



AAMS

Annals of the Academy of Medicine, Singapore

MCI(P) 029/11/2015

VOLUME 44

NUMBER 12

FREE PAPERS

DECEMBER 2015



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“Character is like a tree and reputation like a shadow. The shadow is what we think of it; the tree is the real thing.”

Abraham Lincoln (1809 – 1865)
American president

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Preventive Child Healthcare in Singapore: A Parents' Well-Being Perspective

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Introduction

Singapore has made remarkable achievements in child and maternal healthcare through significant reduction made in childhood and perinatal mortality rates. A number of “new morbidities” however, present emerging child healthcare challenges.^{1,2} Indeed, the Child Development Programme (CDP) under the Ministry of Health has observed about a 2-fold increase of new referrals from 2004 to 2011.³ Primary child healthcare prevention is crucial to address these problems early. Healthcare providers however, need to be cognisant that children’s development and health-promoting behaviours are contingent on primary caregivers’ responsiveness to their needs. Caregivers’ health and well-being constitute a “capacity” that affects the production of future capacities of their children.⁴

This editorial aims to contribute further to this understanding by highlighting findings of a needs analysis study⁵ undertaken by the KK Women’s and Children’s Hospital (KKWCH) on vulnerable families and young children to inform the development of the Kids Integrated Development Service 0-3 programme (KIDS 0-3). KIDS 0-3 targets economically disadvantaged families to minimise poor outcomes of young children associated with disadvantages of growing up in impoverished homes. The editorial describes the psychosocial profile of caregivers used to inform the programme design in supporting children’s healthy development (Table 1).

Using surveys and focus group discussions with primary caregivers and social workers serving these families, the study explored issues pertaining to the physical and psychological well-being of the target population: family financial state, perceived needs, and service gaps. The families were living on a per capita income of \$450 or less, have a child of 3 years in age and below, and were receiving services from a major social service provider in the housing estate under study.

We evaluated parenting capacity with the following measures: Parenting Daily Hassles Scale,⁶ Brief COPE⁷ and Depression, Anxiety and Stress Scale (DASS).⁸ Economic hardships notwithstanding, the caregivers were generally positive about their parenting capability with various routine caregiving tasks. They perceived themselves to be engaging in more adaptive coping strategies when dealing with challenging situations. Positive reframing, acceptance, planning and active coping were identified as the most commonly used adaptive strategies. Self-distraction, venting, self-blame and denial were reported as commonly used maladaptive coping strategies (Table 2).

Self-reported mental health condition of the caregivers, however, appeared poorer than that of the typical population. Between 14% and 31% reported ‘severe’ to ‘extremely severe’ DASS scores, above the reported national statistics of 10% for depressive and anxiety disorders,⁹ indicating the necessity for close attention and monitoring, and preventive support. Significant relationships between maladaptive coping and depression, anxiety and stress reiterated that systematic assistance with the caregivers’ mental health issues should be a pertinent aspect of programme planning to strengthen their caregiving capabilities (Table 3).

No major health concerns relating to their ante-, neo- and post-natal care of the children was reported. Eighty-four percent reported compliance to the immunisation schedule for the first year of the child’s life, dropping to 62% at 15 and 18 months of the child’s age. Forty-nine percent reported missing at least 1 vaccination at the given child’s age. Medical attention was given most frequently to common illnesses but not injuries. Hospital emergency was cited as the most frequently utilised community service. Early dental healthcare was not readily accessible because of the families’ ill affordability. Many reported to not having the money to attend to contingencies deemed less immediately urgent.

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Table 1. Demographic Characteristics of Respondents (n = 35)

Characteristics			
Mean age in years (SD)	33.9 (8.39)		
Gender			
Female	91.9		
Male	8.1		
Relationship with the child (%)			
Mother	83.8		
Father	8.1		
Grandmother	8.1		
Marital status (%)			
Single	10.8		
Married	54.1		
Divorced/separated	27.0		
Widowed	8.1		
Family structure (% of respondents)			
Both parents (nuclear)	34.3		
Single parent	31.4		
Three-generation family (extended)	34.3		
Housing type (% of respondents)			
1-room HDB	16.3		
2-room HDB	37.8		
3-room HDB	18.9		
4-room HDB	8.1		
Interim rental	16.2		
Living with others	2.7		
	Mother (n = 34)*	Father (n = 24)*	Grandmother (n = 3)
Highest education (%)			
Primary	33.3	36.0	-
Secondary	51.5	44.0	100.0
Postsecondary	9.1	16.0	-
Institute of Technical Education (ITE)	6.1	4.0	-
Employment status (%)			
Full time	23.5	45.8	-
Part time	17.6	29.2	-
Odd jobs	2.9	4.2	-
Unemployed	55.9	20.8	100.0
Weekly working hours (SD)	41.3 (17.99)	46.3 (23.25)	-

HDB: Housing Development Board; SD: Standard deviation

*Not all respondents reported their status.

Although caregivers expressed less concerns about their children's physical health, it is notable that there were concerns with the latter's emotional, behavioural, and communication problems. Between 41% and 63% perceived their children as showing "abnormal" levels of emotional symptoms, conduct problems and peer problems on the Strengths and

Difficulties Questionnaire.¹⁰ Scores on the Ages and Stages Questionnaire (ASQ)¹¹ indicated that between 44% and 53% of the children assessed presented serious delays in problem solving, communication and personal-social domains of functioning—skills that can be fostered through sustained parent-child interactions.¹² The focus group discussion noted

Table 2. Mean Scores on the Brief COPE (n = 37)*

Example of Items		Mean (SD)
Adaptive coping		
Active coping	I've been taking action to try to make the situation better.	3.00 (0.86)
Planning	I've been trying to come up with a strategy about what to do.	3.09 (0.87)
Use of emotional support	I've been getting emotional support from others.	2.60 (0.95)
Use of instrumental support	I've been getting help and advice from other people.	2.60 (1.04)
Positive reframing	I've been looking for something good in what is happening.	3.19 (0.71)
Acceptance	I've been learning to live with it.	3.16 (0.74)
Religion	I've been praying or meditating.	2.91 (1.09)
Humour	I've been making jokes about it.	1.90 (0.97)
Maladaptive coping		
Denial	I've been telling myself that "this isn't real".	1.89 (1.04)
Substance use	I've been using alcohol or drugs to make myself feel better.	1.23 (0.68)
Behavioural disengagement	I've been giving up trying to deal with it.	1.84 (1.01)
Self-distraction	I've been turning to work or other activities to take my mind off things.	2.45 (0.85)
Self-blame	I've been criticising myself.	1.91 (0.99)
Venting	I've been expressing my negative feelings.	2.14 (0.82)

SD: Standard deviation

*There were 2 sets of twins and their caregivers completed 2 questionnaires, 1 for each child.

that although caregivers recognised the need for educational and social opportunities for their children, many did not know how they can actively foster these developments (Table 4).

