5%) *E. coli* and 32 (43.2%) *K. pneumoniae* isolates. The predominant ESBL genes present were CTX-M, which were detected in 87% of all ESBL-positive isolates of *E. coli* and *K. pneumoniae*. Plasmid-borne *AmpC* genes were present in 20 (24.7%) *E. coli* and 39 (52.7%) *K. pneumoniae* isolates, with CIT-like genes predominantly found in *E. coli* and DHA-like genes predominantly found in *K. pneumoniae*. As expected, MIC values for cephalosporins were significantly elevated for both *E. coli* (Table 1) and *K. pneumoniae* in the presence of either ESBL or AmpC enzymes (Table 2). The presence of either ESBL or AmpC beta-lactamases did not significantly affect overall susceptibilities to fosfomycin, mecillinam or temocillin ($P > 0.05$) (Tables 1 and 2).

Discussion

In this study of MDR *E. coli* and *K. pneumoniae* urinary

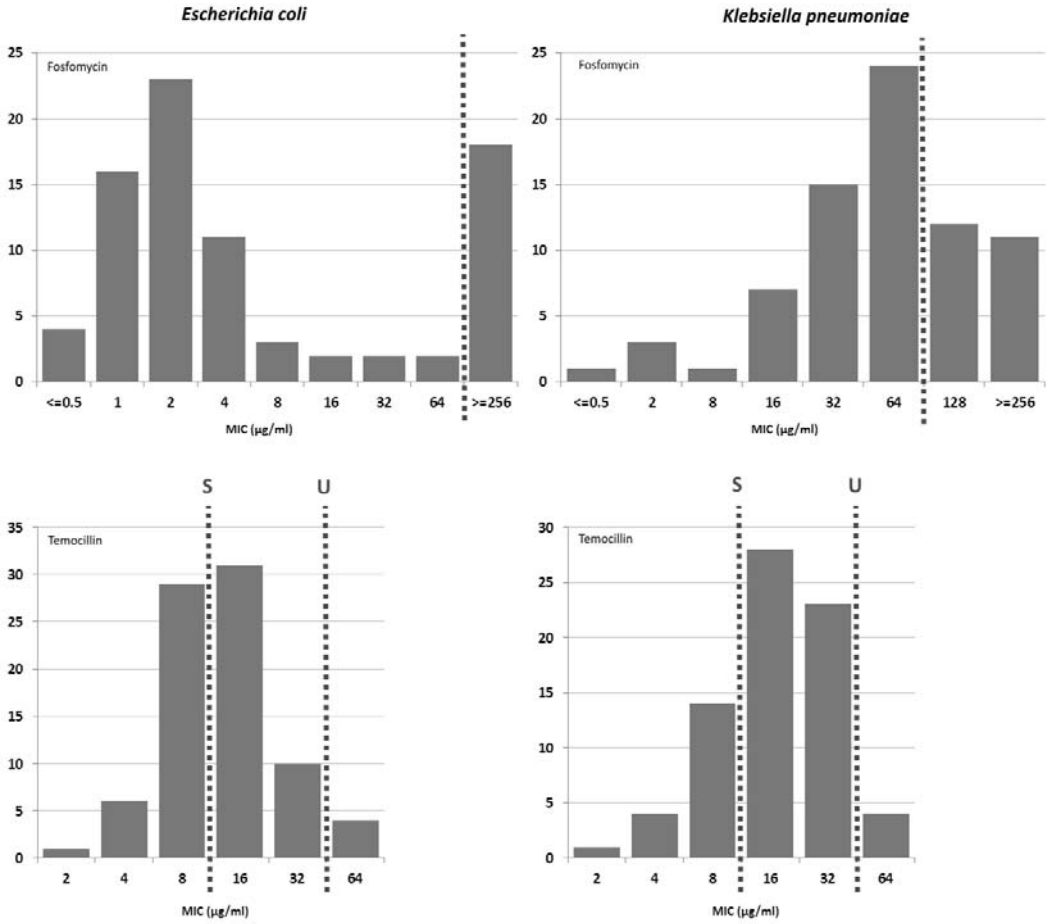

Fig. 1. Charts showing the MIC distributions for fosfomycin and temocillin. Dotted lines show susceptibility breakpoints for fosfomycin (S ≤64, R ≥256) and temocillin (U = "urinary infection" breakpoints, S ≤32; S = "systemic infection" breakpoints S ≤8).

isolates, the oral antibiotic with the best in vitro activity was fosfomycin with susceptibility rates of 77.8% in *E. coli* and 68.9% in *K. pneumoniae*. Temocillin also demonstrated high (>94%) in vitro susceptibility for both *E. coli* and *K. pneumoniae* when the lower "urinary infection" breakpoints were applied. The breakpoints for temocillin fall in the middle of the MIC distributions for *K. pneumoniae* (and to a lesser extent, *E. coli*), which resulted in significantly lower susceptibility rates when "systemic infection" breakpoints were applied. This effect also reduces the reproducibility of susceptibility testing for temocillin against these organisms. Similar temocillin MICs have been reported in other studies on ESBL-producing *E. coli* isolates.[10] In the Singapore context, empirical use of temocillin for MDR-resistant *E. coli* and *Klebsiella* spp. would only be appropriate for the treatment of uncomplicated UTIs, with the added caveat that temocillin is only available for administration via the intravenous route. Both fosfomycin and temocillin remained equally effective in MDR-isolates carrying ESBL or AmpC beta-lactamases.

Ceftibuten is an oral cephalosporin, with enhanced stability against beta-lactamase activity in Enterobacteriaceae. In the absence of either AmpC or ESBL enzymes, 98.5% of urinary isolates were susceptible to ceftibuten, which made this the best alternative antibiotic in strains lacking extended-spectrum cephalosporinases. In contrast, only 46.9% and 24.3% isolates of *E. coli* and *K. pneumoniae* were susceptible to cefpodoxime, with 75.8% susceptibility in isolates without AmpC or ESBL enzymes. A few isolates with ESBL or AmpC enzymes demonstrated in vitro susceptibility to ceftibuten and cefpodoxime, with MIC values in the susceptible range. The clinical extrapolation of these in vitro results to clinical outcomes remains uncertain, but conventional guidance suggests the use of non-cephalosporin agents in ESBL or AmpC-producing strains.

In comparison to other surveys, less than a third of tested isolates were susceptible to mecillinam, even in the absence of ESBL or AmpC enzymes. These results were unexpected because neither temocillin nor pivmecillinam are available in Singapore, and because studies in other geographic regions have shown more promising results. However, in vivo data demonstrates there are multiple genetic pathways that may give rise to mecillinam resistance,[11] and there is one other study from Southeast Asia that similarly reports lower rates of susceptibility to this antibiotic.[12] Additional epidemiological studies would be recommended to adequately assess the extent of mecillinam resistance in this geographic region.

There is a paucity of clinical data for the use of these alternative antibiotics for the treatment of UTIs. The most substantial body of data exists for fosfomycin, both for the treatment of uncomplicated UTI and other UTIs with MDR-organisms,[13] while a study from the United Kingdom reported good clinical and microbiological efficacy for temocillin, provided an optimal dosing regime was used.[14] Several studies reported that ceftibuten demonstrated comparative efficacy to other standard antimicrobials for treatment of lower UTIs, with a few studies also reporting good results for complicated UTIs.[15,16] Pivmecillinam, the oral form of mecillinam, has been widely administered for treatment of acute cystitis in Scandinavian countries for over 20 years, with reports of good safety profile, efficacy and negligible rate of resistance.[17] Despite optimism for mecillinam to be an ideal treatment choice for MDR-pathogens, reports of higher treatment failure rates associated with ESBL-producing Enterobacteriaceae may limit the role of this antibiotic.[18]

Conclusion

This study of alternative antibiotics for MDR-pathogens associated with UTIs has demonstrated few oral therapeutic options. Fosfomycin remains the option with best in vitro activity, while ceftibuten remains an option for Enterobacteriaceae without ESBL and AmpC enzymes. Temocillin may also be considered if an intravenously administered antibiotic is an option, but temocillin susceptibility should be confirmed when treating systemic infections caused by complicated UTI.

Acknowledgement

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REFERENCES

1. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52:e103-20.
2. Hsueh PR, Hoban DJ, Carmeli Y, Chen SY, Desikan S, Alejandria M, et al. Consensus review of the epidemiology and appropriate antimicrobial therapy of complicated urinary tract infections in Asia-Pacific region. J Infect 2011;63:114-23.
3. Bahadin J, Teo SSH, Mathew S. Aetiology of community-acquired urinary tract infection and antimicrobial susceptibility patterns of uropathogens isolated. Singapore Med J 2011;52:415-20.
4. Clinical Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-third Informational Supplement. CLSI document M100-S23. Wayne, PA: Clinical Laboratory Standards Institute; 2013.

5. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18:268-81.
6. Tan TY, Ng LS, He J, Koh TH, Hsu LY. Evaluation of screening methods to detect plasmid-mediated AmpC in Escherichia coli, Klebsiella pneumoniae, and Proteus mirabilis. Antimicrob Agents Chemother 2009;53:146-9.
7. BSAC. BSAC Methods for Antimicrobial Susceptibility Testing. Version 12 May 2013: British Society for Antimicrobial Chemotherapy;2013. Available at: http://bsac.org.uk/wp-content/uploads/2012/02/Version-12-Apr-2013_final.pdf. Accessed on 27 July 2014.
8. Monstein HJ, Ostholm-Balkhed A, Nilsson MV, Nilsson M, Dornbusch K, Nilsson LE. Multiplex PCR amplification assay for the detection of blaSHV, blaTEM and blaCTX-M genes in Enterobacteriaceae. APMIS 2007;115:1400-8.
9. Pérez-Pérez FJ, Hanson ND. Detection of plasmid-mediated AmpC beta-lactamase genes in clinical isolates by using multiplex PCR. J Clin Microbiol 2002;40:2153-62.
10. Rodriguez-Villalobos H, Malaviolle V, Frankard J, de Mendonça R, Nonhoff C, Struelens MJ. In vitro activity of temocillin against extended spectrum beta-lactamase-producing Escherichia coli. J Antimicrob Chemother 2006;57:771-4.
11. Thulin E, Sundqvist M, Andersson DI. Amdinocillin (Mecillinam) resistance mutations in clinical isolates and laboratory-selected mutants of Escherichia coli. Antimicrob Agents Chemother 2015;59:1718-27.
12. Moore CE, Sona S, Poda S, Putchhat H, Kumar V, Sopheary S, et al. Antimicrobial susceptibility of uropathogens isolated from Cambodian children. Paediatr Int Child Health. 2015:2046905515Y0000000008.
13. Falagas ME, Vouloumanou EK, Togias AG, Karadima M, Kapaskelis AM, Rafailidis PI, et al. Fosfomycin versus other antibiotics for the treatment of cystitis: a meta-analysis of randomized controlled trials. J Antimicrob Chemother 2010;65:1862-77.
14. Balakrishnan I, Awad-El-Kariem FM, Aali A, Kumari P, Mulla R, Tan B, et al. Temocillin use in England: clinical and microbiological efficacies in infections caused by extended-spectrum and/or derepressed AmpC β-lactamase-producing Enterobacteriaceae. J Antimicrob Chemother 2011;66:2628-31.
15. Ho MW, Wang FD, Fung CP, Liu CY. Comparative study of ceftibuten and cefixime in the treatment of complicated urinary tract infections. J Microbiol Immunol Infect 2001;34:185-9.
16. Neuhaus TJ, Berger C, Buechner K, Parvex P, Bischoff G, Goetschel P, et al. Randomised trial of oral versus sequential intravenous/oral cephalosporins in children with pyelonephritis. Eur J Pediatr 2008;167:1037-47.
17. Bjerrum L, Gahrn-Hansen B, Grinsted P. Pivmecillinam versus sulfamethizole for short-term treatment of uncomplicated acute cystitis in general practice: a randomized controlled trial. Scand J Prim Health Care 2009;27:6-11.
18. Soraas A, Sundsfjord A, Jorgensen SB, Liestol K, Jenum PA. High rate of per oral mecillinam treatment failure in community-acquired urinary tract infections caused by ESBL-producing Escherichia coli. PLoS One 2014;9:e85889.

Original Article

Aortic Dilatation at Different Levels of the Ascending Aorta in Patients with Bicuspid Aortic Valve

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Abstract

Introduction: Bicuspid aortic valve (BAV) is the most common form of adult congenital heart disease. When compared to patients with a normal trileaflet aortic valve, dilatation of the aortic root and the ascending aorta (Asc Ao) are the common findings in patients with BAV, with consequent higher risk of developing aortic aneurysm, aortic dissection and rupture. We aim to determine the site of the Asc Ao where maximum dilatation occurs in Asian adult patients with BAV. Materials and Methods: All subjects underwent full echocardiography examination. The diameter of the Asc Ao was measured at 3 cm, 4 cm, 5 cm, 6 cm and 7 cm from the level of aortic annulus to the Asc Ao in 2D from the parasternal long-axis view. Results: A total of 80 patients (male/female: 45/35; mean age: 45.3 ± 16.2 years) with congenital BAV and 30 normal control group (male/female: 16/14; mean age: 45.9 ± 15.1 years) were enrolled. The indexed diameters of the Asc Ao were significantly larger than the control group. In patients with BAV, maximum dilatation of Asc Ao occurred around 6 cm distal to the aortic annulus. Conclusion: In patients with BAV, dilatation of Asc Ao is maximal at the mid Asc Ao region around 6 cm distal to the aorta annulus.

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Key words: Valvular heart disease

Introduction

Bicuspid aortic valve (BAV) is the most common form of adult congenital heart disease.[1-4] When compared to patients with a normal trileaflet aortic valve, dilatation of the aortic root and the ascending aorta (Asc Ao) are the common findings in patients with BAV, with consequent higher risk of developing aortic aneurysm, aortic dissection and rupture.[5-8]

The dilatation of any or all segments of the proximal aorta from the aortic root to the aortic arch, called bicuspid aortopathy, is present in approximately 50% of affected persons[9-12] and is a challenging clinical issue. There is not only marked variability in the phenotype of bicuspid aortopathy, but also the presence and severity of the aortic dilation appear to be independent of the degree of valvular dysfunction.[13-16]

Limited data is available on the site of the Asc Ao where maximum dilatation occurs. We aim to determine the site of the Asc Ao where maximum dilatation occurs in adult Asian patients with BAV. This is important in the serial follow-up of BAV patients with dilated Asc Ao to ensure that the region of maximal dilatation is not overlooked and is accurately measured at each follow-up echo study.

Materials and Methods

All adult patients aged from 19 to 70 years old on follow-up at the National Heart Centre, Singapore who were diagnosed with BAV were recruited into the study. In addition, normal controls who had echocardiography done for evaluation of murmurs, other cardiac symptoms and subsequently found to be normal were retrospectively studied for comparison. Patients with aortic coarctation, transposition of the great

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arteries or other congenital cardiac defects, connective tissue disorders like Marfans, Ehlers-Danlos syndrome type IV and Loeys-Dietz syndrome etc. were excluded. Patients with BAV and systolic blood pressure (SBP) of more than 140 mmHg, and those with more than moderate aortic stenosis (AS)[17] and aortic regurgitation (AR)[18] were also excluded. The ethics committee of our hospital and the local research ethics committee had approved this study.

All patients underwent full transthoracic echocardiograms. Echocardiography was performed with Philips iE33 and GE Vivid7 equipped with 2.5 MHz transducers (including 2D, M-mode and color Doppler). The zoom function was used when the aorta was scanned and the commissures were carefully examined. The diameters of the Asc Ao were measured at 3 cm (distance from the centre point of the perpendicular line drawn at the level of aortic annulus to the Asc Ao), 4 cm, 5 cm, 6 cm and 7 cm levels (Figs. 1A and 1B). The image was obtained by 2D in the parasternal long-axis view, perpendicular to the long axis of the vessel, from leading edge to leading edge during end-systole.[19] The indexed diameter (ID) was obtained after correction for body surface area. Dilatations of Asc Ao were defined as an ID greater than the mean +2SD of the values found in controls.

Intra- and Inter-Observer Viability Test

The results of 20 participants were randomly selected and repeat analyses were independently performed by 2 investigators who were each blinded to the other's results. Intra- and inter-observer reproducibility of echocardiographic derived measurements were assessed by calculating the mean difference and standard deviation between the results, with the percentage variability equal to the mean of the absolute values of the differences between the 2 measurements divided by their mean.

Statistic Analysis

All data was analysed using Stata version 13. Continuous data were summarised as mean ± SD. Categorical variables are presented as a count and percentage. The statistical significance of the difference of continuous variables between patients with BAV and normal control group was assessed by student's t-test. Differences in continuous variables among groups were calculated using one-way analysis of variance (ANOVA). Comparing to the dilation at 6 cm distal to aortic annulus, we assessed the sensitivity and specificity at 3 cm, 4 cm, 5 cm and 7 cm.

Results

The data was collected over a 72-month period from December 2007 to December 2013. A total of 200 BAV patients (200/7650 from our database, 2.6%) during the study period and 30 age-matched normal controls with normal tricuspid aortic valves (mean age: 45.9 ± 15.1 years) were retrospectively studied. Out of the 200 BAV patients, only 80 patients (male/female: 45/35, mean age: 45.3 ± 16.2 years) were included in our study after excluding patients with SBP ≥140 mmHg, and those with more than moderate aortic stenosis and regurgitation. The clinical characteristics are shown in Table 1. There is no significant differences between patients with BAV and normal controls in their clinical characteristics. We were not able to measure all the diameters of Asc Ao in all 80 patients with BAV. The

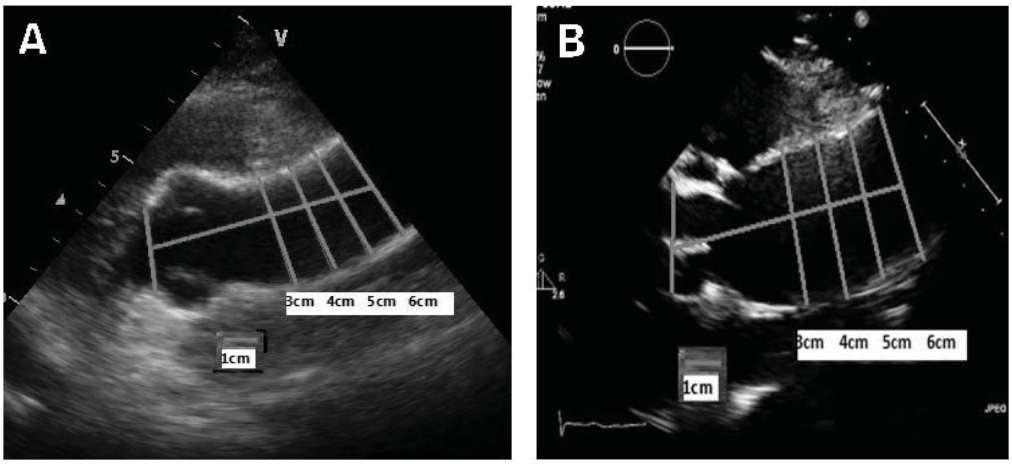

Fig. 1. Measurements of the diameter of Asc Ao at 3 cm, 4 cm, 5 cm and 6 cm from the aortic annulus. Slide A) is of a normal control with diameters of Asc Ao at 3.09 cm, 3.19 cm, 3.25 cm and 3.26 cm at 3 cm, 4 cm, 5 cm and 6 cm from the aortic annulus. Slide B) is of a patient with BAV with diameters of Asc Ao at 3.89 cm, 3.91 cm, 4.07 cm and 4.08 cm at 3 cm, 4 cm, 5 cm and 6 cm from the aortic annulus. The maximal diameter is at the site of 5 cm and 6 cm from the aortic annulus.

