

Violence Against Healthcare Staff – A Multidimensional Problem

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Aggression and violence is prevalent in healthcare, with rates of 60% worldwide.^{1,2} Potentially, 70% of Singapore's hospital staff have experienced physical abuse,^{3,4} given significant under-reporting.⁵ With increasing demand on healthcare services, recognition and management of this problem is essential.

Definition

The Workplace Safety and Health Council defines workplace aggression⁶ as being not limited to physical violence, or to the geographical worksite. It is any abuse, including verbal, physical or emotional abuse and sexual harassment of healthcare providers resulting in injury, psychological harm, mal-development or deprivation. This is commonly termed "healthcare violence". Perpetrators may be patients or relatives against staff,³ or between staff members.⁷

Healthcare Violence Effects

Victims may suffer physical harm and acute and chronic psychosocial effects, for example, post-traumatic stress disorder, depression and burnout. Reluctance to continue healthcare-related work may occur.^{8,9} It can reduce employee productivity, increase medical benefits and sick leave use and result in legal costs.¹⁰ Institutions with increased aggression against staff may develop poor professional and societal reputations. Decreased workforce morale and job satisfaction would further reduce their ability to attract and retain staff.^{8,11} Perpetrators may suffer poorer care, potential caregiver abuse¹¹ and increased restraint use.^{12,13}

Risk Factors

Incidents occur more commonly in certain profiles and environments.^{7,10} Staff factors include: recently employed, younger female staff or those with greater patient contact, for example, nurses or frontline staff, and those in intensive

care, mental health and emergency units.^{7,13}

Older male patients, or those with neuropsychiatric disorders, drug or alcohol intoxication are more likely to perpetrate violence.^{7,13} Personality and social issues, such as unmet expectations, negative perceptions of healthcare providers and difficult circumstances predispose to aggression.⁷

Environmental factors encompass the physical environment,¹⁴ such as the provision of escape routes and protective equipment, effectiveness of crowd-control barriers and the workplace environment. This includes adequacy of manpower allocation, workplace culture supportiveness, training opportunities provision, and security presence.^{6,7}

Managing Healthcare Violence

Management of healthcare violence requires institutional and national involvement, via multiple approaches. The approach adopted could be similar to infectious disease outbreak management: with case surveillance, treatment of affected individuals and incident investigation. Case surveillance includes risk management database creation and maintenance, with institution of staff reporting requirements. Treatment should cover medical and psychological support, with adequate leave, job-scope adjustment^{3,6,9} and worker injury compensation as necessary.¹⁵ Incident investigations and root-cause analysis should be conducted for preventive or control measure implementation.^{3,6}

Alternatively, the hazard-management approach may be adopted. This involves identifying violence as a hazard and implementing preventive measures according to the hierarchy of controls.¹⁶ Elimination or substitution level policies are on a national scale, constituting nationwide education on appropriate behaviour and punitive measures. Engineering controls involve the built environment: creating protective barriers and escape routes for staff, providing appropriate furniture arrangement, reducing isolated or

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enclosed areas¹⁴ and placing visible security presence, ensuring adequate crowd control and limiting workplace accessibility.^{3,6}

In patient-interaction areas, these measures should be balanced against other considerations, for example, easing staff-patient communications, and this may be modified for a more welcoming atmosphere.

Administratively, staff training and education should be provided. Topics should include: acceptable behaviour by patients and family, avenues for surfacing issues, personal precautions and recognition and response to violence, for example, de-escalation skills.^{3,6,17} Adequate manpower allocation to match service demand while providing a “buddy” system and visible security presence are also appropriate. Managerial support for staff feedback and “zero-tolerance” policies should be actively enforced. Lastly, personal protective equipment, for example, alarm buttons, should be utilised.

These approaches are not mutually exclusive and should not be implemented as such. Healthcare violence has strong social components and requires governmental involvement. Legislation for worker protection with changes to the public-at-large,¹⁵ is recommended.^{6,17}

In Singapore, portions of these methods have been implemented and institutional measures targeting certain risk factors or profiles are being utilised. Nationally, the Protection from Harassment Act¹⁸ was revised in 2009 to protect healthcare providers. These are in keeping with recommendations from the Occupational Safety and Health Administration.¹⁷

However, all of the above measures are reactive and one-sided. Responsibility is placed upon staff and institutions to protect themselves during incidents, with few avenues for punitive measures to be visited against abusers. Investigations address only staff or institutional issues and ignore social or patient components. The importance of social and patients’ expectations is underscored in light of China’s healthcare violence incidents.^{19,20}

Management of healthcare violence needs to look at the social components in order to understand and thereby, alter behaviour. Undoubtedly certain factors are immutable, but others, for instance, social norms and expectations are important to address. Unmet expectations is a recognised factor.^{7,20} Management of this includes both raising healthcare quality to realistic and acceptable standards and tempering unrealistic expectations. A second factor is social norms. Staff need to recognise that violence is neither “part of the job” nor socially acceptable. The public needs to recognise violence as a problem, thereby denying it social credence and legitimisation, while making abusive behaviour socially unacceptable. Self-policing

through mechanisms such as social stigmatisation and acceptance of punitive measures against perpetrators should be encouraged.

Identification of issues is easy. The difficulty lies in implementation. Singapore has undertaken important educational first steps such as encouraging media coverage via televised drama serials (‘You Can Be an Angel Too’) regarding the nursing profession and placing posters highlighting the issue (‘Our Staff Are Precious Too’) in public areas. Like managing smoking or obesity, issues with social-behavioural components are difficult to change. Further research should be undertaken in order to aid control and prevention efforts.

Conclusion

A population under stress from illness and disease will inevitably have difficult cases with some level of behavioural issues. In order to prevent and control incidence, measures aimed at altering behaviour and social norms need to be implemented together with providing protective policies for those at risk. Resolving this issue will be a long road involving multiple agencies across all levels, requiring a major shift in society’s perception and expectations.

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Functional Outcomes of the Second Surgery Are Similar to the First in Asians Undergoing Staged-Bilateral Total Knee Arthroplasty

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Abstract

Introduction: Patients suffering from bilateral knee osteoarthritis often require bilateral total knee arthroplasty (TKA) to alleviate symptoms. There is controversy surrounding the approach to the surgical treatment of such patients. We asked if Asian patients undergoing staged-bilateral TKA had any difference in their short-term functional outcomes, comparing the first TKA to the second one and if the interval between the 2 surgeries had any impact of functional outcomes. **Materials and Methods:** We identified 100 patients from a single surgeon from 2006 to 2010 who had staged-bilateral TKA and had at least 2 years of follow-up for each TKA. The time interval between the first and second TKA ranged from 6 months to 1 year. Range of motion, Oxford knee questionnaire scores, knee scores and function scores at 6 months and 2 years of follow-up were then compared between the first and second TKA using the Student's T-test. **Results:** Although length of stay was reduced and time to ambulation was shorter for the second TKA, there were no significant differences in functional outcomes at 2 years. There was also no difference in outcome when patients were stratified according to time interval between TKAs. **Conclusion:** Staged-bilateral TKA continues to be a good option for patients presenting with severe bilateral knee osteoarthritis. The second arthroplasty has similar functional outcomes as the first arthroplasty. Our results can be used in preoperative counselling of patients undergoing staged-bilateral TKA.

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Key words: Counselling, Orthopaedic surgery, Osteoarthritis

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Introduction

Total knee arthroplasty (TKA) is one of the most common elective surgical procedures performed to alleviate pain and disability associated with knee osteoarthritis.¹ Patients suffering from bilateral knee osteoarthritis intuitively would require bilateral TKA. In such patients, the surgeries can be performed either simultaneously or in a staged manner. A simultaneous-bilateral TKA offers an advantage of a single hospital stay and shorter rehabilitation period thereby making it more cost effective.^{2,3} However, there are concerns with the safety of simultaneous-bilateral TKA. A higher risk of serious cardiac complications, pulmonary complications, and mortality was reported with simultaneous-bilateral knee arthroplasty as compared with staged-bilateral or unilateral TKA.³

The literature is still divided on the method of approach of surgery for patients with bilateral knee osteoarthritis. Furthermore, there are no studies done on an Asian population with regards to simultaneous- or staged-bilateral TKA. We asked if Asian patients undergoing staged-bilateral TKA had any difference in their short-term functional outcomes, comparing the first TKA to the second one.

Materials and Methods

This study is a retrospective review of prospectively collected data. From January 2006 to May 2009, 118 patients who underwent elective staged-bilateral TKA in an Asian tertiary teaching hospital were reviewed. Patients from a single surgeon, the senior author of the paper, were selected

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for consistency of surgical technique and postoperative care. All patients underwent the staged-bilateral TKA between 6 months and a year from the first TKA. Our Institutional Review Board approved the study.

Exclusion criteria were: 1) other lower extremity orthopaedic conditions or neurological impairment that limited function, and 2) patients who underwent the second TKA more than a year after the first. A total of 18 patients were excluded from this study based on the above exclusion criteria, leaving a total of 100 patients for the study.

All patients underwent a staged-bilateral posterior-stabilised TKA by a single surgeon. The second surgery was performed at least after 6 months and within a year from the first TKA for all patients. The time interval between the surgery was decided based on patient preference as well as surgeon availability. All patients had tourniquet applied to the operated limb throughout the course of the surgery. The medial parapatellar approach was used for patients with varus knees and the lateral parapatellar approach for those with valgus knees. No patellar resurfacing was performed. Postsurgical drains were inserted for all patients and removed on either postoperative day 2 or when the drainage was less than 70 millilitres, whichever occurred earlier.

All patients received standardised postoperative care, which included appropriate analgesia, pneumatic calf pumps and continuous passive motion from first postoperative day and

daily physiotherapy assessment. None of the patients received oral chemoprophylaxis against venous thromboembolism (VTE) as our institution-based study by Bin Abd Razak et al shows a very low incidence of VTE in low-risk Asian patients undergoing TKA without chemoprophylaxis.⁴

Height and weight on admission were extracted from the standardised medical case notes. Health services utilisation data over the 6 months after discharge were extracted from the local health databases. This data included length of stay (LOS) and readmission to hospitals within the country. Complications were also extracted from the standardised medical case notes. They were categorised as major and minor complications as well as mortality. Adverse cardiovascular or respiratory events, venous thromboembolic phenomenon, blood loss requiring more than 1 litre of transfusion and any complication requiring re-operation within the same admission, a readmission or requiring an extended admission of more than 7 days than the mean LOS was classified as a major complication. All others were considered as minor complications and included superficial wound infection, uncomplicated urinary tract infection, chest infection and thrombophlebitis.

Measured outcomes include the range of motion of the operated knee which was documented daily by the physiotherapist using a goniometer, the Knee Society Score,⁵ SF-36 questionnaire⁶ and the Oxford Knee Score⁷ at 6 months

Table 1. Patient Characteristics

Characteristics	First TKA (n = 100)	Staged Second TKA (n = 100)	P Value
Demographics			
Mean age (range) (years)	66 (43 – 82)	66 (44 – 83)	1.00
Gender: female (%)	72 (72)	72 (72)	1.00
Mean body mass index (range) (kg/m ²)	29.5 (20.8 – 44.6)	29.8 (19.5 – 46.4)	0.889
Medical status			
Primary diagnosis osteoarthritis (%)	94 (94)	94 (94)	1.00
Primary diagnosis inflammatory arthritis (%)	6 (6)	6 (6)	1.00
Cardiovascular disease (%)	35 (35)	35 (35)	1.00
Diabetes mellitus (%)	38 (38)	38 (38)	1.00
Mean number of comorbidities (and SD)	2.2 (± 1.7)	2.6 (± 2.2)	0.152
Health services utilisation			
Hospital LOS (and SD) (days)	5.2 (± 2.7)	4.2 (± 1.8)	0.002
Discharge directly home (%)	82 (82)	93 (93)	0.177
Surgical			
Duration of surgery (and SD) (mins)	72 (± 15.4)	61 (± 12.2)	<0.001
Time to ambulation (and SD) (days)	2.4 (± 1.6)	1.6 (± 1.2)	<0.001
Complications			
Major complications (%)	2 (2)	3 (3)	0.655
Minor complications (%)	7 (7)	10 (10)	0.467
Mortality (%)	0 (0)	0 (0)	-

LOS: Length of stay; SD: Standard deviation; TKA: Total knee arthroplasty

Table 2. Preoperative Range of Motion and Outcome Scores

	First TKA (n = 100)	Staged Second TKA (n = 100)	P Value
Mean range of motion (range) (degrees)	114 (96 – 132)	115 (97 – 133)	0.828
Mean Knee Score (range)	32 (14 – 50)	35 (17 – 53)	0.230
Mean Function Score (range)	47 (27 – 67)	44 (25 – 63)	0.381
Mean Oxford Knee Questionnaire Score (range)	38 (30 – 46)	39 (32 – 46)	0.718
Mean SF-36 Physical Component Score (range)	32 (11 – 53)	30 (9 – 51)	0.502
Mean SF-36 Mental Component Score (range)	50 (19 – 71)	50 (23 – 72)	0.814

TKA: Total knee arthroplasty

and 2-year intervals. The patients were then stratified based on the chronology of the operated knee into 2 groups, the 'First TKA' group and the 'Staged second TKA' group. Differences in the range of motion and outcome scores were then compared between the 2 groups at 6 months and 2 years of follow-up for the respective knee. All statistical analyses were performed using Statistical Package for the Social Sciences Version 17. The Students' T-test was used to compare the means between the 2 groups.

Results

Table 1 shows the patient characteristics. There were 72 female and 28 male patients. The mean age of the patients

was 66 years. The primary diagnosis was osteoarthritis in 94 patients whereas 6 patients were suffering from inflammatory arthritis. Duration of surgery was significantly shorter for the second TKA. Patients undergoing the second TKA also started ambulating earlier as compared to their first TKA and were hospitalised for a significantly shorter period of time. Of note, there were no significant differences in the complication rates as well as mortality. The mean time interval between the first TKA and second TKA was 7.4 months. There was no significant difference in the preoperative range of motion and outcome scores between the 2 knees (Table 2). Similarly, the postoperative range of motion and outcome scores at both 6 months and 2 years showed no significant difference (Table 3).

Table 3. Postoperative Range of Motion and Outcome Scores*

	First TKA (n = 100)	Staged Second TKA (n = 100)	P Value
Mean range of motion (range) (degrees)			
6 months	112 (98 – 126)	112 (97 – 125)	1.00
2 years	116 (103 – 129)	116 (101 – 131)	0.868
Mean Knee Score (range)			
6 months	80 (66 – 94)	79 (6 – 93)	0.614
2 years	84 (75 – 93)	84 (75 – 93)	0.973
Mean Function Score (range)			
6 months	57 (37 – 77)	58 (38 – 78)	0.724
2 years	68 (47 – 89)	67 (46 – 88)	0.946
Mean Oxford Knee Questionnaire Score (range)			
6 months	22 (15 – 29)	23 (15 – 31)	0.348
2 years	20 (13 – 27)	20 (13 – 27)	1.00
Mean SF-36 Physical Component Score (range)			
6 months	52 (28 – 76)	50 (26 – 74)	0.556
2 years	60 (36 – 84)	61 (38 – 84)	0.764
Mean SF-36 Mental Component Score (range)			
6 months	80 (61 – 99)	78 (60 – 96)	0.446
2 years	79 (61 – 97)	81 (64 – 98)	0.420

*All scores are recorded with respect to the operated knee only. For example, the Mean Knee Score of 80 for the 'First TKA' group refers to the Mean Knee Score of the operated knees of patients undergoing the first TKA. The Mean Knee Score of 79 for the 'Staged Second TKA' group refers to the Mean Knee Score of the operated knees of patients undergoing the staged second TKA.