The focus group discussion highlighted that pressing problems faced by these families arose largely from the lack of money in the home, associated with issues in employability, parents' relationship difficulties and deep personal struggles. Other pervasive themes—maternal poor health, inaccessibility of childcare and infant care, big number of young children, thin social support networks—highlighted typical challenges that reduce caregivers' capacity and capability to provide adequate care.

Conclusion

Methodological limitations notwithstanding, the needs analysis provided a concrete picture of challenges and strengths pertinent to the health status of caregivers and their young children from extreme economically disadvantaged families. In particular, it highlighted that the caregivers' capacity to cope adaptively may be compromised by their state of mental health as these relate to the management of stress, depression and anxiety. This can be expected to have repercussions on the physical and mental well-being of the children as inferred from the caregivers' attention to the children's general medical and

Table 3. Scores Obtained on the Depression, Anxiety and Stress Scale (DASS) (n = 37)*

Range	Depression		Anxiety		Stress	
	Range of Scores	No. of Respondents	Range of Scores	No. of Respondents	Range of Scores	No. of Respondents
Normal	0 – 9	19	0 – 7	21	0 – 14	22
Mild	10 – 13	5	8 – 9	2	15 – 18	1
Moderate	14 – 20	4	10 – 14	3	19 – 25	9
Severe	21 – 27	6	15 – 19	3	26 – 33	2
Extremely severe	28+	3	20+	8	34+	3

*There were 2 sets of twins and their caregivers completed 2 questionnaires, 1 for each child.

Table 4. Percentage of Children Delayed in Development as Assessed with the Ages and Stages Questionnaire (ASQ) (n = 23)

Domains of Functioning	Children <36 Months (n = 17)		Children >36 Months (n = 16)	
	Mean Age = 23 Months		Mean Age = 50 Months	
	Delay by		Delay by	
	1 SD	2 SD	1 SD	2 SD
Communication	24%	29%	6%	44%
Gross motor	18%	6%	12.5%	0
Fine motor	24%	35%	0	0
Problem solving	24%	53%	19%	19%
Personal social	35%	24%	12.5%	12.5%

SD: Standard deviation

dental care. Certainly, their capacity to enact is severely constrained by their poor financial state which in turn restricts resource accessibility. More importantly, the children's delayed developmental outcomes raise urgent concerns with their school readiness in a couple of years' time. The findings suggest that interventions designed to support health-promoting behaviours and development of children should aim at strengthening the capability and capacity of their immediate support network that comprises primary caregivers who are themselves at risk and with the potentiality of impaired cognitive and decision-making ability.¹² Preventive programmes need to move beyond hospital-based approaches to interventions that are socially situated and delivered in the "least restrictive, more natural and more inclusive environment".^{1,2} Such models offer surveillance to ensure that essential child healthcare is provided early and foster greater caregiver collaboration. To be effective, the enabling force should emanate from a transdisciplinary framework in which medical and allied health professionals work to support caregivers hands-on with just-in-time knowledge and skills at critical junctures of the children's development.^{2,12-14}

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Acknowledgement

The authors would like to express their appreciation to Temasek Cares CLG Ltd for the funding of KIDS 0-3 programme and for the enabling support and assistance of KK Women's and Children's Hospital and AMKFSC Community Services Ltd.

A Biomechanical Study Comparing Cerclage Wiring Performed with a Power Tool versus the Manual Method

Kevin Koo, ¹MBBS, M.Med (Ortho), FRCS, Zhihong Zhou, ¹MD, B.Eng, Andy KS Yew, ¹PhD, Joyce SB Koh, ¹MBBS, FRCS, Tet Sen Howe, ¹MBBS, FRCS

Abstract

Introduction: We conducted a biomechanical study comparing cerclage wiring using a power tool with the traditional manual method. **Materials and Methods:** Our study consisted of 4 experimental arms based on the method of fixation and diameter of wires. The 4 arms were: 1) power tool method using 0.8 mm cerclage wires, 2) power tool method using 1.0 mm cerclage wires, 3) conventional manual method using 0.8 mm cerclage wires, and 4) conventional manual method using 1.0 mm cerclage wires. Synthetic femur bones were employed in our study. Six specimens were prepared for each arm. Each specimen was cut lengthwise and pressure sensors were placed in between. For the power tool method, while maintaining tension, wires were coiled using the Colibri power tool until just before secondary coiling occurred. For the conventional manual method, each specimen was compressed by plier twisting for 10 rounds, while maintaining tension. Cerclaging and data recording was done thrice for each specimen, giving a total of 18 readings per arm. Peak and steady-state forces were recorded. **Results:** There was no significant difference between the peak forces recorded between the power drill and manual methods. The steady-state forces achieved using the power tool method were significantly higher than that achieved in the manual fixation method (0.8 mm wires: 54.89N vs 27.26N, $P = 0.037$; 1.0 mm wires: 71.59N vs 39.66N, $P = 0.025$). **Conclusion:** The power tool method achieved a superior steady-state force of compression across the fracture site for both 0.8 mm and 1 mm wires.

Ann Acad Med Singapore 2015;44:554-7

Key words: Conventional method, Peak force, Periprosthetic, Steady-state force

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Introduction

Cerclage wiring is a valuable technique used widely in orthopaedic surgery to compress and secure bony or soft tissue elements. Its usefulness extends through the various specialties including trauma and fracture fixation, tumour surgery and arthroplasty (especially in revision total hip replacements).¹⁻⁶ Its indications/uses include primary fracture fixation either alone or in combination with other fixation devices (ie. plate, intra-medullary nail, pins, K-wires), provisional fixation, as a reduction tool, as a tension band, allograft fixation and compression, as well as compression arthrodesis.⁷ This technique represents a cheap, reliable and versatile method that can be used in various surgical situations, whether primarily or as an augment to other techniques.