Table 1. Clinical Characteristics and Echocardiographic Parameters between BAV Patients and Controls

	BAV Patients (n = 80)	Normal Controls (n = 30)	*P* Value
Age (years)	45.3 ± 16.2	45.9 ± 15.1	NS
Height (cm)	163.2 ± 9.2	164.8 ± 8.5	NS
Weight (kg)	61.0 ± 12.5	64.6 ± 12.1	NS
BSA (m^2)	1.7 ± 0.2	1.7 ± 0.2	NS
Male	45 (56.3%)	16 (53%)	NS
SBP (mmHg)	120.8 ± 13.0	120.4 ± 13.5	NS
DBP (mmHg)	71.6 ± 8.6	73.8 ± 8.6	NS
HR (beat/min)	74.7 ± 15.8	73.6 ± 9.3	NS
LVEF (%)	64.5 ± 7.6	65.2 ± 6.7	NS
LV diastolic dimension (cm)	4.6 ± 0.6	4.4 ± 0.5	NS
LV systolic dimension (cm)	2.7 ± 0.5	2.5 ± 0.4	NS
Aortic velocity (m/s)	1.9 ± 0.6	1.1 ± 0.2	<0.05
Indexed diameter of ascending aorta (cm/m^2)	1.86 ± 0.39	1.59 ± 0.21	<0.05
Indexed diameter of sinus of valsalva (cm/m^2)	1.91 ± 0.58	1.62 ± 0.56	<0.05
Indexed diameter of sinotubular junction (cm/m^2)	1.65 ± 0.53	1.48 ± 0.18	<0.05

BAV: Bicuspid aortic valve; BSA: Body surface area; DBP: Diastolic blood pressure; HR: Heart rate; LV: Left ventricle; LVEF: Left ventricular ejection fraction; NS: Not significant; SBP: Systolic blood pressure

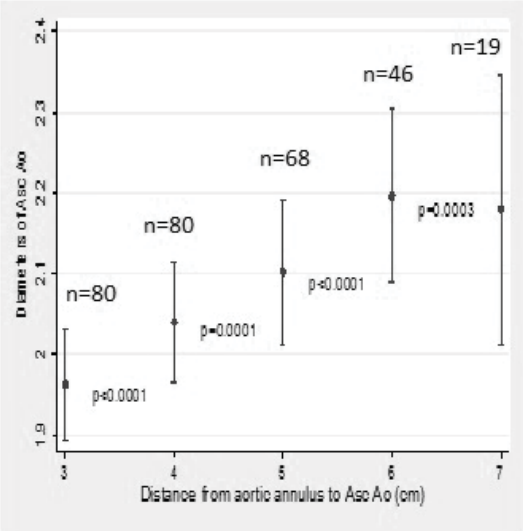

Fig. 2. Indexed diameter of Asc Ao at 3 cm, 4 cm, 5 cm, 6 cm and 7 cm from the aortic annulus (mean) and 95% CI.

respective number of patients in which the measurement was able to be performed at the various distance were 80 (3 cm), 80 (4 cm), 68 (5 cm), 46 (6 cm) and 19 (7 cm) as shown in Table 2. In normal controls, the respective number in which the measurement was able to be performed at the various distance were 30 (3 cm), 30 (4 cm), 28 (5 cm), 25 (6 cm) and 20 (7 cm).

The most common region of dilated Asc Ao and the largest ID of Asc Ao are at around 6 cm distal to the aortic annulus, and the ID of Asc Ao were significantly larger in patients with BAV compared with the normal controls at the same levels of Asc Ao (Table 2). Taking the index of 6 cm as the gold standard, sensitivity and specificity at various distances from aortic annulus to Asc Ao were 83.3%, 90.9% at 3 cm, 87.5%, 90.9% at 4 cm, 100%, 100% at 5 cm, 90%, and 100% at 7 cm, respectively. The ID of Asc Ao and 95% CI are shown in Figure 2. There were significant differences among the groups (Group 3 to Group 4, Group 4 to Group 5, Group 5 to Group 6 and Group 6 to Group 7).

Intra-and Inter-Observer Variability

The intra-observer percentage variability was 8.13 ± 2.41% and inter-observer percentage variability was 6.31 ± 3.52% for the diameter index of Asc Ao.

Discussion

BAV is not just a valvular disorder but is also associated with aortopathy and higher incidence of aortic aneurysm, aortic dissection and rupture,[4,5] which are major causes of

Table 2. Indexed Diameter and Dilatation of the Ascending Aorta at Different Sites

Distance from Aortic Annulus to the Asc Ao	3 cm (n1 = 80) (n2 = 30)	4 cm (n1 = 80) (n2 = 30)	5 cm (n1 = 68) (n2 = 28)	6 cm (n1 = 46) (n2 = 25)	7 cm (n1 = 19) (n2 = 20)
Dilated Asc Ao (BAV) (n)	33	32	33	24	9
Dilated Asc Ao (BAV) (% based on diameter measurable)	41.3%	40.0%	48.5%	52.2%	47.3%
Indexed diameter of Asc Ao (BAV) (cm/m^2)	1.96 ± 0.32	2.04 ± 0.34	2.10 ± 0.38	2.20 ± 0.37	2.18 ± 0.37
Indexed diameter of Asc Ao (controls) (cm/m^2)	1.58 ± 0.22	1.59 ± 0.22	1.60 ± 0.26	1.60 ± 0.23	1.60 ± 0.24

ASc Ao: Ascending aorta; BAV: Bicuspid aortic valve; n1: Number of patients; n2: Number of controls

morbidity and mortality. Patients with BAV have larger aortic dimensions than patients with a normal trileaflet aortic valve.[7,8] Aortic dilatation can occur anywhere between the aortic root and the aortic isthmus, but most commonly occurs in the Asc Ao in BAV disease.[6] Some studies reported that the prevalence of dilatation of the Asc Ao among persons with a BAV ranges from 20% to 84%. [9,10,20-25] This differentiation is related to different study populations, assessment methods, aortic size thresholds and age. But few studies focused on finding the region or site of the Asc Ao at where maximal aortic dilatation occurs.

Bauer M et al[26] reported that the diameter of the Asc Ao in patients with BAV and dilation was significantly larger than in those with a tricuspid aortic valve and dilation. In addition, distances between aortic valve level and point of maximum diameter of the Asc Ao at the outer and inner curves of the vessel in patients with BAV without dilatation were greater than those of the coronary artery disease group. Our study also found that the diameters of Asc Ao in patients with BAV are significantly larger than normal controls at all different sites of the Asc Ao.

In our study, we demonstrated that the indexed aortic dimensions at the sinus of Valsalva, sinotubular junction and Asc Ao in patients with isolated BAV were larger than in normal controls. Our study also found that the maximal dilatation of Asc Ao was at mid-Asc Ao (around 5 cm to 6 cm distal to the aortic annulus), which is probably a combination of haemodynamic and histological changes of the ascending aortic wall in patients with BAV.

Some studies have reported differences in histological and haemodynamic findings of the ascending aortic wall between patients with bicuspid and tricuspid aortic valves.[27,28] Bauer et al reported that patients with a BAV had thinner elastic lamellae of the aortic media and greater distances between the elastic lamellae than patients with a tricuspid aortic valve.[27]

In a study by Viscardi et al[28] looking at ascending aortic flow in patients with BAV, they found asymmetrical distribution of velocity flow towards the convexity region of the mid-Asc Ao and symmetrical blood flow in the distal Asc Ao. On the contrary, blood flow in patients with tricuspid aortic valve was symmetrical in each aortic segment. Comparison between bicuspid and tricuspid models showed asymmetrical and higher flow velocity in bicuspid models. Both the histological and haemodynamic flow changes may contribute to the site of maximal ascending aortic dilatation in this subset of patients.

The ascending aortic diameter and the extention of aortic dilation in the BAV group were found to be significantly associated with patient age, gender and body surface area.[29-32] The 2 groups of patients in our study were matched with respect to age, sex, and body surface area to eliminate these confounding factors and hence our result showing the site of maximal dilatation at 6 cm distal to the aortic annulus is consistent and in agreement with the asymmetrical flow pattern and histological changes in the Asc Ao of BAV patients.

Clinical Implication

Transthoracic echocardiography (TTE) is commonly performed for serial follow-up of Asc Ao dilatation in patients with BAV. It is important to consistently measure the Asc Ao diameter at the site of maximum dilatation during serial echo examinations. In our study, we found that the largest dilatation of Asc Ao occurred at around 6 cm distal to the aortic annulus. The highest percentage is also around 6 cm distal to the aortic annulus. The measurements made at aortic levels at 6 cm would be able to determine the existence of aortic dilatation. Hence, the sensitivity and specificity made at other aortic levels besides 6 cm were also calculated, using 6 cm as the gold standard. High sensitivity and specificity are also found at around 5 cm distal to the aortic annulus. This finding suggests that in patients with BAV, there is a need to measure the diameter not only at the proximal Asc Ao, but also at the mid-part of the Asc Ao (around 5 cm to 6 cm distal to the aortic annulus) where maximum dilatation commonly occurs. Although visualisation of the mid-distal Asc Ao may be difficult in most adults, more than 50% were still measurable in our cohort. Consistent measurement at the same site of maximum Asc Ao dilatation will allow for more accurate monitoring of progressive Asc Ao dilatation in patients with BAV.

Limitations

In our study, each group had a relatively small sample size, particularly those groups at around 6 cm and 7 cm distal to the aortic annulus and normal controls. Due to limited echo window, our sample sizes in this study were sufficient for statistical analysis, but this fact limits the statistical power of our analysis. AR and AS showed different impact on aortic dilatation in different levels of the Asc Ao: the diameter of aortic sinus is affected by AR severity, whereas AS severity shows a linear relationship with the diameter of the tubular portion. For the present study, BAV patients with more than moderate AR and AS were excluded to minimise the effect of valve dysfunction. In addition, in aorta that is tortuous or meandered, there is further inherent limitation in the measurement of the entire length of the Asc Ao; hence the number of possible measurements at increasing distance from the annulus become smaller, especially at 6 cm to 7cm distances from aortic annulus. Other cardiac imaging modalities, including computed tomography (CT) and magnetic resonance

imaging (MRI), may be better for the accurate evaluation of the entire thoracic aorta. We did not try to measure the distal Asc Ao and aortic arch for more complete evaluation and analysis of site of maximal dilatation, because they were not easily seen in some adult patients. So, they were not measured in all patients with BAV.

Conclusion

In our cohort of mainly Asian patients with BAV, Asc Ao dilatation occurs and is maximal at the mid-part of the Asc Ao around 5 cm to 6 cm distal to the aortic annulus. This information is important to ensure that the maximum dilatation of the Asc Ao is measured and documented in each and subsequent echo study performed for serial follow-up of these BAV patients.