Discussion

Patients suffering from advanced osteoarthritis of the knees often require TKA for both knees for alleviation of symptoms. The options of surgery are simultaneous-bilateral and staged-bilateral TKA. Although a simultaneous-bilateral TKA is equally successful as a staged-bilateral TKA in terms of outcome scores and implant survival,^{8,9} it has been shown by various authors that a staged TKA is safer than a bilateral knee replacement done at the same sitting.¹⁰⁻¹⁵ However, Kim et al reported that the operative risk of staged-bilateral knee arthroplasty is underestimated in retrospective studies.¹⁶ Regardless of the controversy, patients who have been counselled for staged-bilateral TKA will wonder if the second TKA would fare as well as the first and may enquire on the ideal interval between the 2 surgeries.

There has been no study done in the Asian population comparing the outcome of the second TKA to the first in a staged-bilateral TKA setting. We asked if Asian patients undergoing staged-bilateral TKA had any difference in their short-term functional outcomes, comparing the first TKA to the second one. An accurate answer to this question would be important during preoperative counselling for patients undergoing staged-bilateral TKA.

Interestingly, the length of stay was significantly less for the second TKA as compared to the first. This could possibly be explained by the fact that the patients undergoing the second surgery already have the “experience” and know the postoperative protocol as well as the rehabilitation regimen. Another observation was that the time to ambulation was also less for the second knee compared to the first knee. In patients undergoing staged-bilateral TKA, the intuitive practice would be to operate on the more symptomatic knee first followed by the other knee. We postulate that at the time of the second TKA, patients were relatively asymptomatic on the contralateral knee. This would have an added benefit on postoperative rehabilitation. These patients are also more likely to be familiar with the postoperative rehabilitation protocols. Gabr et al also reported a better walking ability and reduced LOS following the second knee arthroplasty.¹⁷ Further to this, our study shows that the duration of surgery was significantly shorter for the second TKA. This is presumably due to the fact that the surgeon is already aware of the implant size used for the previously operated knee, which may have decreased the instrumentation time. We also found that there was no significant difference in the complication rates and mortality rates between the first and second TKA. Mangaleshkar et al also reported zero mortality in the staged-bilateral TKA group as compared to the simultaneous-bilateral TKA group.¹⁸ In their study, they compared 54 patients who had simultaneous-bilateral TKA with 34 patients who had staged-bilateral TKA. Four patients

who had simultaneous-bilateral TKA died in the immediate postoperative period while no deaths were observed in the staged-bilateral group. Hence, they concluded that a staged operation appears to be safer than simultaneous-bilateral TKA. Similarly, Meehan et al reported a higher incidence of cardiovascular complications in patients undergoing simultaneous-bilateral TKA.¹¹ In their comparative study of 11,445 simultaneous-bilateral TKA to 23,715 staged-bilateral TKA, patients who underwent simultaneous-bilateral TKA had a significantly higher adjusted odds ratio (OR) of myocardial infarction (OR = 1.6, 95% confidence interval [CI], 1.2 to 2.2) and of pulmonary embolism (OR = 1.4, 95% CI, 1.1 to 1.8) compared to patients who planned to undergo staged-bilateral TKA. The unadjusted 30-day incidence of death or a coronary event was 3.2 events per thousand patients higher after simultaneous-bilateral TKA than after staged-bilateral TKA. We could not find any current literature comparing complication and mortality rates between the first and second TKA in patients undergoing staged-bilateral TKA.

In answering our primary question, our findings lead us to conclude that there are no differences in the short-term outcomes between the first and second surgeries in Asian patients undergoing staged-bilateral TKA. This is supported by the findings of Vulcano et al in a recent study.¹⁹ Ritter et al however, found that patients undergoing staged-bilateral TKA had significantly lower Knee Society scores than the simultaneous bilateral group across all postoperative time-intervals.¹⁰ However, this could be due to lower preoperative Knee Society scores of the patients who underwent staged-bilateral TKA as it has been well established in current literature that preoperative scores are a strong determinant of postoperative outcomes.^{20,21} Controversy will continue to exist with regards to comparison of outcomes, as each centre would have its own set of criteria for risk stratification and patient selection. This makes comparison of studies difficult. From our study, it can be said that one should not recommend staged-bilateral over simultaneous-bilateral (or vice versa) based on short-term outcomes.

Although our study did not analyse the impact of time interval between the 2 surgeries on outcomes due to the relatively small numbers, we have to acknowledge that much controversy still exists with regards to the ideal interval between the 2 TKAs in patients undergoing staged-bilateral TKA. There is also a lack of literature surrounding this topic. Some authors have suggested an interval of as short as 5 to 7 days to be safe.^{22,23} There are very few studies to date that have evaluated the time interval between surgeries with regards to outcomes and this is a potential area of further study.

There were several limitations to this study. This study is retrospective in nature, which limits the number of outcome

variables being studied. The sample size is also small with only 100 patients. Furthermore, there is a gender bias, with 72 patients being female. However, this could also be indicative of the disease epidemiology in the country of origin. Another significant limitation is that no comparison was made with patients undergoing simultaneous-bilateral TKA. As mentioned above, we also did not evaluate the impact of the time interval between the surgeries on the outcomes. This could potentially be a confounder in our study. Notwithstanding the above limitations, the strength of the study lies in the fact that every patient underwent the same operative procedure and received a standard protocol of postoperative care and rehabilitation. The outcomes scores were all prospectively collected. This makes for a meaningful comparison of the functional outcomes.

Currently, there are no clear guidelines or international consensus on the management of patients presenting with severe bilateral osteoarthritis of the knee. A prospective randomised study comparing simultaneous-bilateral and staged-bilateral TKA with regards to outcomes and the ideal interval would be needed for a conclusive answer. However, the results of our study can be used to inform and assure the patients that in the hands of an experienced surgeon, the functional outcomes of the second TKA would be similar to the first one and that they would be able to go home as well as ambulate earlier as compared to the first TKA.

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Fetal Non-invasive Electrocardiography Contributes to Better Diagnostics of Fetal Distress: A Cross-sectional Study Among Patients with Pre-eclampsia

Igor Lakhno, ¹MD, PhD

Abstract

Introduction: Fetal distress is a result of acute or chronic disturbances in the system of “mother-placenta-fetus” in pre-eclampsia (PE). The aim of the investigation was to compare the accuracy of antenatal fetal distress diagnostics in cases of traditional cardiotocography (CTG) waveform evaluation and analysis of morphological non-invasive electrocardiogram (ECG) parameters in antepartum patients with PE. **Materials and Methods:** Fetal non-invasive ECG antenatal recordings of 122 pregnant patients at 34 to 40 weeks of gestation were examined. In Group I, there were 32 women with physiological gestation and normal fetal condition according to haemodynamic Doppler values. Group II involved 48 patients with mild and moderate PE whom were performed Doppler investigation. In Group III, 42 patients with severe PE were monitored with haemodynamic Doppler. **Results:** Fetal autonomic tone was lower with the relative increase of low frequency (LF) branch in the patients of pre-eclamptic group. The increased value of the amplitude of mode (AMo) and stress index (SI) was associated with adrenergic overactivity. It has induced pQ and QT shortening, increased T/QRS ratio and decelerations appearance. The rate of antenatal fetal distress retrospectively was 31.1 % in PE. The traditional analysis of CTG parameters has showed sensitivity (72.7%) and specificity (87.1%). In addition to the conventional CTG analysis, evaluation of ECG parameters has contributed to better diagnostics of fetal distress. Sensitivity and specificity of non-invasive fetal ECG were absolutely equal in this study (100%). **Conclusion:** The results suggest that fetal non-invasive ECG monitoring is more objective than conventional CTG.

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Key words: Fetal heart rate variability, Fetal monitoring, Hypertensive disorders of pregnancy

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Introduction

Autonomic nervous regulation spreads its influence on fetal heart rate, creating cardiac rhythm complexity. Fetal heart rate has a multifractal nature that is largely connected with its biophysical activity.¹⁻⁵ Heart rate variability (HRV) is a convenient instrument of investigation in the field of neurodevelopment. The spectral analysis of HRV could determine the origin of oscillations in the sinus node. Fetal autonomic response on intrauterine activity is associated with an increase in total power (TP) of HRV. Fetal motile activity is also reflected in augmented power of low frequency (LF) and very low frequency (VLF) domains of

HRV.^{4,5} LF component is used as a marker of sympathetic activity.¹ VLF is traditionally associated with the function of hypothalamic-pituitary-adrenal axis. Fetal vagal-mediated reactions are located in high frequency (HF) region of HRV. During “sleep-rest” periods, fetal HRV pattern demonstrates decreased TP and all its fractal components.^{2,4}

Traditional ultrasonographic cardiotocography (CTG) tracing is not absolutely specific for fetal well-being assessment.⁶ The detection of primary bioelectrical processes obtained from maternal abdominal wall with non-invasive fetal electrocardiography (ECG) could provide the higher precision of CTG waveform. The HRV values have

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a very wide range and rather complicated interpretation.⁷⁻⁹ Additional investigation of the fetal ECG parameters could contribute to the advancement of the fetal functional state diagnostics. Previously, the validity of several relative values: P/R, P/Q, R/S, R/T, PR/RR and T/QRS was investigated. And T/QRS has gained most popularity in distress diagnostics.^{10,11} It is known that increased T/QRS ratio because of the elevated T wave is an anaerobic myocardial metabolism marker.^{6,10} Recent investigations have provided the information that fetal hypoxia could cause the shortening of QT interval.⁸

The main experience in fetal ECG morphological parameters assessment is associated with magnetocardiography.^{11,12} This method incurs high cost and therefore is not in routine use now. The Monica AN24 monitor gave the possibility to use fetal non-invasive ECG but it wasn't still widely available.⁹ Ukrainian scientists developed the Cardiolab Babycard fetal non-invasive ECG monitor lately. The quality of the Ukrainian ECG recordings were tested by international experts.¹³

Pre-eclampsia (PE) is a pregnancy-associated disease found only in humans. PE induces systemic changes of maternal haemodynamics due to the failure of utero-placental circulation.¹⁴ It has also shown to cause considerable fetal compromise in pregnancy.¹⁻³ The aim of the investigation was to compare the accuracy of antenatal fetal distress diagnostics in case of traditional CTG waveform evaluation and analysis of morphological non-invasive ECG parameters in antepartum patients with PE.

Materials and Methods

The study protocol was approved by the bioethics committee of the Medical Academy of Postgraduate Education. Observed pregnant patients were informed about the methods of the study, its aim, indications and eventual complications before inclusion in the study. All patients gave written informed consent to participate in the investigation. The study was conducted over a period of 2 years from September 2011 to December 2013. The inclusion criteria were: diagnosis of PE based on a blood pressure of more than 140/90 mm Hg on 2 separate occasions 6 hours apart; and positive proteinuria test in 2 midstream urine samples collected 4 hours apart. The exclusion criteria were: multiple pregnancy; eclampsia; and pre-existing medical disorders such as diabetes mellitus, cardiac diseases, renal disease, thyrotoxicosis, chronic hypertension, and uterine contractions (threatened preterm labour).

Fetal non-invasive ECG antenatal recordings of 122 pregnant patients at 34 to 40 weeks of gestation were examined. Patients were divided into 3 groups randomly. In Group I, there were 32 women with physiological

gestation and normal fetal condition according to fetal non-invasive ECG and haemodynamic Doppler values. Group II involved 48 patients with mild and moderate PE whom were performed fetal non-invasive ECG monitoring and Doppler investigation. In Group III, 42 patients with severe PE were monitored with fetal non-invasive ECG and haemodynamic Doppler.

Fetal ECG parameters were obtained with the application of the fetal non-invasive ECG monitor Cardiolab Babycard (Kharkiv, Ukraine). The registration was carried out over 10 minutes. The value of TP and its spectral compounds (VLF, LF and HF) were estimated. The temporal characteristics of the fetal HRV: standard deviation of normal to normal intervals (SDNN), root mean square of successive differences (RMSSD), the proportion of the number of pairs of successive NNs that differ by more than 50 ms divided by total number of NNs (pNN50), the amplitude of mode (AMo) and stress index (SI) were determined. The CTG waveform analysis was performed with short-term variability (STV) and long-term variability (LTV) scoring. The fetal ECG parameters such as pQ, QT intervals and QRS complex duration, T wave amplitude, T/QRS ratio were calculated. The share of instrumentally determined fetal distress in antenatal period and Apgar score after delivery was examined.

The results were processed by parametric statistical methods (mean-M, error-m) with the application of statistics software package Excel adapted for biomedical research. The results thus obtained were subjected to standard statistical analysis and analysed using the Chi-square test to compare for categorical data between the groups. The significance was set at $P < 0.05$. For the statistical analysis of relationship between X and Y, correlations coefficients were estimated using Spearman's test. Additionally, the sensitivity and specificity of diagnostic tests were calculated.

Discussion

The obtained data demonstrates the significant difference in fetal HRV parameters in the study groups of patients (Table 1). It is determined that TP and SDNN values were decreased in direct proportion to the severity degree of PE. So fetal autonomic tone was lower with the relative increase of LF branch in the patients of Group II and Group III. The predominance of the central sympathetic baroreflex mediated regulation of fetal hemodynamic was the main event in the PE induced scenario. This tendency was stable and showed the abnormally augmented sympathetic tone in severe PE. The revealed peculiarity was associated with almost completely lost autonomic control of cardiac activity and the fallen level of heart rhythm complexity. The increased values of AMo and SI were associated with

Table 1. Fetal HRV Parameters in the Patients

Index, Units of Measure	Group I	Group II	Group III
SDNN, ms	50.5 ± 9.4	30.6 ± 6.8*	24.6 ± 8.4**†
RMSSD, ms	22.3 ± 6.2	14.2 ± 3.5*	8.0 ± 2.4**†
pNN50, %	8.7 ± 2.1	5.7 ± 0.9*	3.5 ± 0.6**†
SI, conv. units	140.6 ± 31.3	654.8 ± 143.5*	1436.8 ± 321.4**†
AMo, %	38.2 ± 12.9	55.8 ± 16.4*	62.5 ± 19.1**†
TP, ms ²	1634.8 ± 364.5	1048.4 ± 126.2*	534.2 ± 81.3**†
VLF, ms ²	1346.2 ± 282.8	670.2 ± 84.6*	349.2 ± 23.8**†
LF, ms ²	192.6 ± 31.1	312.2 ± 66.8*	148.6 ± 25.1**†
HF, ms ²	95.2 ± 19.4	66.1 ± 14.9*	37.2 ± 14.1**†
STV, ms	8.6 ± 2.0	6.2 ± 1.4*	3.9 ± 1.2**†
LTV, ms	38.0 ± 9.4	26.4 ± 5.3*	17.2 ± 8.8**†

*The differences were statistically significant compared to the control group ($P < 0.05$).