By convention, tightening of cerclage wires is done

manually using wire gripping devices such as pliers, wire holding forceps, cerclage twistors or jet wire tighteners. These methods can be slow, cumbersome and can also be subjected to operator fatigue. Commercially available wire twistors can be expensive and not so easily available in the operating theatres. We describe a novel way of tightening cerclage wires using a power tool, and compared it to the conventional manual method in terms of tightening properties via a dry lab study involving synthetic sawbones, and propose this as a simple, inexpensive and readily available alternative to the usual manual technique.

Materials and Methods

Our study consisted of 4 experimental arms based on the method of fixation and diameter of wires as detailed in Figure 1. The 4 arms were: 1) power tool method using 0.8

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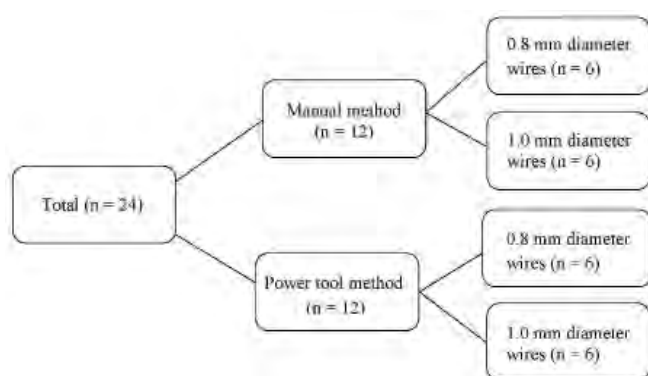


Fig. 1. Chart showing the four experimental arms.

mm cerclage wires, 2) power tool method using 1.0 mm cerclage wires, 3) conventional manual method using 0.8 mm cerclage wires, and 4) conventional manual method using 1.0 mm cerclage wires.

We included cerclage wires of different diameters to analyse if our method is consistently superior across different thickness of wires. Synthetic femur bones (Synbone® model number 2162) were employed in our study. Six specimens were prepared for each arm. Each specimen was cut into half lengthwise and pressure sensors were placed in between the fragments (Fig. 2). K-scan 4000, a piezoresistive contact pressure sensor system (Tekscan, South Boston, Massachusetts), with a standard pressure range of 62.1 MPa, and sensor density of 62 per cm², was used. Resistive pressure sensors have been reported to have higher accuracy and reproducibility than pressure sensitive film for contact pressure measurements.^{8,9} The pressure sensors were calibrated according to manufacturer specifications before each specimen testing.

For the power tool method, we used stainless steel wires 40 cm in length; 5 cm from each end of the wire was fed into the K-wire attachment and tightened. While maintaining tension, the wires were coiled using the power tool (Colibri Power tool, Synthes; speed up to 3200 rpm) until just before secondary coiling (Fig. 3) occurred. At this point, the fracture site does not undergo further compression even if trigger depression on the power tool is maintained. Excessive secondary coiling also weakens the wire construct and may cause the wires to break. Real time data recording was started prior to power drilling.

For the conventional manual method using a pair of pliers, we used wires 30 cm in length. Each specimen



Fig. 2. Each synthetic femur bone specimen was cut into half lengthwise and pressure sensors were placed in between the fragments. The fragments were subsequently compressed via cerclage wiring.

was compressed by plier twisting for 10 rounds, while maintaining tension. The plier-to-bone distance was maintained at 10 mm. Real time data recording was starting prior to pliers twisting.

For each specimen, we repeated the cerclaging and data recording steps thrice, each time with new wires. With 6 specimens in each arm, this gave a total of 18 readings for each arm. The peak force was taken to be the maximum force recorded. Data recording was allowed to continue after each individual wire was either removed from the power drill, or released from the pliers, and the steady-state force was taken to be the value at which the force-time graph reached a plateau. A sample graph of data recording is shown in Figure 4.

Statistical analysis was carried out using SPSS (11 version 11.0; SPSS, Chicago, Illinois). Mann-Whitney tests were carried out to compare peak forces and steady-state forces recorded between manual and power drill fixation, as well as between 0.8 mm and 1.0 mm diameter wires. $P < 0.05$ was taken to be statistically significant.

Results

The results of our study are detailed in Tables 1 and 2. Our results indicate that there was no significant difference between the peak forces recorded between the power drill and manual methods. Likewise, for each method of fixation, there was no significant difference between the peak forces between fixation using the 0.8 mm and 1.0 mm diameter wires.

For the steady-state forces, within each method of cerclaging (power drill and manual fixation), there was no



Fig. 3. Secondary coiling of wires.

significant difference between using 0.8 mm and 1.0 mm diameter wires. However, the steady-state forces achieved using the power tool method were significantly higher than the values achieved using manual fixation (54.89N vs 27.26N for 0.8 mm wires, 71.59N vs 39.66N for 1 mm wires). This difference is statistically significant, $P = 0.037$ and 0.025 respectively.

Discussion

Dry lab testing with synthetic saw bones showed that the power tool method achieved a greater steady-state force of compression across the fracture site for both 0.8 mm and 1 mm cerclage wires. The steady-state force, compared to the peak force, represents the amount of compression across the fracture site once the cerclage procedure is completed, and is the more clinically relevant reading of the 2.

The lack of significant difference in the peak and steady-state forces between the 2 diameters of cerclage wires suggests that the method of cerclaging is the key variable

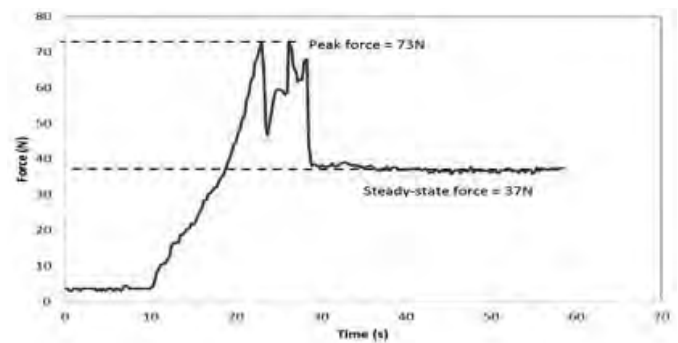


Fig. 4. Sample graph depicting the peak and steady forces recording with each sample.

responsible for the amount of compression across the fracture site. This is in contrast to what Bostrum et al¹⁰ found where increasing the diameter of the wire by 50% resulted in a load-to-failure of up to 169% and doubling the wire diameter from 0.45 to 0.98 mm increased the load-to-failure more than 300%. This disparity in findings could be due to the fact that we only used 2 different diameters in our study, and an increase of 0.2 mm in diameter represents only a 25% increase. To further study the effect of size of cerclage wires on pressure across fracture site, more sizes of wires could be used in a future similar study. Other factors such as knot configuration¹¹ and number of loops¹² also affects fixation strength but this was beyond the scope of our study, whose primary aim was to compare 2 different methods of tightening.