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REFERENCES

1. Edwards JE. The congenital bicuspid aortic valve. Circulation 1961;23:485-8.
2. Basso C, Boschello M, Perrone C, Mecenero A, Cera A, Bicego D, et al. An echocardiographic survey of primary school children for bicuspid aortic valve. Am J Cardiol 2004;93:661-3.
3. Nistri S, Basso C, Marzari C, Mormino P, Thiene G. Frequency of bicuspid aortic valve in young male conscripts by echocardiogram. Am J Cardiol 2005;96:718-21.
4. Roberts WC. The congenitally bicuspid aortic valve. A study of 85 autopsy cases. AmJ Cardiol 1970;26:72-3.
5. Nistri S, Sorbo MD, Basso C, Thiene G. Bicuspid aortic valve: abnormal aortic elastic properties. J Heart Valve Dis 2002;11:369-73;discussion 373-4.
6. Anagnostopoulos CE, Prabhakar MJ, Kittle CF. Aortic dissections and dissecting aneurysms. Am J Cardiol 1972;30:263-73.
7. Larson EW, Edwards WD. Risk factors for aortic dissection: a necropsy study of 161 cases. Am J Cardiol 1984;53:849-55.
8. Roberts CS, Roberts WC. Dissection of the aorta associated with congenital malformations of the aortic valve. J Am Coll Cardiol 1991;17:712-6.
9. Fedak PW, Verma S, David TE, Leask RL, Weisel RD, Butany J. Clinical and pathophysiological implications of a bicuspid aortic valve. Circulation 2002;106:900-4.
10. Siu SC, Silversides CK. Bicuspid aortic valve disease. J Am Coll Cardiol 2010;55:2789-800.
11. Carro A, Teixido-Tura G, Evangelista A. Aortic dilatation in bicuspid aortic valve disease. Rev Esp Cardiol (Engl Ed) 2012;65:977-81.
12. Girdauskas E, Borger MA, Secknus MA, Girdauskas G, Kuntze T. Is aortopathy in bicuspid aortic valve disease a congenital defect or a result of abnormal hemodynamics? A critical reappraisal of a one-sided argument. Eur J Cardiothorac Surg 2011;39:809-14.
13. Keane MG, Wiegers SE, Plappert T, Pochettino A, Bavaria JE, Sutton MG. Bicuspid aortic valves are associated with aortic dilatation out of proportion to coexistent valvular lesions. Circulation 2000;102:35-9.
14. Beroukhim RS, Kruzick TL, Taylor AL, Gao D, Yetman AT. Progression of aortic dilation in children with a functionally normal bicuspid aortic valve. Am J Cardiol 2006;98:828-30.
15. Della Corte A, Bancone C, Quarto C, Dialetto G, Covino FE, Scardone M, et al. Predictors of ascending aortic dilatation with bicuspid aortic valve: a wide spectrum of disease expression. Eur J Cardiothorac Surg 2007;31:397-404.
16. Yasuda H, Nakatani S, Stugaard M, Tsujita-Kuroda Y, Bando K, Kobayashi J, et al. Failure to prevent progressive dilation of ascending aorta by aortic valve replacement in patients with bicuspid aortic valve: comparison with tricuspid aortic valve. Circulation 2003;108:291-4.
17. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. J Am Soc Echocardiogr 2009;22:1-23.
18. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777-802.
19. Albano AJ, Mitchell E, Pape LA. Standardizing the method of measuring by echocardiogram the diameter of the ascending aorta in patients with a bicuspid aortic valve. Am J Cardiol 2010;105:1000-4.
20. Tadros TM, Klein MD, Shapira OM. Ascending aortic dilatation associated with bicuspid aortic valve: pathophysiology, molecular biology, and clinical implications. Circulation 2009;119:880-90.
21. Della Corte A, Bancone C, Quarto C, Dialetto G, Covino FE, Scardone M, et al. Predictors of ascending aortic dilatation with bicuspid aortic valve: a wide spectrum of disease expression. Eur J Cardiothorac Surg 2007;31:397-404.
22. Hahn RT, Roman MJ, Mogtader AH, Devereux RB. Association of aortic dilation with regurgitant, stenotic and functionally normal bicuspid aortic valves. J Am Coll Cardiol 1992;19:283-8.
23. Nistri S, Sorbo MD, Marin M, Palisi M, Scognamiglio R, Thiene G. Aortic root dilatation in young men with normally functioning bicuspid aortic valves. Heart 1999;82:19-22.
24. Novaro GM, Griffin BP. Congenital bicuspid aortic valve and rate of ascending aortic dilatation. Am J Cardiol 2004;93:525-6.
25. Thanassoulis G, Yip JW, Filion K, Jamorski M, Webb G, Siu SC, et al. Retrospective study to identify predictors of the presence and rapid progression of aortic dilatation in patients with bicuspid aortic valves. Nat Clin Pract Cardiovasc Med 2008;5:821-8.
26. Bauer M, Gliech V, Siniawski H, Hetzer R. Configuration of the ascending aorta in patients with bicuspid and tricuspid aortic valve disease undergoing aortic valve replacement with or without reduction aortoplasty. J Heart Valve Dis 2006;15:594-600.
27. Bauer M, Pasic M, Meyer R, Goetze N, Bauer U, Siniawski H, et al. Morphometric analysis of aortic media in patients with bicuspid aortic valve. Ann Thorac Surg 2002;74:58-62.
28. Viscardi F, Vergara C, Antiga L, Merelli S, Veneziani A, Puppini G, et al. Comparative finite element model analysis of ascending aortic flow in bicuspid and tricuspid aortic valve. Artif Organs 2010;34:1114-20.
29. Cecconi M, Manfrin M, Moraca A, Zanoli R, Colonna PL, Bettuzzi MG, et al. Aortic dimensions in patients with bicuspid aortic valve without significant valve dysfunction. Am J Cardiol 2005;95:292-4.
30. Yuan SM, Jing H, Lavee J. The bicuspid aortic valve and its relation to aortic dilation. Clinics (Sao Paulo) 2010;65:497-505.
31. Roman MJ, Devereux RB, Kramer-Fox R, O'Loughlin J. Two-dimensional echocardiographic aortic root dimensions in normal children and adults. Am J Cardiol 1989;64:507-612.
32. Vasan RS, Larson MG, Levy D. Determinants of echocardiographic aortic root size: the Framingham Heart Study. Circulation 1995;91:734-40.

Comparison of Outcomes and Costs of Transcatheter Therapeutic Intervention and Surgical Ligation for the Treatment of Patent Ductus Arteriosus

Dear Editor,

Patent ductus arteriosus (PDA) is a persistence of fetal communication, ductus arteriosus, which connects the aorta and pulmonary artery. One of the most common congenital heart conditions, PDA accounts for approximately 10% of all congenital heart defects.[1] Closure of the PDA (other than the silent duct) is recommended to prevent congestive heart failure, infection and pulmonary hypertension.[2,3] Methods to close PDA have evolved over the years with more options developed with similar safety and efficacy profile. This has opened up avenues for research, looking at not just clinical outcomes, but also taking into consideration costs, which may drive the selection strategy. Therefore, the need for local data on costs to guide practice and influence decision-making is imperative.

We aimed to compare the outcomes and cost of device closure through the transcatheter route using occluder device (ADO) versus surgical ligation (SL) in patients who underwent PDA corrective procedures.

Materials and Methods

Study Design and Population

Two retrospective cohorts of patients who underwent PDA closure via SL or ADO closure, between February 2004 and April 2014 at the National University Hospital (NUH), Singapore were reviewed. Excluded were patients with concomitant pre-existing conditions, preterm infants or patients with other associated congenital heart defects who required interventions other than PDA closure. Patient diagnosis was confirmed on echocardiography with full colour flow mapping and Doppler studies. The study was approved by the Domain Specific Review Board.

Treatment

SL through conventional surgery and ADO closures in the cardiac catheter laboratory were performed under general anaesthesia. The clinical outcomes and complications, including minor (if resolved spontaneously or with minimal intervention) and major (if required a higher level of care or additional procedures) were recorded.

The cost was based on the final hospital financial bills of the patients, considering patients as paying ward B1 patients. This allows for a realistic comparison of the economic advantages of these methods by looking at the total costs incurred by the patient during the entire hospital stay. This cost computation comprised bed charges during the period of hospitalisation, pharmaceutical, diagnostic (echocardiography, laboratory and imaging studies), surgery or device cost, professional fees (cardiologist, surgeon, anaesthesiologist), operating theatre/cardiac catheterisation laboratory fees and other miscellaneous charges related to patient care. The cost estimations obtained in Singapore dollars were converted to US dollars (1 SGD = 0.70 USD), as per the conversion rate prevalent on 7 October 2015.

Statistical Analysis

The chi-square and one-way analysis of variance (ANOVA) were used for statistical analysis.

Results

Study Population

Table 1 shows the comparative characteristics of 35 patients, 10 in the SL and 25 in ADO closure groups.

Clinical Outcomes and Complications

Successful closure of PDA was achieved in both groups with good clinical outcomes. All patients were discharged well. Post-procedure and follow-up echocardiogram at 6-months revealed complete ductal occlusion for all patients in both groups. The complication rate was significantly lower in patients who underwent ADO closure ($P = 0.02$) (Table 1).

Length of Stay (LOS) and Costs

The mean length of stay (LOS) (6 ± 2.4 vs 2 ± 0.3 days, $P < 0.001$) and high dependency (HD) stay (80% with 2.6 ± 2.6 days vs 20% with 0.2 ± 0.4 days, $P < 0.001$) was significantly longer in the SL group.

The mean cost per successful procedure (USD 7716 ± 4058 vs USD 6858 ± 1639, $P = 0.37$), trended higher for SL than the ADO closure (Table 1). The cost of the ADO device and its delivery device (costing approximately USD 2600), contributed to a significant portion of the total

Table 1. Comparison of Demographic and Baseline Characteristics as well as Other Clinical Outcomes, Length of Stay and Charges between the Two Cohorts of PDA—ADO and SL

Variables	Total (n = 35)	ADO Closure (n = 25)	Surgical Ligation (n = 10)	*P* Value
Characteristics				
Number of male patients (%)	15 (42.9)	11 (44.0)	4 (40.0)	0.05
		Mean (SD)		
Age at time of operation, years	7.0 (7.6)	9.0 (7.8)	2.0 (3.7)	0.01*
PDA size, mm	3.8 (1.3)	3.8 (1.3)	3.9 (1.2)	0.69
Body weight, kg	22.0 (9.5)	25.1 (9.0)	15.4 (7.2)	0.01*
LPA before catheterisation, m/s	1.3 (0.3)	1.2 (0.3)	1.5 (0.3)	0.02*
Dao gradients before catheterisation, m/s	1.5 (0.5)	1.4 (0.3)	1.8 (0.6)	0.06
Complications				
Number of patients with minor complications (%)	6 (17.1)	2† (8.0)	4‡ (40.0)	0.02*
Clinical outcomes				
LPA after catheterisation, m/s	1.1 (0.3)	1.1 (0.3)	1.2 (0.4)	0.89
Dao gradients after catheterisation, m/s	1.1 (0.3)	1.1 (0.3)	1.2 (0.3)	0.70
Length of stay				
Hospital stay, days	3.1 (2.2)	2.0 (0.3)	6.0 (2.4)	<0.001*
ICU/HD stay				
Number of patients (%)	13 (37.1)	5 (20.0)	8 (80.0)	<0.001*
Days	0.9 (1.8)	0.2 (0.4)	2.6 (2.6)	<0.001*
Total charges in SGD	10109 (3603)	9760 (2333)	10981 (5775)	0.37
Total charges in USD	7103 (2531)	6858 (1639)	7716 (4058)	0.37

ADO: Amplatzer ductal occlude; Dao: Descending aorta; HD: High dependency; ICU: Intensive care unit; LPA: Left pulmonary artery; PDA: Patent ductus arteriosus; SD: Standard deviation

*Statistically significant values.