†The differences were statistically significant compared to the group II ($P < 0.05$).

SDNN: Standard deviation of normal to normal intervals; RMSSD: Root mean square of successive differences; pNN50: The proportion of the number of pairs of successive NNs that differ by more than 50 ms divided by total number of NNs; AMo: The amplitude of mode; SI: Stress index; TP: Total power; VLF: Very low frequency; LF: Low frequency; HF: High frequency; STV: Short-term variability; LTV: Long-term variability

abnormal myocardial adrenergic stimulation and were similar to the adult patients with acute coronary disease.³ It is speculated that the origin of the antenatal deceleration was presented in the pronounced augmentation of the sympathetic baroreflex. The mean value of short-term mediated parameters RMSSD, pNN50, HF and STV was decreased in mild-moderate and severe PE. The suppression of respiratory sinus arrhythmia was the predisposing condition to rigid rhythm formation. The lack of fetal vagal regulation was determined in patients with PE. In several cases, it was determined by the mutual adrenergic and vagal activation. It is possible to hypothesise that hyperactivity of adrenergic regulation could stimulate meconium passage and latter inspiration during episodes of respiratory activity. The speculation that aspiration syndrome could originate on the basis of the above mentioned autonomic disturbances needs further investigation.

The pQ measurement demonstrated gradual evolution (Table 2). The onset of the fetal deterioration was

initiated by humoral adrenergic substances and is reflected in tachycardia. An increased fetal heart rate has its manifestation in the prolonged pQ.^{9,10,12} The further baroreflex activation changed fetal heart rate to the lower score. The decelerations and bradycardia have shortened pQ intervals. The deceleration pattern of CTG waveform in several patients in Group II and Group III was accompanied with significant pQ shortening. So the decrease of pQ was a mirror of decelerations. A QT reduction could be a marker of anaerobic myocardial metabolism and fetal distress. The lowered QT length and the rise of T wave amplitude are symptoms of β -adrenergic receptors activation.^{8,10-12} The affected myocardium has reacted with high T/QRS ratio.

The investigation of statistically significant correlations between newborn Apgar score 1 and fetal HRV, CTG and non-invasive ECG parameters has revealed certain regularities (Fig. 1). The most considerable negative correlation was determined in pair Apgar score 1 versus T/QRS ($R = -0.46$; $P < 0.05$). So the increased T/QRS ratio was the most valuable

Table 2. Fetal ECG Parameters in the Patients

Index, Units of Measure	Group I	Group II	Group III
pQ, ms	101.2 ± 16.4	105.4 ± 14.3*	95.8 ± 20.4**†
QT, ms	222.4 ± 29.6	198.6 ± 25.4*	195.0 ± 23.9**†
QRS, ms	144.8 ± 8.6	145.6 ± 10.4	65.8 ± 0.2**†
T, mV	2.6 ± 0.4	4.5 ± 0.6*	8.2 ± 2.1**†
T/QRS	0.04 ± 0.01	0.07 ± 0.02*	0.15 ± 0.04**†

*The differences were statistically significant compared to the control group ($P < 0.05$).

†The differences were statistically significant compared to the group II ($P < 0.05$).

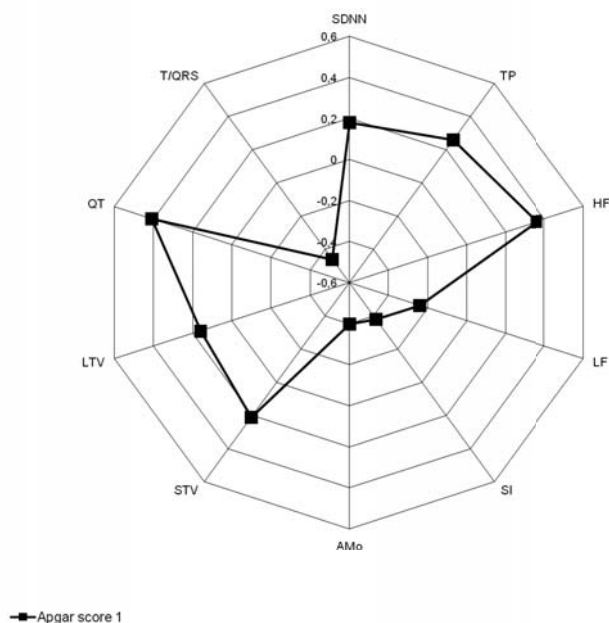


Fig. 1. Correlations between Apgar score 1 and values of HRV, CTG and morphological ECG parameters in the study population.

marker of antenatal distress. The QT interval duration has revealed positive correlation with Apgar score 1 ($R = 0.41$; $P < 0.05$). The validity of fetal HRV parameters was quite different. The negative correlation was determined between Apgar score 1 versus SI ($R = -0.38$; $P < 0.05$) and Apgar score 1 versus AMo ($R = -0.40$; $P < 0.05$). So AMo and SI were independent from fetal stationary status and could

be considered as specific reflection of fetal compromise. It was not determined a considerable relationship between SDNN versus Apgar score 1 ($R = 0.18$; $P < 0.05$) and TP versus Apgar score 1 ($R = 0.26$; $P < 0.05$). It was obvious that autonomic tone has a weak connection with fetal distress. Fetal vagal tone has revealed a correlation with Apgar score 1 ($R = 0.36$; $P < 0.05$). The negative correlation between fetal sympathetic tone and Apgar score 1 has been determined ($R = -0.24$; $P < 0.05$). The parameters of CTG has demonstrated weak correlation with Apgar score 1: STV ($R = 0.21$; $P < 0.05$) and LTV ($R = 0.16$; $P < 0.05$). The obtained data confirms speculation that fetal non-invasive ECG parameters are very valuable in antenatal distress diagnostics.

The rate of antenatal fetal distress retrospectively was 31.1% in PE. This result was rather logical.³ The traditional analysis of CTG parameters has showed sensitivity—72.7% and specificity—87.1%. In addition to the conventional CTG analysis, evaluation of ECG parameters has contributed to better diagnostics of fetal distress. Sensitivity and specificity of non-invasive fetal ECG were absolutely equal in this study (100%). It has made it possible to make a small step in the march toward fewer caesarean deliveries in the era of advanced electronic fetal monitoring. In Figure 2, a prolonged deceleration with a decrease of basal heart rate is seen in a conventional CTG. In patients with PE, it is typical to think about fetal distress and becoming more active. But the mean value of T/QRS ratio is 0.036 ± 0.002 . The range of normal values of T/QRS is up to 0.26.¹⁰ So in this case, we have to wait and repeat the ECG monitoring later.

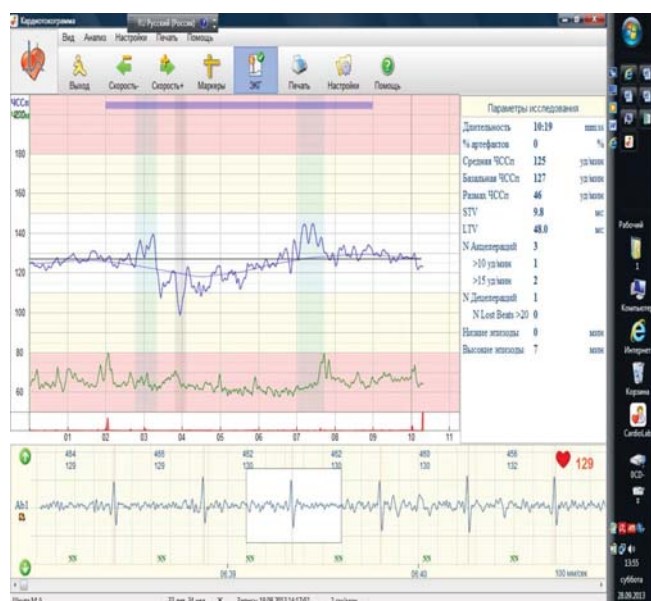


Fig. 2. The “window” in Cardiolab Babycard programme (3 accelerations and single deceleration to 100 beats per minute).



Fig. 3. The “window” in Cardiolab Babycard programme (2 accelerations and 2 decelerations on CTG pattern).

The result was spontaneous vaginal delivery with Apgar score 7-8. Another patient from Group II demonstrated uncertain type of CTG pattern because of 2 low amplitude accelerations and 2 decelerations within a normal heart rate (Fig. 3). The slightly elevated ST segment and determined amplitude of T peak were associated with mean T/QRS ratio 0.096 ± 0.004 . It was a marker of normal fetal condition. In this case, an urgent caesarean section was performed because of cefalo-pelvic disproportion in labour. The Apgar score was 8-9. So fetal non-invasive ECG allows for better diagnostics of fetal distress.

The results show that fetal non-invasive ECG monitoring is more objective than conventional CTG and convenient in urgent situations. ECG investigation is absolutely safe for the fetus and can be performed as a Holter monitoring. Its compatibility with modern wireless communication facilitates the creation of systems for remote fetal monitoring. It is a practical consideration for the fetal surgery department and is timely to introduce it widely in perinatology.

Conclusion

Decreased fetal autonomic tone and augmented sympathetic regulation were marked in PE and were associated with pQ and QT shortening, increased T/QRS ratio and decelerations in appearance. Considerable correlation between the Apgar score 1 and fetal T/QRS ratio was found. Fetal non-invasive ECG was found to have equal sensitivity and specificity in this study (100%) and therefore is a more objective and convenient method for fetal monitoring than conventional CTG.

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Use of In Vitro Fertilisation Prediction Model in an Asian Population—Experience in Singapore

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Abstract

Introduction: This retrospective study was conducted to perform an external validation of the in vitro fertilisation (IVF) predict model developed by Scott Nelson et al in an Asian population. **Materials and Methods:** All IVF cycles registered in the study centre from January 2005 to December 2010 were included. Observed and predicted values of at least 1 live birth per cycle were compared by discrimination, calibration. Hosmer-Lemeshow test was used to assess the goodness-of-fit of the model calibration and Brier score was used to assess overall model performance. **Results:** Among 634 IVF cycles, rate of at least 1 live birth was 30.6%. Causes of infertility were unexplained in 35.5% cases. Fifty-seven percent of women came for their first IVF treatment. First IVF cycle showed significantly higher success in comparison to subsequent cycles. The odds ratio of successful live birth was worse in women with endometriosis. Observed outcome was found to be more than the prediction of the model. The area under the curve (AUC) in this study was found to be 0.65 that was close to that of Nelson model (0.6335) done in internal validation. Brier score (average prediction error) of model was 0.2. Chi square goodness-of-fit test indicated that there was difference between the predicted and observed value ($\chi^2 = 18.28$, $df = 8$, $P = 0.019$). Overall statistical findings indicated that the accuracy of the prediction model fitted poorly with the study population. **Conclusion:** Ovarian reserve, treatment centre and racial effect on predictability cannot be excluded. So it is important to make a good prediction model by considering the additional factors before using the model widely.

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Key words: Infertility, External validation, Live birth

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Introduction

How is the chance of having baby after in vitro fertilisation (IVF) is the frequently asked question since delivery of the first test tube baby in 1978.¹ Success at IVF is a life changing event to a couple and success depends on various factors.²

IVF is expensive, psychologically challenging and carries risks for both the mother and the child.^{3,4} Every couple is keen to know the prediction rate of having a baby from IVF.^{2,5} As the outcome of interest is binary in fertility treatment, the information can be expressed as probabilistic predictions.⁶ In this study, an IVF predict model prepared by Scott Nelson

and Debbie Lawlor was used to determine the chance of a live birth following IVF treatment in an Asian population with an ethnic mixture of Chinese, Malays and Indians.

So far, the model has been found to be realistic only on internal validation with moderate discrimination and excellent calibration to predict live birth following IVF treatment. External validation is very important⁷ to evaluate the prediction of the model in other populations for its generalisability and transportability.

This IVF Predict Calculator was developed on the basis of data of 144,018 cycles of IVF from 2003 to 2007 in a UK population.⁸

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Materials and Methods

This retrospective study included all IVF cycles (from retrieval of eggs after ovulation stimulation to transfer of fertilised eggs into the uterus) registered in the Centre for Assisted Reproduction (CARE), Singapore General Hospital (SGH), Singapore from January 2005 to December 2010. The cycles with incomplete information, involving donor eggs and embryos, frozen embryo transfer and cycles abandoned due to poor follicular development, ovarian hyper stimulation syndrome or poor fertilisation of eggs were excluded. Total IVF cycles in the study period were 1031. After excluding 397 cycles, the final sample size was 634.

Main outcome measure was comparison of observed value and prediction value of at least 1 live birth per cycle. However, some other outcomes like pregnancy rate, live birth rate and common causes of infertility were also measured.

Data were retrieved from case notes at the Medical Record Office (MRO) of SGH. Causes of infertility were categorised mainly into 7 categories as in Nelson's prediction model. Male infertility was diagnosed if semen parameters were abnormal based on WHO criteria (WHO, 1999). Tubal cause was considered if one or both the tubes were blocked, damaged or if there was a hydrosalpinx and were confirmed by transcervical contrast sonography (TCS), hysterosalpingogram (HSG) or a laparoscopic chromopertubation. Anovulatory cycles were diagnosed by hormonal evaluation and ovulation monitoring by transvaginal sonography (TVS) during the menstrual cycle. Endometriosis was diagnosed by clinical features, ultrasound along with CA125 and/or laparoscopic procedure. Only 2 IVF cycles were done for cervical cause, as postcoital test for the detection of sperm antibody in cervical mucus was not performed frequently in the study centre.

Duration of infertility was taken as the period from when the couple started trying for a baby till the beginning of an IVF cycle. For a woman who already delivered a baby following 1 IVF cycle and trying for a second time, the duration was taken as the period from which she had been trying for the second one.

Previous unsuccessful IVF meant the number of previous IVF cycles the patient had undergone without delivering a live baby. Number of cycles was the total number of IVF treatment including the present one. In this study, the term IVF was used when fertilisation was done only by IVF and the term intracytoplasmic sperm injection (ICSI) was used when fertilisation involved injection of a sperm into the oocyte cytoplasm. Clomiphene citrate was used as anti-estrogenic drug and injectable gonadotropin drugs were used for ovulation induction in the study. No hormonal replacement therapy was considered as cases of egg donation were not included in the study.

Data were analysed for cycles with complete information for the 9 predicting factors used by IVF Predict model and the outcome of live births. Univariate logistic regression was used to assess the association of the predictors used in IVF Predict model with at least 1 live birth. Odds ratio and its associated 95% CI of live birth was reported for each predictor. Since the IVF Predict model contained not only simple effects of potential predictors but also several interaction terms of 2 predictors, adjusted odds ratio for each single factor was not reported. The reason was that multivariate logistic regression done was not made up of simple effects alone.