Lenz et al¹³ explored the contact distribution of cerclage cables and wires at the circumferential cerclage-bone interface with a ex-vivo set-up similar to ours. They found that although cables cover larger contact areas, both cerclages exhibited an inhomogenous interface pressure distribution depending on bone surface geometry. Histology revealed intact cortical bone after loading with both cerclage types. They thus concluded that cerclage-bone interface contact is dependent on surface geometry of the bone, cerclages provide a blood supply preserving point contact

Table 1. Peak Force (N)

Wire Diameter (mm)	Power Drill	Manual	
0.8 mm	79.52 +/- 32.32	55.91 +/- 9.91	$P = 0.337$
1.0 mm	105.48 +/- 13.77	79.98 +/- 28.08	$P = 0.109$
	$P = 0.109$	$P = 0.337$	

Note: No significant differences between the methods or cerclage wire diameters used.

Table 2. Steady-state Force (N)

Wire Diameter (mm)	Power Drill	Manual	
0.8 mm	54.89 +/- 23.81	27.26 +/- 6.72	$P = 0.037^*$
1.0 mm	71.59 +/- 14.00	39.66 +/- 22.36	$P = 0.025^*$
	$P = 0.262$	$P = 0.522$	

*Statistically significant

Note: The power drilling method produced significantly higher steady-state forces than the manual method for both diameters of cerclage wires used. No significant difference between the cerclage wire diameters used.

fixation, and that cortical damage and resorption is due to micromotion rather than the centripetal forces of the loaded cerclage. Our study, which explores the pressure effects of 2 different methods of cerclage wiring in a similar ex-vivo set-up, adds to the existing biomechanical knowledge on cerclage wiring.

Frisch et al¹⁴ explored the biomechanical response of different cerclage systems for fixation of periprosthetic femur fractures on synthetic femurs and found that cobalt-chrome cables and hose clamp had the highest construct stiffness and least reduction in stiffness with increased loading in an ex-vivo study that also included monofilament wires and synthetic cables. However, for the purpose of our study using the power tool method, cables would have been too large to fit into the opening of the power tool. Wires are also the most commonly available option in any standard orthopaedic set and thus was used in our study.

The power tool cerclage wiring technique is relatively simple to perform and offers an effective method of tightening multiple cerclage wires at a single setting. This method can be considered as a viable alternative to the conventional method of cerclage tightening, which is time consuming, and subject to operator fatigue. Although there are various commercially available cable tighteners and crimpers, the power tool method utilises instruments readily available in any standard orthopaedic fracture fixation set. In addition, the conventional manual method of cerclaging requires a larger working space because the pliers need to be close to the fracture site to achieve adequate compression. On the other hand, in fractures where access might be impeded by surrounding soft tissue, the power tool method allows compression to be carried out in a tight working space.

The limitations of our study includes the fact that this is an in vitro study which investigates the mechanical forces across the fracture site and does not characterise the biological healing as observed in an in vivo study. In addition, this study measures the compressive forces at the time of fixation, and not the long-term compressive force. However, even in an in vivo model, measurement of long-term compressive forces can be difficult to achieve. Also, there is more working space in our experiments as compared to a surgical setting where working space is limited by soft tissues. However, we have ensured that both types of cerclaging are carried out under the same experimental settings.

Conclusion

The power tool cerclage wiring technique has demonstrated a superior steady-state compressive force across a fracture site in synthetic bone in a dry laboratory setting. This is

consistent across 2 common cerclage wire diameters. The findings from our study can be used as a primer in future cerclage wiring studies using a power tool in an actual clinical setting, and clinical outcomes can be recorded to demonstrate that this method is not inferior and may be more efficient and effective than the conventional method.

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Artificial Hydration at the End of Life – Treating the Patient, Family or Physician?

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The debate surrounding the provision of artificial hydration at the end of life continues to provoke impassioned arguments on both sides of this position, particularly in light of a lack of conclusive evidence for either position. The situation is further complicated by variances in practice locally as well as globally, which is both physician- and setting-dependent, individualised to the patient and family caregivers.

Ethical and Legal Aspects

At the root of this debate is a difference of opinion whether artificial hydration ought to be considered part of basic care or be seen as a medical intervention. Up to 38% of patients and caregivers from a study in United States perceived artificial hydration at the end of life as “food”, 34% as “medicine” and 14% as “both food and medicine”. Patients and caregivers from ethnic minorities perceived it more as food than medicine.¹

By classifying the issue of hydration and nutrition at the end of life under the realm of palliative care and giving the healthcare team discretion to balance the clinical and overall context on a case-specific basis, Singapore’s Advanced Medical Directive Act² circumnavigates much of this debate.

If artificial hydration is indeed considered a medical intervention, which is the current legal perspective, it ought to be prescribed by a physician after consideration of its indications, contraindications, potential benefits and side effects. The patient’s autonomy also allows him to decline this intervention, even if offered, and there is no difference between withholding or withdrawal of it from moral, ethical and most religious viewpoints.

Clinical Aspects

Feeding and hydrating the dying and vulnerable is held to be a sign of love and concern in local culture, and also a means of possibly prolonging life and alleviating symptoms.

Thus it is instinctive to many that hydration, be it artificial or natural, be continued, yet such practice may not fully consider the realities of end-of-life care.

Proponents of artificial hydration argue that it provides comfort and relieve symptoms such as thirst, confusion and neuromuscular irritability. They suggest that it maintains health and therefore may potentially shorten life if withheld or withdrawn. It is thus a part of the most basic of care requirements and an irrefutable human right. It is a measure of hope and means of maintaining familial ties and bonds with healthcare providers. From such a perspective, to deny such an intervention would be tantamount to abandonment.^{3,4}

Opponents of hydration deny that a failure to hydrate would hasten death,⁵ to them overhydration rather than dehydration is ultimately bad for the patient. Dehydration is a natural process in dying as patients’ oral intake decrease. With dehydration there is decreased urine output and with that, less need for catheters, less gastrointestinal secretions, with less vomiting, less pulmonary secretions and chest congestion. Ketones and other metabolic byproducts in dehydration may act as natural anesthetics for the central nervous system, resulting in decreased consciousness, and with that decreased suffering.⁴ If patients are conscious and experience thirst, artificial hydration does not alleviate thirst anymore than local oral measures.⁶ Provision of hydration is also viewed as a perpetuation of unrealistic expectations of cure which run counter to goals of care at this stage of life which ought to be focused on completing important life tasks, nurturing relationships rather than hydration regimens.