†One was a case of mild postprocedural fever and the other had transient diminished pulse on lower extremity postdevice occlusion. Both resolved with no intervention required, other than antipyretics for the former.

‡Three of which were directly related to surgery. There was residual shunting noted on 2 cases; 1 had minimal pleural effusion and the other developed subcutaneous emphysema after chest tube removal which resolved. All the complications in these 4 cases did not require additional intervention or additional hospital stay.

hospitalisation bill incurred by patients who underwent ADO closure.

Discussion

This is the first paper to our knowledge addressing cost considerations of this condition in Singapore. In other countries, conflicting cost analysis on SL versus ADO closure of PDA has been reported.[4] This is likely due to substantial heterogeneity among the studies in terms of PDA diameter, type of device used, patient characteristics, method of cost calculation, and more importantly, the period, as the cost of devices has gone down over time including less utilisation of medical resources due to improvement in the transcatheter procedure similar to our ASD study.[5]

Importantly in our study, there was no difference in terms of long-term successful closure of the PDA regardless of the method, with no major complications. LOS and HD stay were significantly longer in the SL group. Although our study did not find a significant difference in the direct financial cost between the two interventions, the intangible cost associated with complications and LOS may incur a cost burden for the patients undergoing SL.[6] LOS is a key determinant of the other indirect costs such as work days off for parents and lodging/boarding/transportation cost. Reduction in hospitalisation and HD stay also poses less emotional stress on parents.[4] Furthermore, with ever increasing patient load and limited bed space in hospitals, a quick turnaround time will allow more patients to benefit from inpatient medical care and help the community as a whole.

One has to, however, keep in mind that there was a predilection for surgery in younger patients, with the majority of the patients <1 year in the SL group. This is

secondary to known technical difficulties. This includes the use of large devices in small infants which may protrude into the descending aorta or pulmonary artery.[7] Therefore, the use of ADO closure in patients weighing <5 kg is generally cautioned.[8,9] In our experience, ADO closure was successfully used for PDA sizes 2.5 to 8 mm, in agreement with previously published data on PDA up to 12 mm.[10] The prolonged HD stay in the surgical group could have been because of the younger group of children in SL group leading to more complications, requiring longer HD stay.

The cost outlined in the study is not an absolute cost but a relative cost used to compare the two interventions. The costs may vary in other healthcare systems, outside and within Singapore, where the professional and facility fees may differ. Another limitation is, over the study period of 10 years, there may have been inflation of healthcare costs which was difficult to account for. However, all else being equal, cosmesis and less postoperative pain are other important considerations.

Conclusion

The corrective modalities discussed in this study were comparable in terms of effectiveness and safety profile for closure of isolated PDA. The ADO can be used for patients of varying ages, except small babies under 5 kg and small PDA. SL carries with it patient discomfort, longer stay and a surgical scar associated with an operative procedure, but nonetheless, will maintain its importance especially in the very small, such as premature babies.

REFERENCES

1. Shim D, Beekman RH, 3rd. Transcatheter management of patent ductus arteriosus. Pediatr Cardiol 1998;19:67-71;discussion 72-3.
2. Campbell M. Natural history of persistent ductus arteriosus. Br Heart J 1968;30:4-13.
3. Tynan M. The ductus arteriosus and its closure. N Engl J Med 1993;329:1570-2.
4. Human DG, McIntyre L, Gniewek A, Hanna BD. Technology assessment of nonsurgical closure of patent ductus arteriosus: an evaluation of the clinical effectiveness and costs of a new medical device. Pediatrics 1995;96:703-6.
5. Quek SC, Hota S, Tai BC, Mujumdar S, Tok MY. Comparison of clinical outcomes and cost between surgical and transcatheter device closure of atrial septal defects in Singapore children. Ann Acad Med Singapore 2010;39:629-33.
6. Wang K, Pan X, Tang Q, Pang Y. Catheterization therapy vs surgical closure in pediatric patients with patent ductus arteriosus: a meta-analysis. Clin Cardiol 2014;37:188-94.
7. Tometzki AJ, Arnold R, Peart I, Sreeram N, Abdulhamed JM, Godman MJ, et al. Transcatheter occlusion of the patent ductus arteriosus with Cook detachable coils. Heart 1996;76:531-5.
8. Fernandez Ruiz A, del Cerro Marin MJ, Rubio Vidal D, Castro Gussoni MC, Moreno Granados F. Transcatheter closure of patent ductus arteriosus using the Amplatzer duct occluder: initial results and mid-term follow-up. Rev Esp Cardiol 2002;55:1057-62.
9. Chen Z, Chen L, Wu L. Transcatheter amplatzer occlusion and surgical closure of patent ductus arteriosus: comparison of effectiveness and costs in a low-income country. Pediatr Cardiol 2009;30:781-5.
10. Pass RH, Hijazi Z, Hsu DT, Lewis V, Hellenbrand WE. Multicenter USA Amplatzer patent ductus arteriosus occlusion device trial: initial and one-year results. J Am Coll Cardiol 2004;44:513-9.

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Sequential Localised Neuropathic Itch Following Drastic Weight Gain and Loss

Dear Editor,

A 56-year-old Indian woman with obesity underwent bariatric surgery (laparoscopic sleeve gastrectomy). She had gained 10 kg over the 3 years preceding the surgery after changing to a sedentary job. For 2 years, she had been having localised itch over the paraspinal region of her left upper back. Examination revealed a localised hyperpigmented patch over her left upper back (Fig. 1). The diagnosis was notalgia paresthetica (NP).

After her surgery, the patient had rapid slimming initially. For the first 2 weeks postsurgery, the patient was only given clear feeds and had rapid weight loss during this period. She lost 10 kg in the first 3 months postsurgery. Three days postsurgery, she started feeling numbness over her right lower thigh and 13 days postsurgery, she felt itch and pain over the same area with the disappearance of the numbness. For the next 3 months, she experienced intermittent itch and pain over an area that correlated with the distribution of the lateral cutaneous branch of the femoral nerve and was diagnosed to have meralgia paresthetica (MP) (Fig. 2). There were no other external pressures on the nerve such as tight clothing or pressure during surgery.

Discussion

NP is not a rare condition but it is greatly under-recognised. NP is a form of peripheral sensory mononeuropathy and is thought to be secondary to nerve impingement or trauma affecting the posterior rami of the spinal nerves.[1] It may result from compression by a space-occupying lesion or musculoskeletal structures, but no definite cause can be identified in most cases.

MP is another type of localised neuropathic dysaesthesia but it is rare. It is secondary to nerve entrapment of the lateral femoral cutaneous nerve, typically presenting with numbness, burning pain, itching or a tingling sensation localised to the unilateral anterolateral thigh.[1] Numerous predisposing factors have been suggested, including diabetes mellitus, alcoholism, obesity (BMI >30), pregnancy, prolonged sitting, strenuous activity, direct trauma, lumbar disc herniation, iliaceous haematoma and tight clothing.[1,2] Following gastric bypass surgery, the incidence of MP is estimated to be 0.5% to 1.4%.[3] Compression of the thigh by the Gomez retractor has been a proposed mechanism.[4] However, MacGregor and Thoburn reported 11 cases of MP, most beginning shortly after surgery (2 to 13 days),

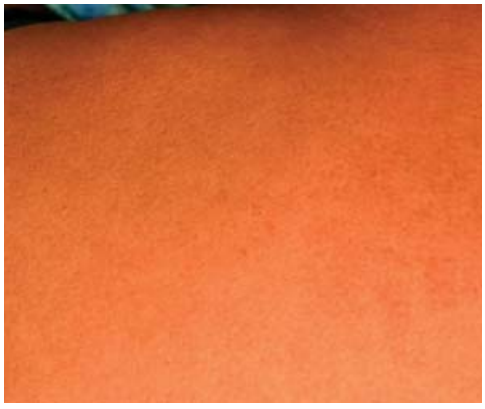

Fig. 1. A hyperpigmented patch at the localised area of itch over the paraspinal region of the patient's left upper back, corresponding to the dermatome of the dorsal ramus of the T2 spinal nerve. This is a typical presentation of notalgia paresthetica.

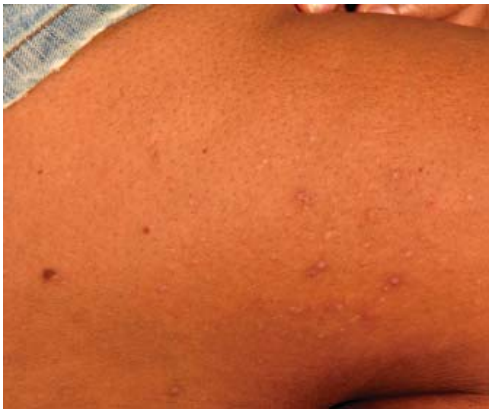

Fig. 2. A localised area of excoriations without the presence of a primary dermatosis over the patient's right lower lateral thigh, which corresponded to the area of itch and pain. Impingement of the lateral femoral cutaneous nerve led to meralgia paresthetica.

despite using an upper midline incision to avoid pressure at the hips.[5]

Our patient appears to be susceptible to different nerve impingements with changes in her habitus. Her weight gain may have led to nerve compression due to a change in posture of her shoulders and back or a shift in positions of muscles due to fat accumulation. Similarly, rapid weight loss with decreased subcutaneous tissue can similarly lead to compression of the lateral femoral cutaneous nerve under the inguinal ligament. To our knowledge, there have not been previous reports of patients experiencing multiple localised neuropathies following drastic weight changes.