The probability of live birth per 100 cycles was given by:

$$P = \frac{100 \times \exp(y)}{1 + \exp(y)}$$

Where $y = -1.1774 + (\text{age and duration effect}) + (\text{age and source of embryo effect}) + (\text{ICSI and cause effect}) + (\text{ICSI and cycle number effect}) + (\text{previous number of unsuccessful IVF attempts}) + (\text{previous obstetric history effect}) + (\text{hormonal preparation effect})$. The values for the single factor effects and the various interaction effects were taken from the supporting document Text S2 of Nelson's IVF Predict model.⁸

External validation of IVF Predict model was evaluated by assessing discrimination and calibration. Hosmer-Lemeshow test was used to assess the goodness-of-fit of the model for our data. The Brier score was used to assess overall model performance. Statistical software, SPSS version 17.0 was used for all analysis. A *P* value of 0.05 and less was used to denote statistical significance.

Results

Out of 634 IVF cycles, pregnancy rate was 37.4 % and of them, 30.6% women had at least 1 live birth. A singleton was delivered in 132 treatment cycles (20.8%), twins in 58 cycles (9.1%) and triplets in 4 cycles (6%). More than half of the treatment cycles (51.7%) were in women between 18 to 34 years. Forty-two percent of the couple was noted to seek treatment after 1 to 3 years of trying. Unexplained infertility (35.5%) was the commonest cause of infertility, low sperm count (23.5%) was the second commonest. Fifty-seven percent (57.4%) did not have any history of IVF and pregnancy.

Univariate association of the 9 predictors of the IVF Predict model with the live birth following treatment was done (Table 1). Increasing maternal age and number of previous unsuccessful IVF cycles were significantly associated with low success rate in terms of live birth ($P < 0.05$). Previous IVF treatment with no pregnancy was found to reduce the chance of live birth (OR 0.34, 95%

Table 1. Univariable Associations of Potential Predictors for Live Birth Following IVF (n = 634)

Characteristic	Categories	Number (%)	Univariate Odds Ratio of Live Birth (95% CI)	P Value*
Maternal age (years)	18 – 34	328 (51.7%)	1	<0.001
	35 – 37	153 (24.1%)	0.47 (0.30, 0.71)	
	38 – 39	85 (13.4%)	0.16 (0.08, 0.33)	
	40 – 42	50 (7.9%)	0.19 (0.06, 0.45)	
	43 – 44	18 (2.8%)	0.08 (0.01, 0.61)	
Duration of infertility (years)	<1	13 (2.1%)	1	0.615
	1 – 3	269 (42.4%)	0.69 (0.22, 2.17)	
	4 – 6	225 (35.5%)	0.78 (0.25, 2.48)	
	7 – 9	89 (14.0%)	0.70 (0.21, 2.33)	
	9 – 12	31 (4.9%)	0.38 (0.09, 1.60)	
	>12	7 (1.1%)	0.27 (0.02, 2.92)	
Cause of infertility	Unknown	225 (35.5%)	1	0.054
	Tubal only	84 (13.2%)	1.04 (0.60, 1.78)	
	Anovulatory only	40 (6.3%)	0.88 (0.41, 1.85)	
	Endometriosis only	84 (13.2%)	0.50 (0.27, 0.94)	
	Cervical only	2 (0.3%)	2.31 (0.14, 37.45)	
	Male only	149 (23.5%)	1.51 (0.98, 2.34)	
	Combination known causes	50 (7.9%)	0.90 (0.46, 1.77)	
Number of previous unsuccessful IVF	0	485 (76.5%)	1	0.003
	1	114 (18.0%)	0.48 (0.29, 0.79)	
	2	23 (3.6%)	0.29 (0.08, 0.98)	
	≥3	12 (1.9%)	0.17 (0.02, 1.35)	
Mutually exclusive categories of previous IVF and obstetric history	No previous IVF, no previous pregnancy	364 (57.4%)	1	0.004
	No previous IVF, at least 1 pregnancy, 0 live births	53 (8.4%)	1.34 (0.75, 2.41)	
	No previous IVF, at least 1 pregnancy, at least 1 live birth	49 (7.7%)	0.76 (0.39, 1.46)	
	Previous IVF, 0 pregnancy	99 (15.6%)	0.34 (0.19, 0.61)	
	Previous IVF, at least 1 pregnancy, 0 live birth	35 (5.5%)	0.56 (0.25, 1.27)	
	Previous IVF, at least 1 pregnancy, at least 1 live birth	34 (5.4%)	0.68 (0.31, 1.50)	
Type of hormonal preparation	Antioestrogens	13 (2.1%)	1	0.106
	Gonadatropins	621 (97.9%)	5.41 (0.70, 1.91)	
	Hormone Replacement	0 (0%)	-	
Cycle number	1	468 (73.8%)	1	0.002
	2	120 (18.9%)	0.56 (0.35, 0.89)	
	≥3	46 (7.3%)	0.29 (0.12, 0.69)	
Source of egg	Donor	0 (0%)	-	-
	Patient	634 (100%)	-	
Type of treatment	IVF	64 (10.1%)	1	0.208
	IVF plus ICSI	570 (89.9%)	0.71 (0.41, 1.21)	

IVF: In vitro fertilisation; CI: Confidence interval; ICSI: Intra cytoplasmic sperm injection

*All P values are likelihood ratio tests of null hypothesis that the odds are the same for each category (i.e. they do not assume linearity).

CI, 0.19 to 0.61) compared to the category of no previous IVF treatment and no previous pregnancy. First IVF cycle showed significantly more success in comparison to 2nd (2nd vs 1st cycle: OR 0.56 and 95% CI, 0.35% to 0.89%) and 3rd cycle (3rd vs 1st cycle: OR 0.29 and 95% CI, 0.12% to 0.69%).

Causes of infertility trended towards significance with the odds ratio of successful live birth being worse in women with endometriosis (OR 0.50, 95% CI, 0.27 to 0.94) and better in male cause (OR 1.51, 95% CI, 0.98 to 2.34) when compared with unknown cause of infertility. Use of gonadotropin tended to increase chance of live birth but statistically was not significant ($P = 0.106$, OR 5.14, and 95% CI, 0.70 to 1.91). Use of both ICSI and IVF did not show an increased chance of live birth in comparison to IVF only ($P = 0.208$).

Calibration is the degree of correspondence between the predicted probability of a live birth and observed proportion of live births. It was assessed by ranking the IVF cycles into deciles based on their predicted probability of live birth by the IVF Predict model and comparing the observed rate of live birth with the mean predicted rate within each decile. A graphical presentation of a calibration plot (Fig. 1) and a table of ratio of predicted to observed probability of live birth in each decile (Table 2) were done. In Figure 1, Nelson's calibration curve from his original study is also superimposed for comparison with our external calibration on Singapore data.

The calibration equation was: observed probability = $0.028 + 1.085 \text{ predicted probability}$. Hosmer-Lemeshow chi-square goodness-of-fit test of observed frequency versus expected frequency of live birth in the 10 deciles of predicted probability showed that the calibration with the IVF Predict model was not good ($\chi^2 = 18.28$, $df = 8$, $P = 0.019$).

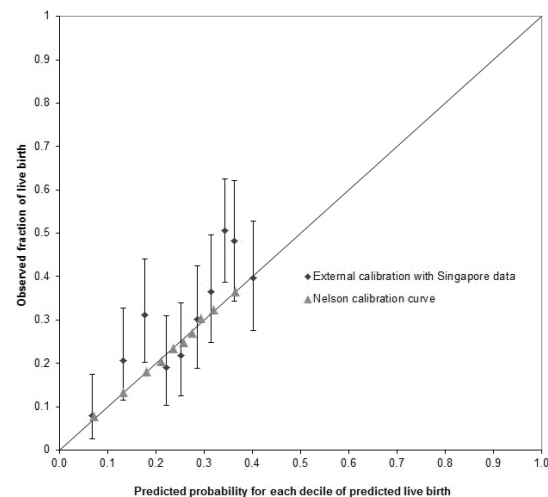


Fig. 1. Calibration plot of observed proportion of live birth to predicted probability of live birth. Note: the error bars represent the 95% confidence interval (CI) for observed fraction of live birth.

Accurate predictions can discriminate between those with and those without the outcome. The concordance (C) statistics is used to measure discriminate ability and for binary outcome C is identical to the area under the curve (AUC). The area under the receiver operating characteristics (ROC) curve here was found to be 0.65 (95% CI, 0.61 to 0.70) (also see Fig. 2).

Brier score was used to quantify how close predictions are to the actual outcome. It is known as an average prediction error, was calculated as $\sum (y_i - p_i)^2 / n$ where y denotes the observed outcome of live birth (0 or 1) and p the prediction for the subject i in the dataset of n subjects. For sensible models, the Brier score ranges from 0 (perfect) to 0.25 (non informative model).⁹ Brier score in this study was found to be 0.20, indicating that the accuracy of the

Table 2. Calibration of IVF Predict Model

Tenth of the Distribution of Predicted Probability	Observed Live Birth Rate per 100 Cycles of Treatment (95% CI)	Predicted Live Birth Rate per 100 Cycles of Treatment	Ratio of Predicted to Observed Probability
Lowest 10 th	7.94 (2.63, 17.6)	6.79	0.86
2 nd	20.63 (11.47, 32.70)	13.29	0.64
3 rd	31.25 (20.24, 44.06)	17.72	0.57
4 th	19.05 (10.25, 30.91)	22.08	1.16
5 th	21.88 (12.51, 33.97)	25.26	1.15
6 th	30.16 (18.91, 42.42)	28.51	0.95
7 th	36.51 (24.73, 49.60)	31.49	0.86
8 th	50.69 (38.72, 62.60)	34.23	0.68
9 th	48.15 (34.34, 62.16)	36.29	0.75
Highest 10 th	39.68 (27.57, 52.80)	40.25	1.01

IVF: In vitro fertilisation; CI: Confidence interval

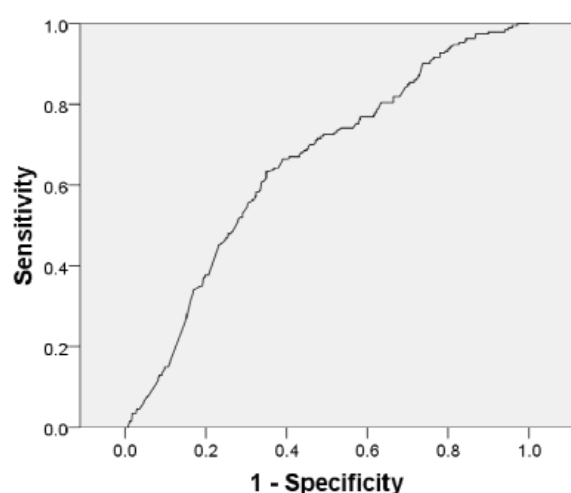


Fig. 2. ROC curve for IVF Predict model using Singapore data.

prediction model was not good.

Discussion

There is an ongoing debate to find out the best ways to assess the performance of a prediction model.^{10,11} As the study population was treatment cycle of IVF, calibration is more perfect to identify external validation of the prediction model than discrimination. Calibration identifies the chance of pregnancy in that specific treatment cycle.¹² A subfertile couple wants to know their chance for pregnancy (calibration) rather than to know which couple will conceive and which will not (discrimination).¹³ Assessment by calibration is also important if model predictions are used to inform patients or physicians in making decisions.⁶ Discrimination is more important in diagnostic test.

In case of perfect calibration, prediction-observation pairs are on the main diagonal and confidence intervals are not overlapping. Figure 1 showed substantial overlap of the confidence intervals of the observed probability for the deciles of predicted probabilities, an indication of poor calibration. If the points are above the diagonal line, it represents an underestimation of the probability of the pregnancy.¹⁴ In contrast, Nelson's calibration curve showed good calibration of the IVF Predict model on his data.

The area under ROC curve (AUC) as shown in Figure 2 was found to be 0.65 (95% CI, 0.61 to 0.70), and was close to that of IVF predict determined by internal validation of the model which was 0.6335 (95% CI, 0.6202 to 0.6367). Though the value of AUC below 0.7 is not good¹⁵ but the value 0.65 represents fair discrimination¹⁶ as the AUC for prediction models for IVF is rather low, ranging between 0.50 and 0.67.¹⁷ Brier score was found to be 0.20, which indicates that the prediction model did not fit well with the

study population.

All 3 methods (graphical presentation of calibration plot, Hosmer-Lemeshow test and Brier score) for assessing prediction model prepared by Nelson et al suggested that this model is not well fitted with the study population.

Study found observed value of pregnancy was underestimated by Nelson's prediction model in most of the deciles. It indicated observed live birth following IVF treatment was more than prediction outcome in the study population. In the Nelson IVF prediction model, sample size was large and not confined in one centre. In this study, sample size was smaller, involved only one centre and there was little alteration of treatment and patient characteristics represented a homogeneous set of subjects. This may be an explanation of underestimation of prediction of this model. Other validation studies have concluded that differences in pregnancy outcome rate between clinics have important limitations for the reproducibility of prediction models.¹⁸

It is assumed that there were no significant differences in patient demographics among the 2 populations except age groups and the races. Nelson study included women up to 55 years of age whereas the current study enrolled women of 45 years or less in accordance with state law. Meanwhile women above the age of 40 years underwent IVF if they had good ovarian reserve. Live birth rate declines with increasing age^{2,8} probably due to decrease in ovarian follicle reserve as a result of diminished quantity and quality of oocyte.¹⁹ Though it is difficult to say after what age the rate of infertility reduces, women of 35 years or older experienced lower rate of success.²⁰ Therefore in addition to chronological age, ovarian reserve should be considered for outcome of IVF. Race was probably another explanation of different outcome in the current study. The Scott Nelson model was based on Caucasian population whereas this study was conducted on mixed Asian population which may suggest there might be an effect of race on the success of IVF cycle. One retrospective study revealed that black women have lower pregnancy following IVF than Caucasians.²¹ However, another study did not find any significant differences between races.²² This study showed that the success rate of IVF treatment was better if the contributory cause of infertility was exclusively tubal which is similar with findings of a retrospective cohort study²⁰ but does not correlate with Nelson's finding. This could be explained by the fact that infertile women with tubal causes undergo IVF treatment at relatively younger age which was also evident in this study. In this series, endometriosis had the worst outcome following IVF treatment whereas infertility due to male factors showed a better outcome in the study population due to ICSI which has been a boon for male factor infertile couples.²³ Infertility due to male

factor in the study population seemed to have better outcome than predictive model, probably due to liberal use of ICSI.

Factors which markedly reduced the outcome of IVF treatment were maternal age, duration of infertility, endometriosis and previous unsuccessful IVF treatments. Ovarian reserve which is in most cases determined by antral follicular count (AFC)²⁴ and basal FSH, LH and estradiol level²⁵ have a better prediction value than age. The study showed that a long waiting time prior to IVF had a detrimental effect on the outcome similar to the findings of Nelson study.⁸

The external validation of IVF model given by Scott and Nelson in the Singaporean population has found that the model has limitations to predict IVF success. Therefore, it may be concluded that a model might have racial limitations in terms of success and may need to include this concern for its wider application. Moreover, ovarian reserve, treatment centre and aetiology of infertility should be considered for determining the IVF prediction. Hence, each region may need to formulate its own IVF predict model for the local population for a better predictive value. Variation of model performance is a great limitation in generalisability of the reproductive model. Current resources of prediction at success for an individual couple needs further research for the best prediction models.