We now know that artificial hydration does not prolong life in patients with advanced cancer at the end of life, with prognosis of days to short weeks.^{5,7} It has no correlation with thirst⁸ and does not relieve dehydration symptoms like sedation, fatigue, myoclonus and hallucinations.⁵ On the other hand, concerns about fluid overload symptoms with hydration also seem unwarranted as less than 1 litre per day seems well tolerated by most patients.

Yet, before we are tempted to be led solely by this data,

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sociocultural factors that play just as significant a part in the provision of holistic care, cannot be ignored.

Local Practice

Despite low clinical utility, patients and their family still see artificial hydration as providing hope and comfort, nourishing the body, mind and spirit.⁹ They deem this an important issue and want to be involved in the discussion of its benefits and burden. Even though most patients would be willing to be guided by doctors and many would be happy for their doctors to make the final decision, this decision to cease hydration remains emotive and context-sensitive.¹⁰

Most terminally ill patients cared for at home or at inpatient hospices rarely receive artificial hydration and nutrition, yet within the acute hospital setting, up to 60% of terminally ill Singaporeans received artificial hydration in the last 48 hours of life.¹¹ This difference in practice may be accounted for by beliefs of the physician-in-charge, the relative ease of organising artificial hydration in hospital and difficulty of prognostication in hospital where life prolonging interventions are ongoing. Family members who have decided to send their loved ones to the acute hospital may also be those who desire more active medical interventions and thus likely to be more distressed without artificial hydration.

Navigating the Course

As a patient-centred approach is key to addressing such difficult decisions, it will be helpful to explore patient's and family's understanding about artificial hydration and their philosophical position on end of life care when the patient can still participate in decision-making.¹⁰ Exploration of their goals during this phase of life and discussion on the limited benefits as well as potential burdens of this intervention will be seen as guidance by their healthcare providers. Most patients and families are appreciative of this and consider it a critical facet in their determinative process.

If decision is to withhold or withdraw artificial hydration, assuring families that care will still be taken that patient remains comfortable and teaching them how to demonstrate care via other nurturing activities is often sufficient to allay their concerns. If the medical opinion is to withhold artificial hydration but patient or family is distressed by this, it is reasonable to start a time-limited trial as long as there are no contraindications like fluid overload states or oedema. This involves delineating goals of the trial, setting a date for review and specifying criteria for discontinuation. In the event of a decision for artificial hydration and patient is to be cared for in the community, it will be prudent to hold a discussion with the home or inpatient hospice team on the reasons and feasibility of this decision. This will ensure a

smooth transition of care from one setting to the next. The most challenging setting to provide artificial hydration is at home. In the local context, where most carers are family members or foreign live-in helpers rather than nurses, training of carers to be confident with administration of artificial hydration and ongoing support from the home hospice team is needed to ensure success of the intervention. Hypodermoclysis, which is the subcutaneous infusion of fluids, is the preferred route at home, compared to intravenous infusion. This route reduces technical expertise needed from carers to care for injection sites as well as to monitor and adjust flow rates.

Conclusion

The use of artificial hydration at the end of life should be a case-specific decision-making process led by a holistic review of the patient's condition. Decision to cease, withhold or start such an intervention should be delineated by clinical considerations, with appropriate consideration of the patient's and family's overarching goals of care, beliefs, culture and values.

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Severe Cutaneous Adverse Reactions Following Intravenous Contrast: A Report of 2 Cases¹

Dear Editor,

With the advent of computer tomography (CT) imaging and cardiac catheterisation procedures, radiologic investigations employing the use of iodinated contrast media have experienced rapid growth in the last 20 years, with increasing numbers of patients receiving contrast.¹

Most contrast-related adverse events (AE) are mild, including nausea, vomiting and urticaria. However, some are severe, resulting in renal impairment, shock and cardiac arrest. Of the severe cutaneous AEs, there are immediate reactions such as anaphylaxis, as well as delayed reactions such as maculopapular exanthems, drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

The use of high-osmolar contrast media (HOCM), which was prevalent from 1985 onwards, gave way to the safer low-osmolar contrast media (LOCM) in the early 1990s. This has led to a fall in the incidence of AEs attributed to contrast media from 6% to 8% to 0.2% to 0.7% as described by Cochran et al² in 2001.

Nevertheless, severe and delayed dermatologic manifestations can still result from contrasted scans. We report 2 patients who suffered from SJS/TEN overlap after receiving iodinated contrast.

Case 1

A 61-year-old Malay female was admitted for an acute ST-elevation myocardial infarction (STEMI). Her past medical history was significant for hypertension, hyperlipidaemia, type 2 diabetes mellitus complicated by end-stage renal failure and ischaemic heart disease. She underwent coronary artery bypass graft surgery (CABG), which was complicated by pericardial tamponade, sternal wound dehiscence and multiple hospital-acquired infections (HAIs). She also had a history of urticaria secondary to amlodipine 2 years ago; this suspected drug allergy was not formally evaluated.

During her inpatient stay, she received a total of 3 CT scans with intravenous contrast (Omnipaque) administration.

The first scan performed on 12 November 2013 was uneventful. Two weeks later, a second scan was performed. Two weeks thereafter, she complained of generalised pruritus. An inpatient dermatology referral was then made by the primary team. The initial assessment was widespread xerotic eczema. Moisturisers and topical corticosteroids were prescribed.

Over the next 5 days, from 13 to 17 December 2013, a dusky reticulate erythema assumed prominence over her dry scaly erythematous plaques, and it rapidly spread over her face, trunk, and limbs. Nikolsky's sign was positive in lesional and perilesional skin. Body surface area (BSA) involvement was 5% sparing the mucosal surfaces. At this juncture, SCORTEN was 1 in view of her age.

A skin biopsy revealed almost a complete separation of necrotic epidermis from the underlying dermis, associated with perivascular and interstitial lymphocytic infiltrate and scattered apoptotic bodies.