REFERENCES

1. Runger AM. In: Bolognia JL, Jorizzo JJ, Schaffer JV, editors. Dermatology. 3rd ed. Beijing: Elsevier; 2012. p 120-3.
2. Cheatham SW, Kolber MJ, Salamh PA. Meralgia paresthetica: a review of the literature. Int J Sports Phys Ther 2013;8:883-93.
3. Koffman BM, Greenfield LJ, Ali II, Pirzada NA. Neurologic complications after surgery for obesity. Muscle Nerve 2006;33:166-76.
4. Grace DM. Meralgia paresthetica after gastroplasty for morbid obesity. Can J Surg 1987;30:64-5.
5. Macgregor AM, Thoburn EK. Meralgia paresthetica following bariatric surgery. Obes Surg 1999;9:364-8.

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Perioperative Outcomes of Therapeutic Breast Surgery in the Elderly

Dear Editor,

Female Singaporeans currently have a life expectancy of 84.5 years[1] and a lifetime risk of 6.5% of developing breast cancer.[2] It is estimated that by the year 2050, 11.2% of the population will be aged more than 80 years.[3] One in 16 women will develop breast cancer by the age of 80, and there will potentially be 1500 cases of newly diagnosed breast cancer among octogenarians each year.

Surgery is curative in early breast cancer and various centres have reported no difference in the cancer specific survival rates of the elderly age group compared to their younger counterparts, 5 to 10 years after surgery for breast cancer.[4,5] Surgery is also indicated in advanced breast cancer as a form of palliation in patients with fungating and bleeding tumours. Despite its therapeutic role, Lavelle et al[6] found that the proportion of older women receiving surgery fell with increasing comorbidity and many clinicians still do not discuss surgical options with elderly patients.

We wanted to objectively report the postsurgical mortality and morbidity of the very elderly, aged above 80 years in our institution. We also hoped to identify risk factors that may predict for a poorer outcome. To our knowledge, this is the first study in an Asian population.

Materials and Methods

Patients diagnosed with breast cancer after age 80 years, and had therapeutic surgery under general anaesthesia at the National Cancer Centre Singapore (NCCS) and Singapore General Hospital (SGH), between January 1997 and December 2010 were identified.

Functional status was measured in the form of American Society of Anesthesiologists (ASA) physical classification status and Eastern Cooperative Oncology Group (ECOG) score. Outcomes were measured in the form of perioperative morbidity and mortality, length of hospital stay, and incidence of postoperative complications.

Results

A total of 109 females with a mean age of 83.2 years (range, 80 to 96 years) were identified. Ninety-eight (89.9%) patients had at least 1 comorbidity, with hypertension being the most common condition. The majority, 78%, were ECOG 0 or 1, while 75.2% were ASA I or II. Most (59.6%) had early breast cancer of stages I or II (Table 1). Surgery was performed with curative intent in 82.6% of patients. The rest were performed for palliation of symptoms. Ninety-seven (89.0%) patients had a mastectomy while 12 (11.0%) patients underwent wide excision. The median duration of surgery was 90 minutes amongst all patients (range, 30 to 295 minutes) (Table 2).

There were no cases of perioperative mortality in the 30-day period. The median duration of hospitalisation was

Table 1. Patient Demographics, Comorbidities and Disease Stage

Performance Status	No. of Patients (n = 109) (%)
ASA status	
I	5 (4.6%)
II	77 (70.6%)
III	26 (23.9%)
IV	1 (0.9%)
ECOG score	
0	50 (45.9%)
1	35 (32.1%)
2	16 (14.7%)
3	8 (7.3%)
No. of comorbidities	
0	11 (10.1%)
1 – 2	45 (41.3%)
3 – 4	43 (39.4%)
>4	10 (9.2%)
Types of comorbidity	
Hypertension	77 (70.6%)
Dyslipidaemia	32 (29.4%)
Diabetes mellitus	27 (24.8%)
Ischaemic heart disease	22 (20.2%)
Existing or old stroke	16 (14.7%)
Stage of cancer	
0	7 (6.4%)
1 – 2	65 (59.6%)
3 – 4	37 (33.9%)

ASA: American Society of Anesthesiology; ECOG: Eastern Cooperative Oncology Group

Table 2. Operative Details

Surgery	No. of Patients (n = 109) (%)	Duration/Minutes
Type		Mean (range)
Wide excision only	11 (10.1%)	62.5 (35 – 130)
Wide excision and axillary surgery	1 (0.9%)	70 (70)
Mastectomy	11 (10.1%)	82.5 (50 – 135)
Mastectomy and axillary surgery	86 (78.9%)	97.8 (45 – 150)
Intent		
Curative	90 (82.5%)	
Palliative	19 (17.4%)	

Table 3. Surgical Outcomes

Factor	No. of Patients (n = 109) (%)
30-day mortality	
Alive	109 (100%)
Death	0 (0%)
Postoperative relocation	
General ward	96 (88.1%)
High dependency	13 (11.9%)
Intensive care unit	0 (0%)
Length of stay (days)	
1 – 3	11 (10.1%)
4 – 7	45 (41.3%)
8 – 14	43 (39.4%)
>14	10 (9.2%)
Complications	
Nil	66 (60.6%)
Total	43 (39.4%)
After wide local excision	3/12 (25%)
After mastectomy	40/97 (41.2%)
Minor*	40 (36.7%)
Seroma	35 (32.1%)
Bleeding	6 (5.5%)
Wound infection	6 (5.5%)
Major	3 (2.7%)
Acute myocardial infarction	1 (0.9%)
Deep vein thrombosis	1 (0.9%)
Wound dehiscence†	1 (0.9%)

*Some patients had more than 1 complication.
†Patient required repeat surgery.

3 days (range, 2 to 28 days). Two patients stayed beyond 2 weeks due to postoperative deconditioning and required time for placement to a step-down facility (Table 3).

The most common minor complication (32.1%) was the development of a seroma that required needle aspiration. Bleeding and wound infection occurred in 6 (5.5%) patients respectively. Major complications were rare and occurred in only 3 (2.8%) patients. One patient had an acute myocardial infarction, 1 developed deep vein thrombosis, and 1 had wound dehiscence requiring resuturing of surgical wound in the operating theatre.

Among patients without comorbidities, only 1 of 11 (10%) patients developed a complication. This is in comparison to the complication incidence rate in 18 out of 45 (40%) patients with 1 or 2 comorbidities; 19 of 43 (44.1%) of patients with 3 or 4 comorbidities and 5 out of 10 (50%) patients with more than 5 comorbid conditions. Major complications were more likely to happen in those with higher ASA and ECOG scores. Of the 3 patients who had major complications, 1 had an ASA score of II while 2 patients scored III. Two patients had an ECOG score of 2 while the other scored 3. However, when comparing rates of all complications against ASA and ECOG status, there were no statistically significant differences.

Discussion

In the very elderly, surgery under general anaesthesia may pose more risks than yield benefits. Patients and their surgeons often adopt a very considered approach.

Newschaffer et al[7] reported that older women were less likely to receive surgery than their younger counterparts despite adjustments for aggregate comorbidity. However, European studies[8,9] assessing the surgical outcomes amongst elderly above 80 years of age, showed that very elderly patients can still be safely treated with surgery, with acceptable perioperative morbidity and mortality rates.

In our study, 80% of patients had between 1 to 4 comorbidities, consistent with a typical elderly profile.[10] Seventy percent of the patients were of ASA II status, which was reflective of well controlled and mild systemic disease with no functional limitation. Eight in 10 patients had ECOG status less than 2, and were at least ambulatory and able to carry out self-care, if not light work.

We found that elderly women may still have breast surgery safely despite having co-existing medical problems. The 30-day perioperative mortality was 0 and 60% of patients had no complications. Patients with more comorbidities were more likely to develop complications but complication patterns were similar in younger women and were considered minor enough to be managed conservatively.

Although the incidence of complications appear to be higher in elderly patients, less than 5% of our patients had major complications. This was consistent with findings by Chatzidaki et al[8] who reported major complication rates

of 5.7%. The 3 patients who had major complications were not ideal candidates for surgery in view of their medical comorbidities, but we proceeded with palliative mastectomies as they had debilitating symptoms arising from locally advanced tumours. Palliative mastectomy does not shorten survival[11] and can help to improve local control of bulk disease and reduce symptoms. Such patients are often not candidates for palliative chemotherapy, while radiotherapy often provides short-lived relief and has its inherent side effects.[12] In our series, 15% of the patients developed complications after undergoing a palliative mastectomy, and we consider this an acceptable risk considering the lack of better options.

Evron et al[9] illustrated the benefits of surgery, where they found that 101 of 135 (75%) octogenarians were still alive 6 years after diagnosis of breast cancer, and 22 of the 34 (64.7%) deaths were due to non-related conditions. Studies[13,14] showed that fit elderly patients who had surgery —with or without adjuvant tamoxifen—had a significant improved progression-free survival, compared to those who were treated with tamoxifen only.

Surgery plays an important therapeutic role in the treatment of breast cancer, regardless of it being curative or palliative in nature.[15] On the other hand, major complications arising from a curative surgery is undesirable and proper patient selection for surgery should be undertaken. Based on our findings, complications were less likely to occur in patients with less than 4 comorbidities that are well controlled, and if they have performance status of ASA I or II and ECOG score of 0 or I. A limitation of this study was that this was a highly selected group of patients who were expected to do well, as patients who were deemed extremely high risk were unlikely to have been operated on. Nonetheless, at our institutions, patients deemed fit for surgery by surgeons and anaesthetists generally have a good outcome.

Conclusion

Both curative and palliative breast cancer surgery may be performed safely for selected patients aged above 80 years, even in the presence of pre-existing medical problems, with low morbidity.