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Causative Pathogens of Febrile Neutropaenia in Children Treated for Acute Lymphoblastic Leukaemia

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Abstract

Introduction: Treatment of acute lymphoblastic leukaemia (ALL) using intensive chemotherapy has resulted in high cure rates but also substantial morbidity. Infective complications represent a significant proportion of treatment-related toxicity. The objective of this study was to describe the microbiological aetiology and clinical outcome of episodes of chemotherapy-induced febrile neutropaenia in a cohort of children treated for ALL at our institution. **Materials and Methods:** Patients with ALL were treated with either the HKSGALL93 or the Malaysia-Singapore (Ma-Spore) 2003 chemotherapy protocols. The records of 197 patients who completed the intensive phase of treatment, defined as the period of treatment from induction, central nervous system (CNS)-directed therapy to reinduction from June 2000 to January 2010 were retrospectively reviewed. **Results:** There were a total of 587 episodes of febrile neutropaenia in 197 patients, translating to an overall rate of 2.98 episodes per patient. A causative pathogen was isolated in 22.7% of episodes. An equal proportion of Gram-positive bacteria (36.4%) and Gram-negative bacteria (36.4%) were most frequently isolated followed by viral pathogens (17.4%), fungal pathogens (8.4%) and other bacteria (1.2%). Fungal organisms accounted for a higher proportion of clinically severe episodes of febrile neutropaenia requiring admission to the high-dependency or intensive care unit (23.1%). The overall mortality rate from all episodes was 1.5%. **Conclusion:** Febrile neutropaenia continues to be of concern in ALL patients undergoing intensive chemotherapy. The majority of episodes will not have an identifiable causative organism. Gram-positive bacteria and Gram-negative bacteria were the most common causative pathogens identified. With appropriate antimicrobial therapy and supportive management, the overall risk of mortality from febrile neutropaenia is extremely low.

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Key words: Infective complications, Bacterial infections, Mortality, Toxicity

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Introduction

Acute lymphoblastic leukaemia (ALL) is the most common form of childhood cancer in Singapore, accounting for 44% of all causes of childhood cancer annually.¹ Treatment of childhood ALL consists of a period of intensive chemotherapy followed by maintenance chemotherapy for up to 2 years, with the objective of producing lasting remission of the disease. In Singapore, chemotherapy protocols that have been used in the treatment of childhood ALL include the Malaysia-Singapore (Ma-Spore)-ALL

2003 and the HKSGALL 93 protocols. These have resulted in high cure rates, with 5-year overall survival rates of more than 80%.^{2,3}

The initial intensive phase of treatment typically consists of an induction phase followed by central nervous system (CNS)-directed therapy and reinduction chemotherapy. Myelosuppression and generalised immunosuppression are expected consequences of this intensive phase of therapy, leading to episodes of infection that can result in treatment delays, dropouts and mortality.⁴ The objective

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Table 1. Episodes of Febrile Neutropaenia According to Treatment Risk Groups and Phase of Treatment

Risk Group	No. of Patients	No. of Episodes of Febrile Neutropaenia in Each Phase of Treatment			Total	Mean No. of Episodes Per Patient
		Induction	Protocol M	Reinduction		
Standard risk	70	93	21	95	209	2.99
Intermediate risk	109	141	29	139	309	2.83
High risk	18	23	14	32	69	3.83
Total	197	257	64	266	587	
Mean		1.30	0.32	1.35		

of the study was to describe the microbiological aetiology and clinical outcome of episodes of chemotherapy-induced febrile neutropaenia in children being treated for ALL at our institution.

Materials and Methods

This is a retrospective cohort study of 197 patients who were treated for ALL at KK Women's and Children's Hospital from June 2000 to January 2010. Patients included in the study were those who developed febrile neutropaenia during the intensive phase of treatment, defined as the period of treatment from induction, CNS-directed therapy to the end of reinduction therapy.

The treatment protocol used in our institution from June 2000 to December 2006 was the HKSGALL 93 protocol.² From January 2007, the Ma-Spore ALL 2003 protocol³ was used instead. Both protocols are based on the Berlin Frankfurt Munster (BFM) backbone and only differ in terms of treatment strategy, with the Ma-Spore ALL 2003 being a minimal residual disease (MRD)-directed treatment protocol. Treatment intensity differed according to risk stratification. Patients who were treated with either protocol were analysed together and not differentiated.

Neutropaenia was defined as an absolute neutrophil count of less than $1 \times 10^9/L$. Fever was defined as a temperature more than or equal to 38°C on 2 or more occasions or a temperature of 38.5°C or higher on a single occasion. All patients admitted for febrile neutropaenia were extensively investigated for a source with blood, urine, stool cultures and other tests as clinically indicated, according to the protocols in place in our institution. The individual case records of the patients were analysed to gather information on the clinical presentation and other supportive investigations, including chest X-rays and other radiological findings, to determine if positive isolates were causative organisms and not merely commensals.

Severe episodes of neutropaenic fever were defined as cases requiring admission into a high dependency unit

(HDU) or intensive care unit (ICU) due to any clinical presentation requiring a higher level of care.

Data was analysed using SPSS Version 12. This study was approved by the Singhealth Central Institutional Review Board.

Results

There were a total of 587 episodes of febrile neutropaenia in 197 patients, translating to an overall rate of 2.98 episodes per patient during the intensive phase of chemotherapy. Patients on high-risk protocols who received the most intensive treatment had the highest mean number of episodes per patient (3.83). The treatment phases associated with the higher mean number of episodes per patient were the induction (1.30) and reinduction (1.35) phases of therapy. The frequency of episodes of febrile neutropaenia according to treatment phase and risk group is given in Table 1.

Causative Pathogens

A causative pathogen was isolated from either blood, urine, stool cultures or nasopharyngeal aspirates in 133 out of 587 (22.7%) episodes of febrile neutropaenia. Multiple organisms were isolated in some cases. Organisms identified in order of frequency were Gram-positive bacteria (36.4%) and Gram-negative bacteria (36.4%), followed by viral pathogens (17.4%), fungal pathogens (8.4%), and other bacteria (1.2%). The majority of positive bacterial and fungal isolates were from peripheral or central line blood cultures. The most common bacteria isolated were *Staphylococcus aureus* (27/124, 21.8%), *Escherichia coli* (20/124, 16.1%), *Pseudomonas aeruginosa* (13/124, 10.5%), *Bacillus* sp (8/124, 6.5%) and *Klebsiella pneumoniae* (8/124, 6.5%). A breakdown of the specific organisms identified is given in Table 2 and Figure 1.

We further analysed the microbiological profile of severe episodes of febrile neutropaenia requiring admission into a high dependency unit (HD) or intensive care unit (ICU). There were 20 of such episodes, accounting for 3.4% of

Table 2. Types of Causative Pathogens Isolated

Type	Organism	No.	%
Gram-positive bacteria	<i>Staphylococcus aureus</i>	27	36.4
	<i>Bacillus</i> species	8	
	Coagulase-negative <i>Staphylococcus</i>	6	
	Other <i>Staphylococcus</i> species	6	
	<i>Enterococcus faecalis</i>	3	
	<i>Streptococcus salivarius</i>	2	
	Other <i>Streptococcus</i> species	2	
	<i>Micrococcus</i> species	2	
	<i>Dermabacter hominis</i>	1	
	<i>Streptococcus agalactiae</i>	1	
	<i>Streptococcus mitis</i>	1	
	<i>Streptococcus pyogenes</i>	1	
	<i>Streptococcus viridans</i>	1	
Gram-negative bacteria	<i>Escherichia coli</i>	20	36.4
	<i>Pseudomonas aeruginosa</i>	13	
	<i>Klebsiella pneumoniae</i>	8	
	<i>Proteus mirabilis</i>	4	
	<i>Acinetobacter baumannii</i>	3	
	<i>Salmonella</i> species	3	
	Unidentified Gram-negative bacilli	2	
	<i>Aeromonas hydrophilia</i>	1	
	<i>Chryseobacterium indologenes</i>	1	
	<i>Enterobacter cloacae</i>	1	
	<i>Enterobacter hormaechei</i>	1	
	<i>Fusobacterium nucleatum</i> *	1	
	<i>Morganella morganii</i>	1	
	<i>Neisseria</i> species	1	
	<i>Proteus vulgaris</i>	1	
Other bacteria	<i>Mycoplasma pneumoniae</i>	2	1.2
Viral	Respiratory syncytial virus	8	17.4
	Influenza A	6	
	Parainfluenza 3	4	
	Rotavirus	4	
	Varicella zoster	3	
	Parainfluenza 1	2	
	Epstein-Barr virus	1	
	Influenza B	1	
Fungal	<i>Candida albicans</i>	4	8.4
	<i>Aspergillus fumigatus</i>	2	
	<i>Candida tropicalis</i>	2	
	Other <i>Candida</i> species	3	
	<i>Candida parapsilosis</i>	1	
	<i>Pneumocystis jirovecii</i>	1	
	<i>Ulocladium</i> species	1	

*Anaerobic bacteria

Table 3. Types of Causative Pathogens Isolated from Severe Cases of Febrile Neutropaenia Requiring HD/ICU Admissions

Type	Organism	No.	%
Gram-negative bacteria	<i>Escherichia coli</i>	1	38.5
	<i>Klebsiella pneumoniae</i>	1	
	<i>Enterobacter hormaechei</i>	1	
	<i>Aeromonas hydrophilia</i>	1	
	<i>Pseudomonas aeruginosa</i>	1	
Gram-positive bacteria	<i>Staphylococcus aureus</i>	1	30.8
	<i>Streptococcus viridans</i>	1	
	<i>Bacillus</i> species	2	
Fungal	<i>Candida albicans</i>	1	23.1
	<i>Candida tropicalis</i>	1	
	<i>Aspergillus fumigatus</i>	1	
Viral	Influenza A	1	7.7

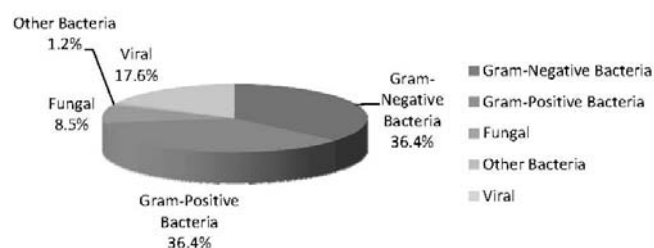


Fig. 1. Chart showing the types of organisms that cause febrile neutropenia.

all cases of febrile neutropaenia. Causative pathogens were isolated in 9/20 (45%) of these episodes (Table 3). Multiple organisms were again isolated in some cases. Organisms isolated in order of frequency were Gram-negative bacteria (38.5%), Gram-positive bacteria (30.8%), fungal pathogens (23.1%) and viral pathogens (7.7%).

Outcome

The majority of cases of febrile neutropaenia resolved with appropriate antimicrobial therapy and supportive management. There were 3 deaths from infection, accounting for 1.5% of all patients and 0.5% of all episodes of febrile neutropaenia. Cases requiring HD/ICU admission had a significantly higher mortality rate of 15%, reflecting the clinical severity of these cases. Two of these deaths occurred in patients with underlying trisomy 21. One occurred during the initial induction phase of treatment when he presented with febrile neutropaenia in acute respiratory distress to the ICU. Despite extensive workup for a source of infection, no organisms were isolated.

The other patient with trisomy 21 succumbed to systemic *Candida albicans* infection during the reinduction phase of chemotherapy, with the organism isolated from urine, stool and bronchial washings. The third death occurred in a child without any comorbidities during the reinduction phase of chemotherapy. Blood and endotracheal cultures were positive for *Pseudomonas aeruginosa*. Novel influenza A (H1N1) virus was also isolated from bronchial washings. The child eventually died of acute respiratory distress syndrome despite aggressive use of appropriate antibiotics and oseltamivir (Tamiflu).

Discussion

In our study, a causative pathogen was isolated in only 22.7% of all episodes of febrile neutropaenia. This concurs with prior studies which found that the aetiology for the majority of episodes of febrile neutropaenia will remain unknown despite comprehensive diagnostic workup.^{4,5} For microbiologically documented episodes, the pathogen profile in our cohort was also consistent with findings in similar studies conducted both within Southeast Asia^{6,7} and from other regions of the world,^{5,8} with bacterial organisms being the predominant cause of infections.

Gram-positive and Gram-negative bacteria were the most common causative organisms. This finding suggests that empirical antimicrobial therapy for episodes of febrile neutropaenia should include agents that have activity against both Gram-positive and Gram-negative bacteria. The empirical antimicrobial therapy in use at our institution from 2000 to 2010 was a combination of intravenous ceftriaxone and gentamicin. However, subsequent review of antibiotic susceptibility patterns from 2006 to 2011 showed a trend in increasing antibiotic resistance to cephalosporins, especially amongst Gram-negative bacteria. Empirical antimicrobial therapy for treatment of neutropaenic fever in our institution was hence amended to piperacillin/tazobactam from 2012, which provided better coverage against Gram-positive, Gram-negative and anaerobic bacteria.

Severe infections requiring HD or ICU care are of particular concern, as these are the cases with a higher risk of morbidity and mortality. The rate of identification of a causative organism was higher in these cases, with just under half of all episodes associated with positive microbial isolates. Although bacterial organisms were again the predominant pathogens identified, fungal organisms accounted for a much larger proportion of these severe cases requiring HD or ICU care compared to clinically milder cases (23.1% vs 8.4%). Our findings suggest that empirical antifungal agents in addition to antibiotics should be commenced at presentation for clinically severe cases of febrile neutropaenia, which is the current practice at our institution.

The highest number of episodes of febrile neutropaenia occurred during the induction and reinduction phases of chemotherapy, and also in patients on high-risk protocols who received the most intensive treatment which would result in greater myelosuppression. This is not a surprising finding, as the degree of neutropaenia has been found to correlate with the frequency and severity of febrile neutropaenia.⁹ Despite the multiple episodes of febrile neutropaenia seen in our cohort, the mortality rate was low at 1.5%, as compared to previously reported infection-related mortality rates of 0.6% to 19.2% in paediatric febrile neutropaenia studies.^{6,7,8}

Two of the 3 deaths recorded within the duration of the study occurred in patients with underlying trisomy 21. This concurs with existing literature which showed that ALL patients with Down syndrome had increased rates of infective complications with higher treatment-related morbidity and mortality.¹⁰ This particularly vulnerable group of patients would need to be monitored carefully during periods of neutropaenia for development of sepsis, and treated aggressively with antibiotics and antifungal agents at presentation during episodes of febrile neutropaenia even before any organisms are isolated.

Conclusion

Febrile neutropaenia continues to be of concern in ALL patients undergoing intensive chemotherapy. The majority of episodes will not have an identifiable causative pathogen. Gram-negative and Gram-positive bacteria were the most common causative pathogens identified. With appropriate antimicrobial therapy guided by antibiotic sensitivity patterns of each individual institution and supportive management, the overall risk of mortality from febrile neutropaenia is extremely low.