Three new medications (cefazolin, linagliptin and metoclopramide) had been started 3 weeks prior to the onset of her symptoms. Cefazolin was given from 29 October to 18 November 2013; metochlorpromide and linagliptin were each given as single doses on 22 November. They were deemed possible inciting agents of a suspected severe cutaneous drug reaction and were discontinued. She was started on oral prednisolone at 0.5 mg/kg/day on 18 December.

On the same day, she underwent a third CT scan with intravenous contrast in an attempt to investigate the source of persistent sepsis.

The next day after the third episode of contrast administration, the patient reported skin pain and painful swallowing. Clinical examination revealed increased skin denudation and erosions over the upper back, face, trunk and limbs. Detached BSA was 16%. There was conjunctival injection and haemorrhagic crusting of her lips (Figs. 1 and 2). Her diagnosis was revised to SJS/TEN overlap and intravenous immunoglobulin (IVIG) infusion was commenced at 1 g/kg/day for 2 days. Intravenous contrast was implicated as the most likely culprit agent.



Fig 1. An increasingly dusky reticulate erythema seen over the extensor surfaces of the lower limbs.



Fig 2. Skin denudation and erosions over the upper chest and face.

She did not have clinical evidence to suggest other organ involvement. Transaminases were normal with an alanine aminotransferase (ALT) of 29 U/L and an aspartate transaminase (AST) of 6 U/L. Eosinophils were elevated at $1.49 \times 10^9/L$. Her creatinine was elevated at 466 $\mu\text{mol/L}$ consistent with her background of end-stage renal failure.

After 1 day of IVIG, she succumbed to severe sepsis without re-epithelialisation.

Case 2

A 60-year-old Malay male with end-stage renal failure from poorly controlled hypertension had an ascending aortic aneurysm requiring yearly CT aortograms for the past 4 years prior to presentation. He had no previous history of drug allergies.

He was admitted on 29 November 2013, after receiving intravenous contrast (Iopaque) during a routine imaging scan 3 days earlier. This was his fourth CT aortogram. There was no exposure to new medications.

He complained of a 2-day history of fever, painful lips, multiple episodes of diarrhoea, and increasingly painful skin.

Clinical examination revealed dusky erythematous patches over the arms, neck, upper back, thighs and calves.

There were multiple flaccid bullae seen over the upper outer arms and thighs. Nikolsky's sign was positive with exquisite cutaneous tenderness. Detached BSA was 11%. Haemorrhagic crusts were seen on the lips. SCORTEN was 4 in view of the patient's age, urea of 37 mmol/L , bicarbonate of 37 mEq/L and BSA.

A diagnosis of SJS/TEN overlap was made and he was commenced on intravenous immunoglobulin at 1 g/kg/day for 3 days. Skin biopsy revealed a completely necrotic epidermis lifted off the dermis, with mild oedema and a sparse lymphocytic.

There was no clinical evidence of other organ involvement. Transaminases were normal with an ALT of 48 U/L and AST of 41 U/L. Eosinophils were $0.61 \times 10^9/L$. His creatinine was elevated at 1251 $\mu\text{mol/L}$ consistent with his background of end-stage renal failure.

Though the detached BSA eventually extended to 18%, he recovered with complete re-epithelialisation by day 12 of admission and was discharged.

Discussion

The use of contrast media has become increasingly commonplace with radiological procedures used for both

diagnostic and therapeutic purposes. In the last 20 years, the use of CT scans has increased by 8 times.³ It is important that physicians remain cognisant of the inherent risks of contrast media.

Immediate reactions include anaphylactoid reactions which occur unpredictably and independently of the dose or concentration of the agent without an identifiable antigen-antibody response.^{4,5} Common risk factors for these reactions include patients who have had a previous anaphylactoid event to contrast media, atopic individuals with multiple allergies, and asthmatics.⁵ Physicians are most watchful for these immediate contrast-related reactions; the inciting agent is usually appropriately identified and intervention is administered. On the other hand, delayed allergic-like events are defined by the The American College of Radiology as those that occur between 3 hours to days after administration of contrast.⁶ Severe cutaneous adverse reactions (SCARs) such as DRESS, SJS and TEN fall under this category of reactions.⁷

The longer latency period for the development of SCARS^{8,9} translates to a lower likelihood that the managing physician connects the adverse cutaneous reaction to contrast administration. In fact, by this time, many physicians may not even consider contrast as a possible inciting agent. New drugs may have been administered in the intervening time frame which complicates an aetiological search. Complex medical patients with a septic picture may even be subjected to further contrasted scans. This was evident in our first case, where repeated contrasted scans were done, resulting in worsening of her skin condition.

Interestingly, there are striking similarities in both our patients who suffered from a SJS/TEN overlap following the use of contrast media. Both were of Malay ethnicity and suffered from end-stage renal disease. The contrast medium used in both cases was iohexol, a LOCM with an osmolality of 322 mOsm/kg.

Pre-existing renal disease is an established risk factor for physiological chemotoxic reactions to contrast media due to specific physicochemical effects of the contrast agent which leads to renal-specific effects such as renovascular constriction, decreased blood flow, and alteration in glomerular permeability.⁴ However, it is unclear if this is associated with an increased risk of cutaneous adverse effects. We postulate that in our 2 cases, the delayed renal clearance of the contrasted medium might have played a role in the development and severity of the SCARs. The elimination half-life of iodinated contrast increases progressively with renal impairment, and it is with dialysis that the contrast is removed. Approximately 58% of a 50 mL dose administered will be removed after a single dialysis session.¹⁰

It is also known that genetic factors influence an

individual's susceptibility to develop SCARs. There is a strong association of allopurinol-related SCARs with the *HLA-B*5801* allele¹¹ in Han Chinese populations as well as carbamazepine-induced SJS with the *HLA-B*1502* allele that are found in Indians.¹² Similarly, it is possible that ethnic and thus, genetic factors play a role in the development of SCARs with contrast media as both of these patients were of Malay ethnicity. Further studies are needed to elucidate the possibility of pharmacogenetic influence on the development of SCARs with contrast media.

Conclusion

Whilst delayed and severe cutaneous reactions such as SJS and TEN due to LOCM may be uncommon, they do indeed occur. A high index of suspicion is required to accurately identify and cease the culprit agent, and thereby reduce morbidity and mortality.