REFERENCES

1. Department of Statistics, Singapore. Population Trends 2013. Available at: http://www.singstat.gov.sg. Accessed on 14 July 2015.
2. Teo MC, Soo KC. Cancer trends and incidences in Singapore. Jpn J Clin Oncol 2013;43:219-24.
3. Saw Swee-Hock. Implications of demographic trends in Singapore. In: Ooi Kee Beng, editor. ISEAS Perspective: Selections 2012-2013. Singapore: Institute of Southeast Asian Studies; 2013.
4. Herbsman H, Feldman J, Seldera J, Gardner B, Alfonso AE. Survival following breast cancer surgery in the elderly. Cancer 1981;47:2358-63.
5. Hunt KE, Fry DE, Bland KI. Breast carcinoma in the elderly patient: An assessment of operative risk, morbidity and mortality. Am J Surg 1980;140:339-42.
6. Lavelle K, Downing A, Thomas J, Lawrence G, Forman D, Oliver SE. Are lower rates of surgery amongst older women with breast cancer in the UK explained by co-morbidity? Br J Cancer 2012;107:1175-80.
7. Newschaffer CJ, Penberthy L, Desch CE, Retchin SM, Whittemore M. The effect of age and comorbidity in the treatment of elderly women with non-metastatic breast cancer. Arch Intern Med 1996;156:85-90.
8. Chatzidaki P, Mellos C, Briese V, Mylonas I. Perioperative complications of breast cancer surgery in elderly women (≥80 years). Ann Surg Oncol 2011;18:923-31.
9. Evron E, Goldberg H, Kuzmin A, Gutman R, Rizel S, Sella A, et al. Breast cancer in octogenarians. Cancer 2006;106:1664-8.
10. Yancik R, Ganz PA, Varricchio CG, Conley B. Perspectives on comorbidity and cancer in older patients: approaches to expand the knowledge base. J Clin Oncol 2001;19:1147-51.
11. Rapiti E, Verkooijen HM, Vlastos G, Fioretta G, Neyroud-Caspar I, Sappino AP, et al. Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. J Clin Oncol 2006;24:2743-9.
12. Dulley LF, Li S, Ah-See MW. Efficacy of hypofractionated palliative radiotherapy in locally advanced breast cancer. Clinical Oncology 2001;23:S35-6.
13. Hind D, Wyld L, Reed MW. Surgery, with or without tamoxifen, vs tamoxifen alone for older women with operable breast cancer: Cochrane review. Br J Cancer 2007;96:1025-29.
14. Mustacchi G, Ceccherini R, Milani S, Pluchinotta A, De Matteis A, Maiorino L, et al. Tamoxifen alone versus adjuvant tamoxifen for operable breast cancer of the elderly: long-term results of the phase III randomized controlled multicenter GRETA trial. Ann Oncol 2003;14:414-20.
15. Dordea M, Jones R, Nicolas AP, Sudeshna S, Solomon J, Truran P, et al. Surgery for breast cancer in the elderly – how relevant? Breast 2011;20:212-4.

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A 40-Year-Old Man with Rashes and Palpitations

A 40-year-old Singaporean Indian man with no significant past medical history presented with worsening non-pruritic rashes primarily involving his limbs over a 6-month period. He also reported a near fainting episode associated with recurrent palpitations over the past few weeks. Clinical examination revealed the presence of multiple waxy yellowish-brown dermal papules and plaques over his limbs (Fig. 1) as well as an irregular pulse, but was otherwise unremarkable. A full blood count showed lymphopenia at 200 cells/μL, while serum electrolytes including calcium levels, liver and thyroid function tests were normal. Cardiac enzymes were not raised, but an electrocardiogram showed complete heart block (Fig. 2).

What is the diagnosis?

A. Xanthomas with ischaemic heart disease
B. Primary systemic amyloidosis with cardiac involvement
C. Sarcoidosis
D. Lepromatous leprosy
E. Adult T-cell leukaemia/lymphoma

Discussion

On histopathological examination of a punch-biopsy specimen taken from a representative lesion on the patient's arm, numerous granulomas without caseous necrosis were seen in the superficial and mid-dermis (Fig. 3). There was no nerve involvement. Periodic acid-Schiff, Gomori methenamine silver and Ziehl-Neelsen stains were negative for infective organisms. Two-dimensional echocardiography showed a normal left ventricular ejection fraction of 65%, and coronary arteries were normal on angiogram. The patient declined endomyocardial biopsy. Our patient's angiotensin-converting enzyme (ACE) level was elevated at 101 units (normal range: less than 53 units). Computed tomography scan of the thorax and an eye screen were normal.

The above investigations were consistent with a diagnosis of sarcoidosis with cutaneous and cardiac involvement. Lymphopenia may be observed in over 50% of patients with sarcoidosis.[1] Our patient was treated topically with mometasone furoate 0.1% cream, and underwent a pacemaker insertion. He also received tailing courses of oral prednisolone (maximum dose of 50 mg daily) and oral azathioprine (maximum dose of 125 mg daily) for about 2 years. The patient responded well to therapy, with resolution of the skin lesions and no recurrence of his cardiac symptoms after a follow-up period of 2 years.

Eruptive and tuberous xanthomas are possible differentials, with yellow-hued skin lesions favouring the extensor surfaces of the extremities. However, eruptive xanthomas often appear in crops with involvement of the buttocks, and they are frequently itchy. Tuberous xanthomas are usually more nodular in appearance. There is a predominant facial distribution in primary systemic amyloidosis, with firm skin-coloured to pink to yellow-brown waxy papules and plaques that can become purpuric. Lepromatous leprosy is a consideration in view of the finding of granulomas in the biopsy specimen. However, the absence of ear lobe

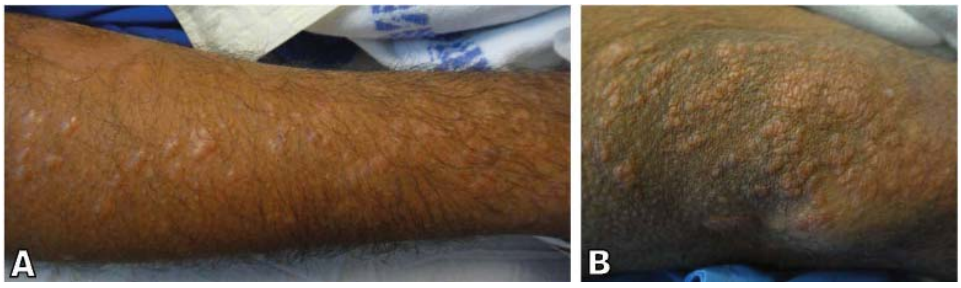

Fig. 1. A) shows yellowish-brown papules on the patient's right forearm; B) shows similar lesions involving the patient's right knee.

Answer: C

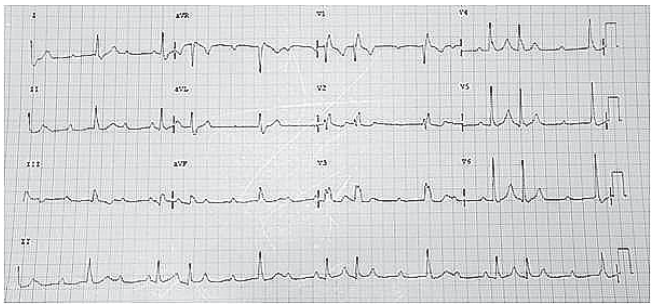

Fig. 2. The patient's electrocardiogram showing complete heart block.

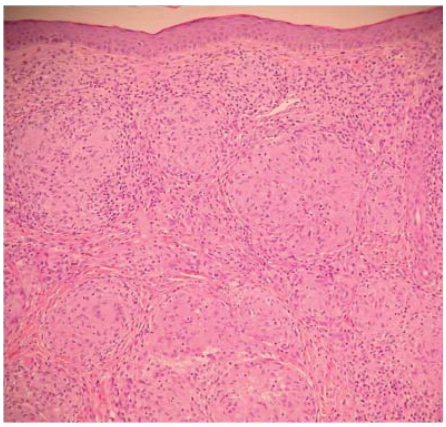

Fig. 3. Histology showing multiple non-caseating granulomas (haematoxylin and eosin stain, original magnification x 40).

involvement clinically, as well as the presence of intact nerve bundles and the lack of acid-fast bacilli on histology point against this diagnosis. Adult T-cell leukaemia/lymphoma (ATLL) is characterised by skin lesions resembling those found in mycosis fungoides or Sezary syndrome, which can range from atrophic patches to indurated plaques to ulcerated tumours. The acute form of ATLL also presents with lymphadenopathy, hypercalcaemia and bone lesions. Apart from the clinical features, histology also helped to clinch the diagnosis of sarcoidosis in our case.

First described by Sir Jonathan Hutchinson in 1875, sarcoidosis is a non-caseating granulomatous disorder of unknown aetiology that can affect virtually any organ system.

Cutaneous sarcoidosis is seen in about 25% to 33% of cases. Notably, the extent and type of cutaneous involvement does not correlate well with the degree of systemic disease. In general, the skin lesions are typically asymptomatic red-yellow brown dermal papules and plaques. However, sarcoidosis is termed a "great imitator" as it can present with almost any morphology, and more than 1 subtype can be present in the same patient. Cutaneous involvement in sarcoidosis can be classified as either specific or non-specific, with specific lesions showing non-caseating granulomas on histological examination. Some examples of specific disease include lupus pernio, as well as the angiolupoid, annular, erythrodermic, ichthyosiform, lichenoid, maculopapular, nodular, papillomatous, plaque, psoriasiform, scar, subcutaneous nodular, ulcerative, vasculitic and verrucous forms. Lupus pernio is characterised by bluish-red to violaceous infiltrated papulonodules and plaques that usually affect the ears, nose, cheeks and extremities. The angiolupoid variant of sarcoidosis tends to be localised to the malar region, bridge of the nose, or around the eyes, and consists of livid nodular lesions that coalesce to form plaques. Erythema nodosum is the main non-specific cutaneous manifestation. Our patient had a combination of both the papular and plaque forms of cutaneous sarcoidosis.

The prevalence of cardiac sarcoidosis with clinical symptoms or electrical signs is about 5% in various series, but evidence of cardiac disease has been found in up to 20% to 30% of autopsies.[2] Arrhythmias, infiltrative cardiomyopathy, pericarditis, congestive cardiac failure and sudden death can occur. As cardiac involvement is responsible for 50% of patient deaths from this disorder, it is imperative that this should not be missed.[3]

ACE is produced by sarcoidal granulomas but does not correlate with the severity of skin involvement. Although it has limited diagnostic value, it serves as a useful monitor of disease activity.

For mild, localised cutaneous sarcoidosis, potent topical and intralesional corticosteroids remain the treatments of choice. Systemic treatment is indicated when there is disfiguring skin disease and/or myocardial involvement. Corticosteroids as well as immunosuppressants such as azathioprine, methotrexate and mycophenolate mofetil can be considered.

The clinical course of sarcoidosis in general is highly variable. Approximately 60% of cases experience spontaneous resolution within 2 to 5 years. A further 20% settle with treatment, and the last 20% of patients tend to have chronic recurrent disease despite therapy.