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Optimising Aesthetic Reconstruction of Scalp Soft Tissue by an Algorithm Based on Defect Size and Location

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Abstract

Introduction: Scalp soft tissue defects are common and result from a variety of causes. Reconstructive methods should maximise cosmetic outcomes by maintaining hair-bearing tissue and aesthetic hairlines. This article outlines an algorithm based on a diverse clinical case series to optimise scalp soft tissue coverage. **Materials and Methods:** A retrospective analysis of scalp soft tissue reconstruction cases performed at the Singapore General Hospital between January 2004 and December 2013 was conducted. **Results:** Forty-one patients were included in this study. The majority of defects <100 cm² were reconstructed with local flaps and were subdivided by location. Methods included rotation, transposition and free flaps. The most common type of reconstruction performed for defects ≥100 cm² was free flap reconstruction. Multistage reconstruction using tissue expanders aided in optimising cosmetic outcomes. There were no major complications or flap failures. **Conclusion:** By analysing our experience with scalp soft tissue reconstruction, we have developed an algorithm based on defect size and location, achieving excellent closure and aesthetic outcome while minimising complications and repeat procedures.

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Key words: Flaps, Reconstruction Algorithm, Scalp

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Introduction

Full-thickness scalp soft tissue defects are common and causes include trauma, tumour resection, radiation necrosis and infection. The need for adequate coverage is important as the scalp provides protection to underlying structures such as the calvarium, meninges and brain parenchyma. Poor decision-making in reconstructive choice can lead to wound breakdown, repeated operations, exposed implants and patient distress. Factors such as a previously irradiated or infected field increase these risks.

The goal of scalp soft tissue reconstruction is tension-free, durable coverage, especially in areas where calvarium or implants are exposed. The availability of modern reconstructive knowledge and methods also demands maximising cosmetic outcomes by maintaining hair-bearing tissue and aesthetic hairlines. In some cases, this may require staged procedures and tissue expansion.

Primary closure, while providing for minimal morbidity and hairy coverage, is only suitable for defects up to 2 to 3 cm².¹ Larger defects require the use of local, regional or free flaps to provide adequate coverage. To date, the literature describes many methods of scalp soft tissue reconstruction encompassing the entire reconstructive ladder.²⁻⁴ The appropriate choice should ultimately achieve the goals set out above, ensuring successful wound coverage, minimise donor site morbidity, and as far as possible returning a fully hair-bearing scalp to the patient.

We thus reviewed our experience with flap coverage of scalp soft tissue to determine wound factors affecting reconstructive choice. This article aims to outline our decision-making process which has helped to optimise anatomical as well as aesthetic coverage. Utilising this, we propose an algorithm for scalp soft tissue reconstruction based on defect size and location, providing a step-ladder

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guide to coverage of full-thickness scalp wounds.

Materials and Methods

A retrospective analysis was conducted on consecutive full-thickness scalp soft tissue reconstruction cases done at the Singapore General Hospital (SGH) between January 2004 and December 2013. Full-thickness defects were defined as those involving all layers of the scalp down to calvarium, cranioplasty implant or dura mater. Information was obtained from patient medical records, and data regarding patient and wound characteristics, size and location of defect, reconstructive procedure undertaken and postoperative details and outcomes were recorded and analysed. Wound sizes (cm²) were recorded according to the surgical notes, and calculated based on surface area length (cm) x width (cm). The study was conducted under Institutional Review Board approval.

General Operative Procedure and Flap Types

All operations were conducted under general anaesthetic. In cases of malignancy, resection was done by the plastic, head and neck and/or neurosurgeons. For cases of trauma, irradiated tissue or infection, adequate debridement of all infected and necrotic tissue was done before reconstruction was considered. Where cranioplasty implants were infected or exposed, decision to remove part of or the entire implant, along with debridement, was left to the neurosurgeons. If the wound bed was deemed unsuitable, temporary dressing with negative-pressure wound therapy was instituted, along with intravenous antibiotics.

Reconstructive methods used were divided into local flaps, free flaps or multistage reconstruction with tissue expansion. Local flaps were raised in the subgaleal plane and included transposition, unilateral (Fig. 1A) and bilateral rotation flaps in a 'Yin-Yang' pattern (Fig. 1B). In selected cases, galeal scoring perpendicular to the direction of closure was done to aid mobility of the flaps.

For free flaps, the superficial temporal vessels were invariably used as recipient vessels. These vessels are located in the pre-auricular area just anterior to the root of the helix. When these were not available, the neck vessels such as the facial or superior thyroid vessels were used as recipients, with interpositional saphenous vein grafts if pedicle length was insufficient.

For cases where tissue expansion was used, there was an interval of at least 6 months between the initial operation and expander insertion. The expanders were inserted in the subgaleal plane, and incision lines were made away from the site of the wound respecting aesthetic hairlines. All wounds were closed without tension to ensure adequate wound healing.

Results

Patient characteristics and reconstructive choice are summarised in Table 1. Forty-one patients were identified including 24 males and 17 females, with a mean age of 53 years (range, 26 to 87 years). The commonest cause of full-thickness scalp defects in our patients was malignancy followed by exposed or infected cranioplasty implants (Fig. 2). Mean scalp defect area was 98.0 cm² (range, 2 to 750 cm²). Location of defects included the vertex (n = 20),

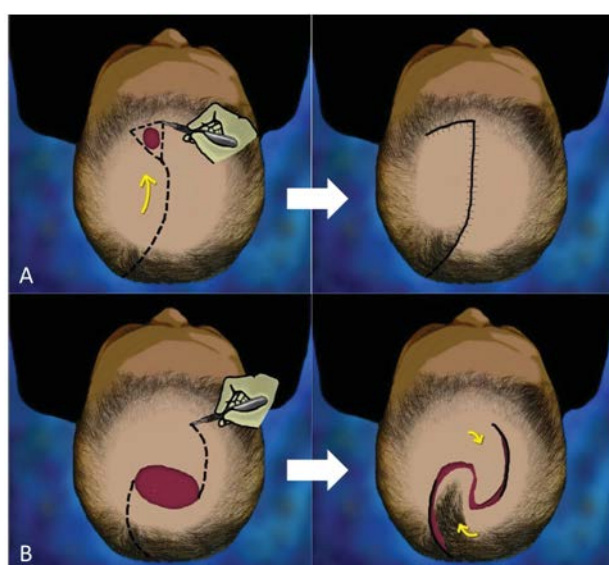


Fig. 1. In A, a unilateral rotation flap is shown while B exemplifies bilateral rotation flaps ('Yin-Yang').

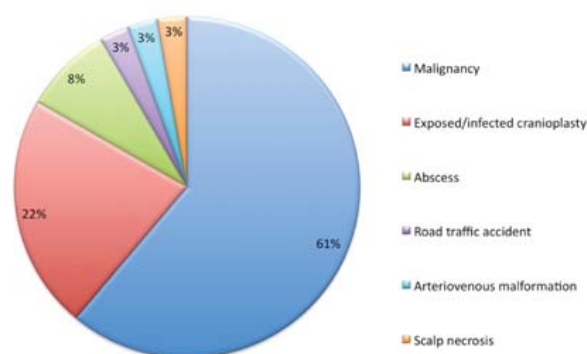


Fig. 2. Pie chart showing the breakdown of scalp defect aetiology.

Table 1. Patients with Full-thickness Scalp Defects Requiring Soft Tissue Reconstruction (n = 41)

	Patient No.	Defect Location	Size* (cm ²)	Reconstructive Method	Hair-bearing Scalp?
≤100 cm ²	1	Vertex	12	Unilateral rotation flap	Y
	2	Vertex	14	Bilateral rotation flap in Yin-Yang pattern	Y
	3	Vertex	15	Bilateral rotation flap in Yin-Yang pattern	Y
	4	Vertex	16	Unilateral rotation flap	Y
	5	Vertex	18.5	Unilateral rotation flap	Y
	6	Vertex	20	Unilateral rotation flap	Y
	7	Vertex	20	Transposition flap + SSG	N
	8	Vertex	25	Transposition flap + SSG	N
	9	Vertex	25	Bilateral rotation flap in Yin-Yang pattern	Y
	10	Vertex	28	Transposition flap + SSG	N
	11	Vertex	30	Transposition flap + SSG	N
	12	Vertex	40	Bilateral rotation flap in Yin-Yang pattern	Y
	13	Vertex	40	Unilateral rotation flap	Y
	14	Vertex	49	Bilateral rotation flap in Yin-Yang pattern	Y
	15	Occipital	12	Unilateral rotation flap	Y
	16	Occipital	22	Unilateral rotation flap	Y
	17	Occipital	90	Regional flap (trapezius)	N
	18	Temporal	6	Unilateral rotation flap	Y
	19	Temporal	20	Transposition flap + SSG	N
	20	Temporal	49	Unilateral rotation flap	Y
	21	Parietal	16	Transposition flap + SSG	N
	22	Parietal	40	Transposition flap + SSG	N
	23	Parietal	70	Transposition flap + SSG	N
	24	Parietal	96	Unilateral rotation flap	Y
	25	Forehead	56	Free radial forearm	Y
	26	Forehead	64	Free radial forearm	Y
≥100 cm ²	27	Vertex	100	Free LD	N
	28	Vertex	100	Transposition flap + SSG	N
	29	Occipital	100	SSG, tissue expansion and advancement	Y
	30	Occipital	100	Free ALT	N
	31	Parietal	120	Free ALT	N
	32	Parietal	120	Free LD	N
	33	Parietal	130	Free ALT	N
	34	Parietal	150	Free LD	N
	35	Vertex	180	Free LD	N
	36	Vertex	200	Free LD	N
	37	Vertex	200	Free ALT	N
	38	Parietal	200	Transposition flap + SSG	N
	39	Parietal	300	Free LD	N
	40	Vertex	300	SSG, Tissue expansion and advancement	Y
	41	Vertex	750	Free LD	N

*Defects <100 cm² are ranked according to size and location. Defects ≥100 cm² are ranked according to size.

ALT: Anterolateral thigh flap; LD: Latissimus dorsi muscle flap; N: No; SSG: Split-thickness skin grafting; Y: Yes

Table 2. Breakdown of Reconstructive Methods Utilised

Flap Type	Total	Percentage (%)
Free flap	13	32
Latissimus dorsi	7	
Anterolateral thigh	4	
Radial forearm	2	
Transpositional flap	10	24
Unilateral rotational flap	10	24
Yin-Yang flap	5	12
Tissue expander and advancement	2	5
Regional flap	1	3

parietal region (n = 10), occipital region (n = 6), temporal region (n = 3) and forehead (n = 2).

Flap types used are summarised in Table 2. These included free flaps (n = 13), transposition (n = 10), unilateral rotation (n = 10), bilateral rotation (n = 5), regional pedicled (n = 1), and tissue expansion with advancement (n = 2). Of the free flaps, there were 7 latissimus dorsi (LD) muscle flaps with split-thickness skin graft (STSG), 4 anterolateral thigh (ALT) fasciocutaneous flaps, and 2 radial forearm flaps (RFF).

There were no reconstructive failures in our series. Three early minor complications included 2 haematomas and 1 partial wound breakdown. The haematomas were evacuated successfully without further complication, while the wound breakdown healed by secondary intention. At a mean follow-up period of 33.6 months, all patients had healed well with intact scalp coverage. In terms of a complete hair-bearing scalp, this was achieved in 19/41 (47%) of patients.

Case Examples

Case 1 (Patient 31): Reconstruction with Free ALT Fasciocutaneous Flap

A 43-year-old male sustained left extradural hemorrhage in a road traffic accident and underwent titanium cranioplasty.

He developed pressure necrosis around the cranioplasty site which fistulated into the dura, and subsequently underwent plate removal and replacement. The resultant 120 cm² defect was reconstructed with a free ALT flap. The wound healed well with acceptable contour (Fig. 3).

Case 2 (Patient 3): Reconstruction of Vertex Defect with Bilateral Rotational Flaps

A 38-year-old female underwent debridement of a scalp vertex abscess, resulting in a full-thickness defect measuring 5 x 3 cm (15 cm²). Subsequently, she underwent scalp soft tissue reconstruction with bilateral rotation flaps in a ‘Yin-Yang’ pattern. There were no postoperative complications, and at 2-months post-op, the wound healed well and her scalp was bearing hair evenly (Fig. 4).

Case 3 (Patient 40): Reconstruction of Fronto-Parietal Scalp Defect with Tissue Expansion

A 28-year-old female with dermatofibrosarcoma protuberans underwent wide excision followed by transposition flap and STSG to the donor site. At 1-year postop, the flap was stable with no recurrence. To recruit hair-bearing tissue for the skin grafted region, tissue expansion of the left hair-bearing scalp was done. These were subsequently removed and the hair-bearing scalp was advanced. There were no postoperative complications and at 7-months review, the scalp was bearing hair with a good aesthetic outcome (Fig. 5).

Discussion

With careful planning and selection, we were able to attain 100% reconstructive success with our patients, with almost half of them maintaining completely hair-bearing scalps and aesthetic hairlines. Prior to committing to a particular method of reconstruction, care must be taken to resect all non-viable tissue, especially in cases of infection, radiation or tumour. Where infected calvarial bone graft or implants are present, adequate debridement and antibiotic treatment is paramount to prevent intracranial infection



Fig. 3. Slide A shows a patient in the preoperative stage. Note the skin necrosis around craniotomy site. Slide B shows the immediate postop with free anterolateral thigh flap. In slide C, the patient is seen 1-year postop after several flap debulking procedures. In slide D, the patient is at 5-years follow-up.



Fig. 4. In slide A, a 5 x 3 cm full-thickness scalp defect is seen at vertex. Intraop views in B; C: bilateral rotational flap raised in a 'Yin-yang' pattern and inset. In D, the scalp was bearing hair evenly at 2-months postop.

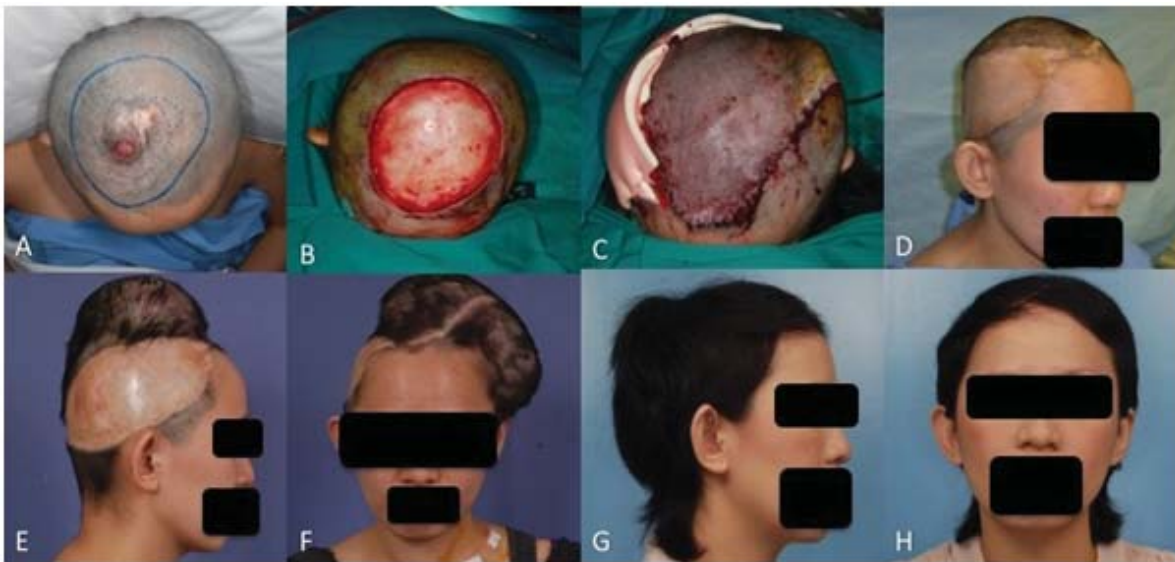


Fig. 5. In slide A, dermatofibrosarcoma protuberans at fronto-parietal region and in B and C, wide excision followed by transpositional flap and temporising skin graft. In D, patient is at 1-year postop prior to insertion of tissue expander. Slides E and F depict the expander insertion and expansion. At G and H, patient is shown 7 months after removal of tissue expander. Scalp was bearing hair with excellent aesthetic outcome.

and complications, and close collaboration with the neurosurgeons may be necessary.