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Killed by Internet Addiction? A Real Possibility

Dear Editor,

The article entitled, 'Internet Addiction in Young People' published in *Annals*¹ referred to a conference paper² on cardiopulmonary-related deaths among the most severe cases of internet addiction. Fatal pulmonary thromboembolism plays a role in a number of these cases. Compared to the more widely known 'economy class syndrome' secondary to long flights, there is scarcity of published data and fewer clinicians recognise the potential risk of fatal pulmonary thromboembolism resulting from excessive computer usage.

The association between prolonged sitting and venous thromboembolism (VTE) was first reported during the London Blitz in World War 2 when cases of fatal pulmonary thromboembolism emerged among those who sat for prolonged periods in deck chairs while taking refuge in air raid shelters. In 1954, Homans published evidence of VTE associated with prolonged sitting in various situations including air travel, automobile trips and even attendance at the theatre.³

'e-Thrombosis' was the term proposed for VTE occurring from prolonged computer use in the first case report by Beasley et al in 2003,⁴ which described a 32-year-old man who suffered a life threatening pulmonary thromboembolism. His only risk factor was regularly working 12 hours per day at his computer. The same author coined the term 'seated immobility thromboembolism' (SIT) syndrome to encompass all situations of prolonged sitting that contribute a risk for VTE, such as long distance travel by air, car or train, work- and recreation- related immobility.

Another report described a 24-year-old unemployed Korean who died from pulmonary thromboembolism after continuously playing a computer game for 4 days with minimal sleep.⁵ More recently a case-control study demonstrated a 2.8-fold increased risk of VTE associated with prolonged work- and computer-related seated immobility, which was defined as sitting for at least 10 hours over 24 hours and 2 hours seated at any time without getting up.⁶

In Singapore, a 16-year-old Chinese student addicted to computer gaming (>13 hours/day in the recent period prior to his first presentation), with no predisposing factors for VTE and no prior family history of thrombotic

diseases, developed deep vein thrombosis (DVT) and massive pulmonary embolism (PE), for which he received thrombolysis and 6 months of anticoagulation treatment. A thrombophilia screen was done including antinuclear antibodies, anti-double-stranded DNA, lupus anticoagulant and cardiolipin antibodies which were negative. Protein C, protein S and anti-thrombin 3 levels were normal. Six months later, he developed a recurrent DVT and life threatening PE (Fig.1). The patient underwent thrombolysis, but developed massive haemoptysis and cardiovascular collapse midway, necessitating resuscitation and emergency surgical pulmonary embolectomy. He subsequently had an inferior vena cava (IVC) filter insertion in addition to anticoagulation treatment. The patient was advised by the primary physician to avoid prolonged immobility, although no formal assessment or intervention by a professional counsellor or psychiatrist was made. Anticoagulation was continued for 2 years and was stopped after repeated screen for antinuclear antibodies, anti-double-stranded DNA, lupus anticoagulant and cardiolipin antibodies was negative, and the lower limb duplex and computed tomography scans showed no evidence of VTE. The IVC filter was left in situ. Unfortunately, he suffered a fatal episode of massive PE 9 months later. This illustrates how successful treatment of a medical condition but persistence of the underlying problem, gaming addiction, as a case in point, could result in a devastating outcome.

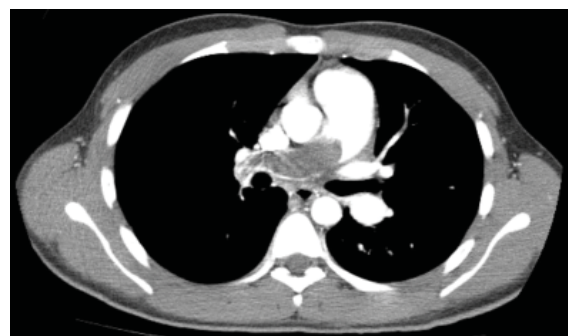


Fig. 1. CT pulmonary angiogram showing large embolus in the right main pulmonary artery.

In conclusion, although internet addiction is largely perceived as a psychosocial problem, more attention should be given to address its detrimental and fatal effect on physical health in young healthy individuals. It is expectant that younger lives including children and teenagers may not be spared as electronic gadget and computer exposure is introduced early both at home and in school. Recognising this is the first step to the development of long-term preventive measures such as education to raise public awareness of the SIT syndrome and increasing accessibility to counselling services for the high-risk population. Given the evidence, future studies may be considered to evaluate the role of lower limb duplex screening in selected cases of severe internet addiction. In subjects engaging in excessive video or computer cyberspace activity, consequently the risk of e-Thrombosis leading to e-Pulmonary embolism (e-PE) increases exponentially when addiction is established. In those with e-Thrombosis, there may be an indication to maintain indefinite anticoagulation till the addiction is completely treated with absolute certainty.

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Costs of Patients Admitted for Diabetic Foot Problems

Dear Editor,

Singapore has a high prevalence of diabetes, with 12.4% of the adult population living with diabetes in 2013. Up to 1 in 6 diabetic patients develop diabetic foot problems¹ and these are estimated to account for 15% to 25% of healthcare costs for treating diabetes.² At present the costs of treating diabetic foot problems in Singapore are not known. Our study aims to evaluate the costs of inpatient treatment of diabetic foot problems.

Materials and Methods

This is a retrospective study of 214 patients admitted to the Department of Orthopaedic Surgery, National University Hospital (NUH) for a diabetic foot problem, from January 2011 to December 2011. We defined a diabetic foot problem as a foot wound, infection, arthropathy or deformity due to underlying diabetes mellitus. Patient data based on clinical records was documented based on a predesigned study protocol. Financial records were obtained from hospital financial records. Data was recorded by the co-authors of this paper.

Patient data documented included demographic data, clinical data, and treatment received. Clinical data included presence of complications of diabetes including retinopathy, nephropathy, and peripheral vascular disease (PVD); and comorbidities such as ischaemic heart disease (IHD), hypertension, hyperlipidaemia, critical limb ischaemia and end-stage renal failure. We defined critical limb ischaemia as an arterial brachial index (ABI) less than 0.4 and peripheral vascular disease as an ABI less than 0.9.

Treatment received included conservative treatment, minor surgery, minor amputation and major amputation. Conservative treatment consisted of antibiotics, podiatric interventions and dressings. Minor surgery included incision and drainage, debridement and skin grafting. Minor amputations included all amputations at and below the level of the ankle joint. Major amputations referred to amputations above the ankle joint. Other factors studied included stay in high dependency/intensive care units (ICUs), dialysis treatment and readmissions. Total duration of hospital stay was also recorded.