Physicians should always consider sarcoidosis as a possible differential in a patient presenting with cutaneous dermal papules and plaques and/or protean manifestations. It is also important to keep in mind that no organ is exempt from sarcoidal granuloma deposition. In all patients, attempts should be made to delineate the full extent of disease to avoid any adverse outcomes. The following tests should be considered: a full blood count, renal and liver function, calcium levels, chest X-ray, electrocardiogram, urinalysis and an ophthalmology evaluation. Other investigations should be guided by each patient's symptomatology.

REFERENCES

1. Sweiss NJ, Salloum R, Gandhi S, Alegre ML, Sawaged R, Badaracco M, et al. Significant CD4, CD8, and CD19 lymphopenia in peripheral blood of sarcoidosis patients correlates with severe disease manifestations. PLoS One 2010;5:e9088.
2. Chapelon-Abric C. Cardiac sarcoidosis. Curr Opin Pulm Med 2013;19:493-502.
3. Perry A, Vuitch F. Causes of death in patients with sarcoidosis. A morphologic study of 38 autopsies with clinicopathologic correlations. Arch Pathol Lab Med 1995;119:167-72.

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Inflamed Bipedal Nodules with a Distant Occult Cause

A 76-year-old Chinese male presented with red and tender rashes associated with progressive swelling over both lower limbs for 2 weeks. Concurrently, he had fever and non-bloody diarrhoea. There was no abdominal pain, joint pain, loss of appetite or weight. He was otherwise systemically well. His past medical history was significant for diabetes mellitus, hypertension and hyperlipidaemia. Long-term medications included glipizide, metformin, enalapril, nifedipine and simvastatin. There were no new medications commenced 6 months prior to the onset of his rashes.

On examination, there were warm tender erythematous nodules over both anterior shins, posterior aspect of calves and thighs (Figs. 1A and 1B). Pitting oedema up to the level of the knees was present. Cardiovascular, respiratory and abdominal examination was unremarkable.

Histological examination of a skin biopsy from the left thigh showed fat necrosis with "ghost-like" cells, characterised by anucleated adipocytes with a partially digested cell membrane (Fig. 2). This was also accompanied by basophilic deposits of saponified fat (Fig. 3).

What is the diagnosis for these cutaneous lesions?

A. Erythema nodosum
B. Erythema induratum
C. Lupus profundus
D. Subcutaneous panniculitis-like T cell lymphoma (SPTCL)
E. Pancreatic panniculitis

Discussion

The serum amylase was 767 U/L (normal 36-128 U/L) and serum lipase was >400 U/L (normal 5-50 U/L). The leukocytes was mildly elevated at 9.5 (3.6-9.3 x 10^9/L), c-reactive protein was 112 mg/L (0-5), pro-calcitonin was 0.33 ug/L (0-0.05) and adjusted calcium was 2.44 mmol/L (2.15-2.58). His liver function test was as follows: alkaline phosphatase 527 U/L (38-126), gamma-glutamyl transpeptidase 492 U/L (7-50), alanine aminotransferase 67 U/L (17-63), aspartate aminotransferase 62 U/L (15-41), bilirubin 17 μmol/L (7-31) and albumin 25 g/L (35-48). Magnetic resonance imaging (MRI) of the pancreas revealed

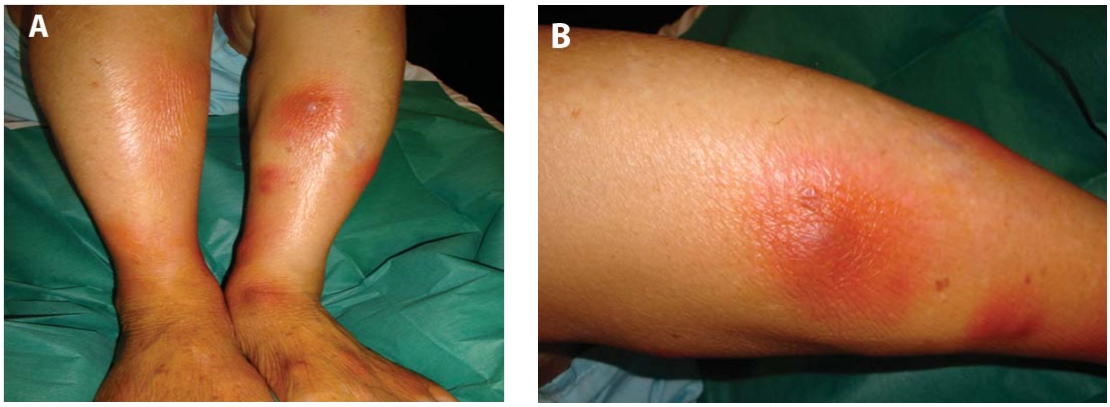

Fig. 1. Images showing the nodules in the patient. In A), inflamed subcutaneous nodules on a background of lower limb oedema are seen. In B), a closer look of the multiple tender erythematous nodules over the patient's left anterior shin.

Answer: E

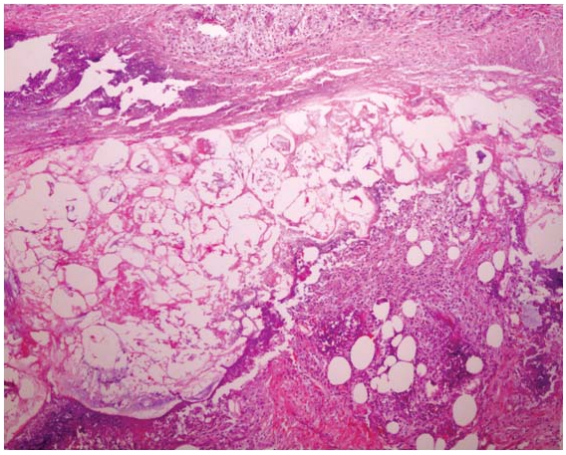

Fig. 2. Adipocytes within fat lobules with fat necrosis and retention of ghost outline. There is an infiltrate of neutrophils admixed with eosinophils and histiocytes within the fat septae, associated with surrounding necrotic adipocytes. (Haematoxylin and eosin, x 200).

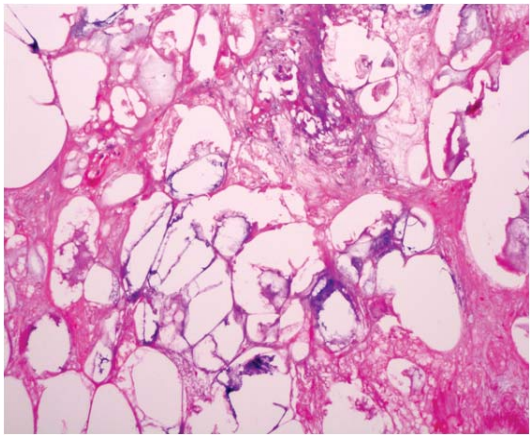

Fig. 3. Amorphous basophilic material due to deposition of calcium salts is present within ghost cells. (Haematoxylin and eosin, x 400).

a fluid-filled collection in the pancreatic head, reminiscent of a pseudocyst. The pancreatic head, body and tail appeared swollen with peripancreatic fat stranding. This was consistent with a diagnosis of acute on chronic pancreatitis complicated by a pseudocyst. Although there were no gallstones visualised in the common bile duct on imaging, gallstones with pericholecystic fluid were noted in the gallbladder, which may be the aetiology for his pancreatitis. Otherwise, he did not report any history of chronic alcohol ingestion. He was managed conservatively for his pancreatitis with intravenous antibiotics and supportive treatment after declining all further investigations. Fobancort, a potent topical corticosteroid cream containing betamethasone dipropionate 0.064% with fusidic acid 2% and local wound care were administered to some of the nodules that had begun to ulcerate. The nodules gradually healed within the next 3 months. A repeat MRI 6 months later showed resolution of the pancreatic pseudocyst with no relapse of his panniculitis.

Pancreatic panniculitis is rare, occurring in patients with acute or chronic pancreatitis or less commonly, pancreatic carcinoma (especially of the acinar type). In many cases, the cutaneous lesions are the initial presenting sign, preceding pancreatic disease by months.[1]

Clinical presentation includes tender erythematous subcutaneous nodules typically on the lower limbs that may become fluctuant or ulcerated with an associated oily exudate. Systemic involvement can include visceral, periarticular and intraosseus fat necrosis. The condition can also comprise of an inflammatory polyarthritis, polyserositis, fever and abdominal pain. As in our patient, signs of pancreatic disease upon presentation of panniculitis are not a prerequisite for its diagnosis.[1]

It is believed that the release of pancreatic enzymes; such as amylase, lipase, phosphorylase and trypsin, play an important role in the pathogenesis of pancreatic panniculitis. Trypsin increases the permeability of blood vessels, allowing enzymes such as lipases to act on lipids in the adipocyte cell membrane and interior, leading to fat necrosis and inflammation. Another potential aetiology is blood vessel damage via inflammation or oedema during an infection, resulting in increased endothelial cell permeability.[2]

The diagnosis of pancreatic panniculitis is confirmed by the presence of pancreatic disease and typical histopathological findings. Histopathological features include a mostly lobular panniculitis without vasculitis. However, in the very early stage, a septal pattern has been described. Enzymatic damage allows pancreatic enzymes to cross from blood to fat lobules resulting in coagulative necrosis of the adipocytes and pathognomonic "ghost cells". These are anucleate necrotic cells with thick walls and fine basophilic granular material within their cytoplasm from dystrophic calcification.[3] Treatment is primarily supportive and should be directed to the underlying pancreatic disease.

We describe a case of pancreatitis diagnosed through the presentation and histological analysis of panniculitic nodules on the legs. As demonstrated in this case, gastrointestinal symptoms may be absent or subtle, and an early diagnosis could be made through measurement of serum pancreatitic enzymes levels.

REFERENCES

1. Tran KT, Hughes S, Cockerell CJ, Yancey KB. Tender erythematous plaques on the legs. Pancreatic panniculitis (PP). Clin Exp Dermatol 2010;35:e65-6.
2. Gou DE, Turrentine JE, Motaparthi K. Tender leg nodules in a hospitalized patient. JAMA Dermatol 2015;151:95-6.
3. Laureano A, Mestre T, Ricardo L, Rodrigues AM, Cardoso J. Pancreatic panniculitis - a cutaneous manifestation of acute pancreatitis. J Dermatol Case Rep 2014;31:35-7.

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