As much as possible, scalp soft tissue defects should be covered with local flaps to maintain hair-bearing tissue. Knowledge of scalp vascular anatomy is key to planning these flaps, with the inclusion of at least 1 of the 5 paired major arteries (supratrochlear, supraorbital, superficial temporal, postauricular and occipital) supplying the scalp.² Furthermore, due to muscular and ligamentous attachments and the ovoid shape of the skull, mobility of soft tissue varies over different areas of the scalp. Over the vertex and occiput, the scalp is tensioned by the frontalis and occipitalis

muscles, leading to limited mobility compared to the more mobile peripheral regions of the scalp.⁵

On analysis of our results, a distinctive pattern of flap selection can be seen at a cut-off defect area of 100 cm² (Table 1). The majority of defects <100 cm² could be covered with local flaps and recruitment of hair-bearing tissue was the primary consideration, which was achieved with unilateral or bilateral local rotation flaps in a 'Yin-Yang' pattern. For defects of this size, transposition flaps with donor site skin graft coverage were reserved for wounds ≥ 20 cm² in the less mobile vertex region or for larger wounds in the peripheral regions. In these patients, excision of the skin grafts with

or without tissue expansion are options for future cosmetic improvement. When required, undermining of surrounding tissues in the subgaleal plane can help in closure, as can galeal scoring perpendicular to the line of closure at 1 to 2 cm intervals, with each cut earning 1.67 mm of elongation.⁶ However, limitations of local tissue transfer include large defects, previous irradiation or surgery, and a skin grafted donor site in the case of transposition flaps. In the forehead region, the aponeurotic layer adheres to the pericranium leading to minimal scalp mobility. For the 2 defects we encountered in this area where hair-bearing tissue was not an issue, the free radial forearm flap provided the best contour and texture match, and is consistent with the most widely used flap in the literature for reconstruction of forehead defects.⁷

Where more local tissue is required for maximal aesthetic outcomes, and when immediate, permanent wound coverage is not essential, tissue expansion represents an excellent option. One limitation is in cases where postoperative irradiation is contemplated, as prolonged expansion may result in unacceptable delays in oncologic treatment. In these patients, the wound can be temporised with local flaps and skin grafts until remission, whereby expansion can be done for completion of reconstruction (Fig. 5). In a normally hair-bearing area of the scalp, tissue expansion and rotation flaps represent the best choice for reconstruction. Tissue expansion does require a stable calvarial base and adequate expandable tissue (>50% of scalp), as well as a patient who is able to remain compliant to prolonged expansion and staged procedures.^{4,8}

In cases where defects were large (>100 cm²) and there was insufficient local tissue for recruitment, microsurgical reconstruction with free flaps enabled the transfer of large amounts of composite tissue to the scalp.⁹ In these cases, due to the size of the defects and exposed underlying structures expedient durable coverage is the aim and hair-bearing tissue should no longer be a primary consideration. Free tissue transfer is also indicated in salvage of patients with radiation or local flap failure.¹⁰

The main considerations for free flap selection include defect size, pedicle length, and donor site morbidity. Many different types of flaps have been used, with the free LD muscle flap preferred as it is relatively thin, broad and well vascularised.¹¹ It is usually harvested without a skin paddle and covered with a skin graft, and as it atrophies over time usually results in a thickness that closely resembles that of the native scalp. However, this may also result in the potential drawback of calvarial or implant exposure or there is too much thinning of the flap. Other muscular free flaps described but are less commonly used include the serratus anterior and rectus abdominus flaps.^{10,11} In select patients with minimal subcutaneous fatty tissue, fasciocutaneous free

flaps can achieve an excellent result for scalp reconstruction. The ALT flap has been well described and is now the preferred flap for many reconstructive surgeons.^{12,13} It has the advantage of a long vascular pedicle, large amount of soft tissue and skin, the ability to be harvested simultaneously with resection, and minimal donor-site morbidity. The criticism of these flaps has been their bulkiness which may require secondary debulking procedures to regulate the contour. However, advances in techniques and knowledge have now allowed elevation of ultra-thin ALT flaps which can circumvent this problem.¹⁴ In their series of 37 patients, Fischer et al found no difference in efficacy between the free LD or ALT flaps for scalp reconstruction.¹⁵ The main disadvantage of free flaps is that transfer of hair-bearing tissue is not possible. Hair transplants to the flap have been described but have met with limited success.¹⁶ The use of a free flap is therefore a sacrifice of aesthetics for functionality.

A major consideration of free tissue transfer to the scalp is the choice of recipient vessels. Among the commonly described pedicles, the superficial temporal system is the closest to the scalp. However, these may not always be available due to resection, and are prone to arterial vasospasm and venous outflow sufficiency, especially in irradiated fields. In these cases, the recipient vessels in the neck such as the facial and superior thyroid systems can be used. This requires either maximal flap pedicle length harvest and careful tunnelling, or the use of vein grafts.¹⁷

In our series, the majority of large scalp defects were reconstructed with free flaps, and we used mainly the LD muscle or ALT flaps for this purpose. The LD muscle flap with skin graft has been our workhorse flap as it provides a large surface area and contours nicely to the skull. More recently, the free ALT fasciocutaneous flap has gained favour.

The drawback of our study is that it involves solely soft tissue reconstruction. Calvarial reconstruction methods were not included, but can be significant as artificial implants have a higher rate of complications than autologous bone.¹⁸ Also, the use of size as a cutoff in our population was limited to adult patients only. In addition, it must also be remembered that patient preoperative status and comorbidities play a role in decision-making. In selected patients who were poor candidates for free flap reconstruction, we used transpositional flaps with split thickness skin grafting for more expedient coverage and shorter intraoperative time.

Conclusion

In our experience, the common reconstructive methods for scalp soft tissue reconstruction are the unilateral rotation flap, bilateral rotation flap in a 'Yin-Yang' pattern, transposition flap with donor sites skin grafting and free flap

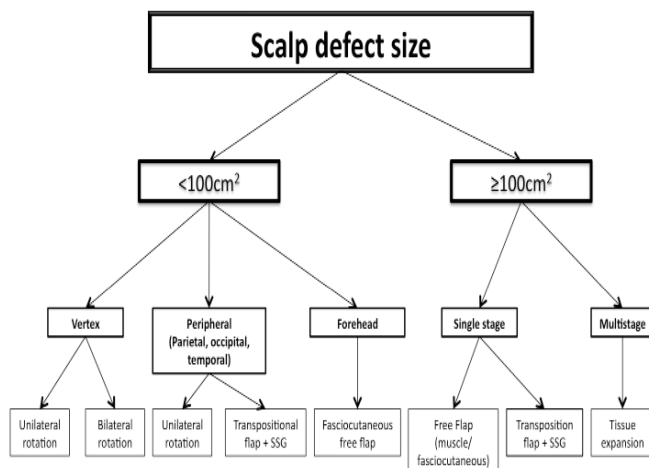


Fig. 6. An algorithm for reconstruction of full-thickness scalp soft tissue defects based on size and location.

reconstruction. By selecting the appropriate option based on size and anatomical location, we were able to achieve high reconstructive success rates while respecting aesthetic hairlines and maximising hair-bearing scalp tissue. Upon analysis of our results, we found 100 cm² as the “critical size” determining the tendency towards free flap reconstruction. We thus propose our algorithm to optimise full-thickness scalp soft tissue reconstruction (Fig. 6).

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Treatment of Recurrent Pancreatic Pseudocysts with Proven Communication between Pseudocyst and Pancreatic Duct by Long-term Percutaneous Drainage

Dear Editor,

Patients with communication between pancreatic pseudocysts (PPC) and pancreatic duct (PD) require a longer duration of drainage, due to the short-term drainage resulting in very high recurrence rates. However, with prolonged drainage period, the risk of septic complications is also potentially increased.¹⁻³ The aim of the study was to evaluate the results of prolonged percutaneous catheter drainage (PCD) in the treatment of recurrent PPC with PPC-PD communication, including its outcome and complications.

Materials and Methods

We performed a prospective analysis of 18 patients with recurrent symptomatic PPC and proven PPC-PD communication, and were treated by prolonged PCD. Indications for prolonged PCD are shown in Table 1. All procedures were performed under ultrasound control. Careful localisation of the cyst and proper selection of the entry site were performed. The drainage route depended on the location and available “window” for an optimal access to the cystic collection. The applied percutaneous technique was the trocar method using an 8F multisidehole pigtail catheter, which was introduced into the cyst cavity. Procedure was performed using local anaesthesia, having patients supine. No conscious sedation was applied. Cystic fluid was aspirated through the catheter as much as possible. Evaluation of the cyst size before treatment and during follow-up examinations was based on ultrasound examinations. Patients were followed up for 12 months after the drain retrieval. Primary outcome was long-term success of the procedure. Secondary outcomes were procedure-related adverse events and re-intervention.

Results

The demographic characteristics, clinical and laboratory data of patients, indication for prolonged PCD and duration of the treatment are shown in Table 1. The initial PCD was technically successful in all patients and amount of obtained liquid immediately after catheter placement into the PPC ranged between 140 mL and 660 mL. PPC content culture was negative in all patients. The initial level of amylase (normal serum level 20 U/L to 160 U/L) and lipase (normal

serum level 73 U/L to 393 U/L) in the PPC content was more than 10 times higher in comparison to their normal serum level and did not decrease during drainage. All patients experienced relief of symptoms, remission of clinical signs and improvement of their general status immediately after the procedure. During PCD, catheter was changed in 4 patients due to the inadequate drainage and problems with the catheter (clogging, kinking or displacement of catheter).

During the follow-up, none of the patients had any recurrence of PPC. Overall, the procedure was well tolerated by patients and no major complications were observed. Six patients reported mild abdominal pain during or after the procedure. Slight fever occurred in 5 patients and was successfully treated with antibiotics. These minor complications were managed with bed rest and they all subsided within 24 hours.

Discussion

Our study shows that management of recurrent symptomatic PPC with PPC-PD communication, with prolonged PCD is effective and safe, without complications directly attributable to the procedure. During the follow-up evaluation, there were no major complications or PPCs recurrence.

Several conditions must be met to achieve the complete obliteration of the cyst cavity. Much overlap exists in the treatment options offered by interventional radiologists, gastroenterologists, and surgeons. The recent trend in the management of symptomatic PPCs has moved toward less invasive approaches such as endoscopic drainage (ED) and image-guided PCD.

The major advantage of ED is that it creates a permanent pseudocysto-gastric track with no spillage of pancreatic enzymes in contrast to PCD, thereby reducing the risks of formation of pancreatico-cutaneous fistulas (PCF). However, with the drainage problems (which could appear with both techniques), monitoring, manipulation or change of stent and the analysis of cystic content are much easier using PCD than ED.^{2,4} Besides, long-term PCD is less aggressive compared to surgical and endoscopic (especially with endoscopic retrograde cholangiopancreatography) methods, suitable for the treatment of all PPCs regardless of their

Table 1. Characteristics of 18 Patients with Recurrent Pancreatic Pseudocysts

Characteristics	Value
Age, years	45.4 ± 9.6
Sex (male/female)	13/5
Aetiology of PPC, n (%)	
Acute pancreatitis	7 (38.9)
Chronic pancreatitis	5 (27.8)
Trauma	3 (16.7)
Unknown cause	3 (16.7)
Pancreatic duct abnormalities, n (%)	
Normal duct/with duct-cyst communication	7 (38.9)
Duct with stricture and duct-cyst communication	6 (33.3)
Chronic pancreatitis/with duct-cyst communication	5 (27.8)
Initial treatment of PPC before recurrence, n (%)	
PCD	7 (38.9)
Endoscopic	2 (11.1)
Laparoscopic	2 (11.1)
Open surgery	7 (38.9)
Indication for prolonged PCD, n of patients (%)	
Abdominal pain	16 (88.9)
Fever	5 (27.8)
Jaundice	5 (27.8)
Gastric outlet obstruction	2 (11.1)
Abdominal tenderness	12 (66.7)
Laboratory data	
Amylase level in PPC content, mean, x10 ³ U/L	13.6 ± 7.9
Lipase level in PPC content, mean, x10 ³ U/L	15.0 ± 14.5
Initial maximal diameter of PPC, median, mm	102.0 (73 – 163)
Initial volume of PPC, median, mL	227.5 (120 – 660)
No. of cysts according to location	
Head of pancreas	7 (38.9)
Body of pancreas	4 (22.2)
Tail of pancreas	7 (38.9)
No. of PPC according to appearance of aspirates	
Clear	8 (44.4)
Dark	10 (55.6)
Duration catheter placement, median, days	59.5 (41 – 111)

PPC: Pancreatic pseudocysts; PCD: Percutaneous catheter drainage

location and can be carried out without general anaesthesia. Therefore, this treatment is especially recommended for patients who are unsuitable for more aggressive methods and those with high risk for general anaesthesia.

Several reports evaluated the efficacy of PCD in the treatment of PPC.¹⁻⁵ PD anatomy is an important factor

impacting on the treatment results. PCD has better results and lower recurrence rates in patients without PPC-PD communication.^{1,2,4} Patients with PPC-PD communication require longer drainage duration as short-term drainage results in very high recurrence rates. However, some authors consider that with prolonged drainage period, the risk of septic complications and PCF is potentially also increased.^{1,3}

We conducted evaluation of our patients with recurrent PPC and proven communication between PD and PPC and subjected them to prolonged drainage (until no catheter output was detected within 7 days of the last procedure) without the introduction of stents in the PD. We started from the fact that long-term PCD with complete removal of PPC content avoids pancreatic-enzyme lytic action, keeping the cyst walls in close contact, and leads to the complete obliteration of the cyst cavity and disruption of PPC-PD communication. During the 12-month follow-up, our results proved supportive of the hypothesis. In our patients, there were no septic complications during PCD although the drainage lasted an average of 60 days. We have theorised that an alkaline environment caused by pancreatic content (levels of amylase and lipase in the obtained content remained high throughout the drainage) was not suitable for the development of infection in the case of prolonged retention of the catheter during pseudocyst drainage. Also, in the case of PCF (after catheter removal), where estimated as necessary, the introduction of a new catheter into the cyst cavity residue was planned only for a short-term until the fistula closed. However, PCF did not show up in any of the patients.

Conclusion

Prolonged PCD is a safe and effective management for symptomatic recurrent PPC with PD communication. Despite the fact that this is a small series of patients, we consider our study to be a good step forward towards clarification of the optimal treatment of PPC with PD communication. Large-scale and multicentre studies are needed to clearly determine whether this method improves efficacy and safety, and provides better outcomes compared to other drainage techniques.

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Disseminated Lymphoma Evolving into Neurolymphomatosis during Mid-cycle of Chemotherapy Detected by ^{18}F -FDG PET/CT

Dear Editor,

Neurolymphomatosis is a rare clinical entity and has mainly been described as primary lymphomatous infiltration of the nerves and as a relapse or progression of disease after previous treatments. In this case report, we describe an unusual occurrence of neurolymphomatosis evolving in mid-cycle chemotherapy.

Case Report

An 80-year-old Chinese lady was diagnosed with diffuse large B-cell lymphoma (DLBCL) involving cardiac, nodal and bony disease. She was first investigated for chest pain with breathlessness and a 2D echocardiogram showed a large circumferential pericardial effusion with evidence of cardiac tamponade as well as an echodense mass seen adherent and anterior to the right ventricle and right ventricle outflow tract (RVOT) region with RVOT compression. She underwent a left anterior thoracotomy, pericardial window, mediastinoscopy and biopsy; histology of her mediastinal lymph node was consistent with DLBCL. ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) was performed using a GE Healthcare Discovery PET/CT machine with 10.0 millicurie of FDG injected. The scan was performed 75 minutes after the radiotracer administration. Hypocount measurement was 6.0 mmol/L prior to the scan. Findings showed a hypermetabolic nodular soft tissue thickening along the pericardium as well as pericardial effusion. Multiple foci of FDG uptake were also seen in the bones and in lymph nodes above and below the diaphragm. Bone marrow aspirate had no morphological evidence of lymphomatous infiltration but trephine showed mildly hypocellular trilineage haematopoiesis with minimal, concordant B-Lymphomatous infiltration. Flow cytometry noted approximately 3% atypical B lymphocytes which express CD19+, CD20+, SMIG+, predominantly CD5-, CD23-, FMC7- with lambda light chain restriction compatible with clonal B cells. The International Prognostic Index was 4. She was treated with her first cycle of R-CHOP chemotherapy regimen consisting of rituximab, cyclophosphamide, hydroxydaunorubicin (doxorubicin), Oncovin (vincristine) and prednisolone displaying good clinical improvement. A repeat 2D echocardiogram done

16 days later showed resolution of the cardiac mass and pericardial effusion.

The patient presented after her third cycle of R-CHOP with complaints of new onset glove and stocking numbness. Physical examination revealed hand numbness up to wrist and lower limb numbness up to mid-calf on both sides. A magnetic resonance imaging (MRI) study of the brain and spine was performed (Siemens MAGNETOM Avanto, 1.5 Tesla). Apart from degenerative changes such as disc bulges and lumbar spondylosis, the MRI study showed no overt leptomeningeal enhancement, or any intracranial abnormality detected and no MR features to suggest transverse myelitis. A lumbar puncture performed showed elevated protein 0.99 g/L (normal: 0.1 to 0.4 g/L) with absent white blood cell count. The cerebrospinal fluid was also negative for lymphomatous large cells. Nerve conduction studies showed evidence of bilateral absent H reflexes and prolonged right tibial and left peroneal F wave latencies which were compatible with early changes in Guillain-Barré syndrome. She was initially treated as for Guillain-Barré syndrome and completed 5 days of intravenous immunoglobulin (IVIG) with no improvement in symptoms. A subsequent FDG PET/CT study (9.4 millicurie of FDG injected, scan performed at 75 minutes post radiotracer administration with hypocount 5.9 mmol/min prior to scan) showed near complete resolution of the previous sites of disease (Fig. 1). However, new FDG-avid perineural soft tissue thickening were found in multiple peripheral nerves, suspicious for tumour. The nerves involved included the bilateral brachial plexi, right femoral nerve and left sciatic nerve. FDG uptake was also seen beginning from the L5 nerve roots with perineural thickening suspicious for tumour infiltration as opposed to inflammatory nerve conditions (Fig. 2). A repeat lumbar puncture was performed which then showed atypical lymphoid cells suspicious for lymphomatous involvement. Flow cytometry of the cerebrospinal fluid noted a population of atypical B-lymphocytes constituting approximately 30% of the analysed cells. The lymphocytes were CD19+, CD10-, CD5-, CD20+ and cytoplasmic lambda light chain restricted; suspicious of involvement of the cerebrospinal fluid by a B-cell lymphoproliferative disorder. The patient deteriorated neurologically and also developed a nosocomial pneumonia during her inpatient stay. The decision was made

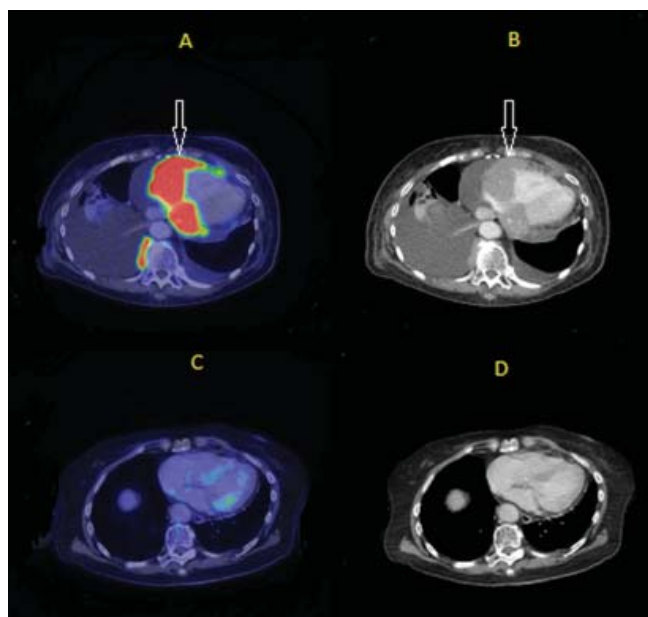


Fig. 1. Diffuse large B-cell lymphoma involving the myocardium (arrowheads in A and B). Follow-up PET/CT showed interval metabolic resolution of the previous disease, including the cardiac lesion (C and D).

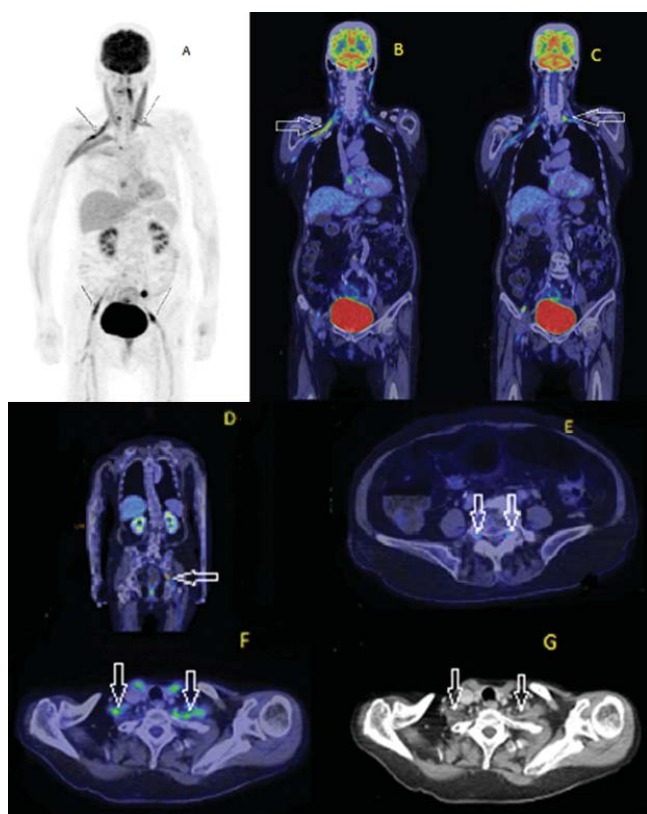


Fig. 2. FDG-avid perineural soft tissue thickening in multiple peripheral nerves, suspicious for tumour (A). The nerves involved included the bilateral brachial plexi (arrowheads in B and C), right femoral nerve (not shown) and left sciatic nerve (D). FDG uptake can also be seen beginning from the L5 nerve roots (arrowhead in E) with perineural thickening that is suspicious for tumour infiltration as opposed to inflammatory nerve conditions (arrowheads in F and G).

for palliation after consultation with the family and she then passed away shortly after terminal discharge.

Discussion

Neurolymphomatosis is a rare syndrome of peripheral nerve dysfunction secondary to infiltration by lymphoma, nearly always B-cell non-Hodgkin's lymphoma.^{1,2} A high index of suspicion is required as presenting symptoms are varied; conventional radiology has only modest sensitivity, and pathological diagnosis is often difficult. A number of differential diagnoses need to be considered (e.g. nerve damage from herpes zoster, chemotherapy with vinca alkaloids such as vincristine, Guillain-Barré syndrome, radiation plexopathy, nerve root compression, amyloidosis and lymphoma-associated vasculitis).³ The diagnosis and localisation of neurolymphomatosis may be supported by FDG PET-CT imaging.³⁻⁸ There is no known standard treatment for neurolymphomatosis and management usually consists of either chemotherapy alone or combined with radiotherapy. Most institutes employ a methotrexate monotherapy regime or combined with other drugs particularly cytarabine. Early recognition and treatment of this rare neurologic manifestation of lymphoma may improve outcome.^{1,8-9} Previously reported cases of neurolymphomatosis have described cases as first presentation of malignancy and as relapse or progression of disease after previous treatment, including a single case report of cardiac lymphoma relapsing as neurolymphomatosis.⁸⁻⁹ It seems likely that the blood-nerve barrier presents a barrier to the entry of large molecules such as cyclophosphamide, doxorubicin, vincristine, and rituximab into these areas, possibly resulting in lymphomatous infiltration. Ours is a rare case demonstrating a disseminated lymphoma involving cardiac, nodal and bony disease responding well to standard treatment that subsequently evolved into neurolymphomatosis mid-cycle through chemotherapy.¹⁰ To the best of our knowledge, this is the second such reported case in the published literature. This report adds to the small but growing literature on neurolymphomatosis and care must be taken to correctly diagnose this clinical entity in such settings to avoid delays in therapy.

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A Child with Rapid-onset Respiratory Distress after Chemotherapy, Lung Irradiation, General Anaesthesia, and Blood Transfusion

A 5-year 11-month-old male with recurrent nephroblastoma was admitted for insertion of a totally implanted central venous device under general anaesthesia. The malignancy involved both kidneys when he was 12 months old and complete remission was attained after chemotherapy and surgery. Seven months ago, he was diagnosed to have intra-abdominal relapse with bilateral, multiple lung metastases. Five months into treatment with chemotherapy (etoposide and ifosfamide), abdominal and lung irradiation (total dose to the lungs, 12 Gy), he achieved a second complete remission. A central venous device was deemed necessary because of difficulty in venous access. Because of anaemia (haemoglobin, 7.8 g/dL) and thrombocytopenia (platelet, $19 \times 10^9/L$), group-matched leuko-reduced apheresis platelet was transfused just prior to the commencement of the procedure. Right after the surgery, the transfusion of a matched unit of red cell was commenced. In total, 600 mL (30 mL/kg) of blood products were transfused over a period of 5 hours. At 2-hours postoperatively, the child was noticed to have mild tachypnoea (35 breaths/minute). The physical examination did not reveal any signs of consolidations in the lungs or fluid overload, and no hypoxaemia on transcutaneous oximetry. However, the condition deteriorated within the next hour with increasing respiratory distress and failure to maintain oxygen saturations above 93% without oxygen supplement. He was then admitted into intensive care and required nasal continuous positive airway pressure for respiratory support. A chest radiograph was obtained and the fluoroscopic film during the central venous access device insertion was retrieved for comparison (Fig. 1).

What was the most likely diagnosis?

- A. Transfusion-related acute lung injury
- B. Volume overload
- C. Acute atelectasis
- D. Radiation-induced pneumonitis
- E. Pneumocystis jiroveci pneumonia

Discussion

Transfusion-related acute lung injury (TRALI) is an uncommon but perhaps under-recognised complication

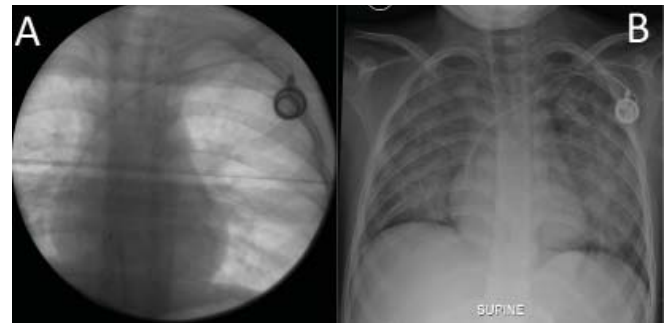


Fig. 1. Slides showing the investigative outcomes of the patient. At A, fluoroscopic image during the insertion of the implanted central venous device showing normal lung markings. At B, chest roetgenograph at 3-hours postoperatively showing bilateral lung infiltrates and a normal sized cardiac silhouette.

after blood transfusion. However, it is the leading cause of fatal complications after transfusion therapy. The exact pathogenetic mechanisms are still unclear but the non-cardiogenic pulmonary oedema is believed to be the result of cytokines released from activated neutrophils trapped in the pulmonary micro-circulation. In the majority of cases, antibodies against the human leukocyte antigens or the neutrophils present in the donor plasma are responsible for the neutrophil activation.^{1,2}

Treatment of TRALI is largely supportive and some patients may require mechanical ventilation. The case mortality rates have been reported to be 5% to 10%.² The child described in the report had a complete recovery with a normal chest radiograph 72 hours later. Pre-emptive treatment with broad spectrum antibiotic was discontinued after 24 hours when a normal procalcitonin level was found. The occurrence of TRALI may be prevented by exclusion of donors harbouring human leukocyte antibodies from blood products of high plasma content. Hence, the recognition and reporting of incidents of TRALI is an important issue in national haemovigilance.¹

The diagnosis of TRALI remains clinical, with onset of acute respiratory distress within 6 hours of transfusion being the hallmark of the condition. Although TRALI can occur in otherwise healthy individuals, patients who are septic, requiring intensive care, or undergoing treatment

Answer: A

for malignancies are at higher risk of developing TRALI. The medical literature concerning TRALI in children is scarce. In 2014, the Canadian Blood Service reported a series of 17 cases of paediatric TRALI over a period of 11 years,³ which is by far the largest series of paediatric cases of TRALI. A bimodal distribution is noted with 5 neonates and 11 adolescents above the age of 14 years. The mortality rate is 5.9%. Under-recognition of the occurrence of TRALI in children is likely the reason for the unusual age distribution among the cases.

The present case illustrates how a diagnosis of TRALI can be potentially distracted in a child with pre-existing medical and surgical problems. Malignant disease in the lungs, toxicities of lung irradiation, cardiac toxicities from chemotherapy, opportunistic infections, surgical and anaesthetic complications need to be considered in the paediatric oncology patient who presents with acute respiratory distress. However, a normal radiograph immediately prior to the incident, the characteristic clinical and radiologic course, and the rapid resolution on supportive care make TRALI the most probable diagnosis in this case.

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