Cost components studied included the total cost of inpatient treatment (total cost), ward and high dependency/ICU charges (cost of hospital stay), costs of surgery, costs

of antibiotics, costs of dressings, cost of investigations and cost of allied healthcare (podiatry, physiotherapy and occupational therapy). These costs in Singapore dollars SGD (\$) were calculated based on the total hospital bill from January to December 2011.

Statistical Analysis

All statistical analyses were performed using SPSS 18.0 with statistical significance set at $P < 0.05$. Predictive factors for high cost were determined using univariate and stepwise logistic regression analysis. Mann-Whitney U test was used for numerical prognostic factors, and chi-square test was used for categorical factors.

Results

Patient Profile

In our cohort of patients, the mean age was 60.5 years with an age range between 20 to 92 years. There was an equal gender distribution of patients and the racial distribution in our study was 41.1% Chinese, 44.9% Malay and 14% Indian. There was a high rate of critical limb ischaemia, 50.5% (108) patients and other associated comorbidities.

Hospital Stay

The mean length of hospital stay was 24 days, with non-operatively treated and operatively treated patients having a mean stay of 8 and 30 days respectively. Patients undergoing major amputations had a mean length of hospital stay of 53 days, 6.5 times that of non-operatively treated patients, which was statistically significant $P < 0.05$.

Type of Treatment

In this study, 25.5% (54) of patients were conservatively managed, 28% (60) had minor surgery, 22.9% (49) had minor amputations and 51 (23.8%) had major amputations. There was a high rate of multiple admissions and high dependency/ICU stay in this cohort of patients, 32.7% (70) and 34.1% (73) respectively.

Analysis of Predictive Factors

Table 1 shows the various factors studied as potential predictive factors for high cost (cost >SGD (\$) 5000)

Table 1. Results of Evaluation of Predictive Factors

Predictive Factors	Value (%)	Univariate Analysis	Multivariate Analysis
Demographics			
Age			
>60	116 (54.21%)	P = 0.03	P = 0.723
<60	98 (45.79%)		
Gender			
Male	113 (52.8%)	P = 0.721	-
Female	101 (47.2%)		
Race			
Chinese	88 (41.12%)	P = 0.242	-
Malay	96 (44.86%)		
Indian	30 (14.02%)		
Comorbidities			
Hypertension			
Yes	183 (85.51%)	P = 0.001	P = 0.615
No	31 (14.49%)		
Hyperlipidaemia			
Yes	159 (74.3%)	P = 0.004	P = 0.305
No	55 (25.7%)		
Ischaemic heart disease			
Yes	83 (38.76%)	P <0.001	P = 0.482
No	131 (61.24%)		
Cerebrovascular disease			
Yes	38 (17.76%)	P = 0.01	P = 0.412
No	174 (81.24%)		
Peripheral vascular disease			
Yes	128 (59.81%)	P <0.001	P = 0.687
No	86 (40.19%)		
Critical limb ischaemia			
Yes	108 (50.47%)	P <0.01	P = 0.033
No	106 (49.53%)		
Nephropathy			
Yes	114 (53.27%)	P = 0.092	P = 0.728
No	100 (46.73%)		
End stage renal failure			
Yes	57 (26.64%)	P = 0.044	P = 0.198
No	154 (73.36%)		
Treatment			
Non-major amputation		P <0.001	P = 0.01
• Conservative	54 (25.23%)		
• Minor surgery	60 (28.04%)		
• Minor amputation	49 (22.9%)		
Major amputation			
		51 (23.83%)	
Treatment factors			
Multiple admissions	70 (32.71%)	P <0.01	P = 0.01
High dependency/intensive care unit stay	73(34.11%)	P <0.001	P <0.001
Dialysis	40 (18.69%)	P <0.03	P = 0.528
Non-compliance/refusal of surgery	38 (17.76%)	P = 0.01	P = 0.028

Note: Predictive factors for high cost were determined using univariate and stepwise logistic regression analysis. Mann-Whitney U test was used for numerical prognostic factors, and chi-square test was used for categorical factors.

Table 2. Total Cost of Each Cost Component for Each Type of Treatment Per Year

Type of Treatment	Cost of Hospital stay SGD (\$)	Cost of Dressings SGD (\$)	Cost of Antibiotics SGD (\$)	Cost of Investigations SGD (\$)	Cost of Surgery SGD (\$)	Cost of Dialysis SGD (\$)	Cost of Allied Healthcare SGD (\$)	Total Cost SGD (\$)
Conservative	\$30,634.96	\$7,423.74	\$10,562.36	\$20,145.61	NA	\$1244.83	\$1707.98	\$71,719.48
Minor surgery	\$75,372.62	\$39,685.92	\$32,315.83	\$42,494.38	\$28,677.84	\$2389.00	\$5220.79	\$226,156.38
Minor amputation	\$79,629.67	\$68,836.65	\$43,413.46	\$29,842.82	\$19,662.75	\$5090.97	\$7580.17	\$254,056.49
Major amputation	\$196,128.03	\$48,316.28	\$72,447.25	\$63,704.51	\$60,829.93	\$31,522.57	\$21,506.85	\$494,455.43
All patients	\$381,765.28	\$164,262.59	\$158,738.90	\$156,187.32	\$109,170.52	\$40,247.37	\$36,015.80	\$1,046,387.78

NA: Not applicable

and the result of our analysis. On multivariate analysis, only critical limb ischaemia, major amputation, multiple admissions and high dependency/ICU stay were found to be significant predictive factors ($P < 0.05$).

Cost

Table 2 shows the total cost in SGD (\$) of each cost component for each type of treatment. The total cost of treatment was SGD (\$) 1,046,387.80. In this cohort, patients undergoing major amputation accounted for nearly half of the total cost, SGD (\$) 494,455.40. The cost of hospital stay was the largest cost component with 35.9% (SGD (\$) 381,765.30) of the total cost spent on hospital stay costs.

Table 3 shows the mean cost of each cost component for each type of treatment. The mean cost of treatment was SGD (\$) 4907.30 per patient. Patients undergoing major amputations had the highest mean hospital stay cost of SGD (\$) 3845.70 per patient, which was 6.8 times that of non-operative patients. Patients undergoing major amputation also had the highest mean cost of antibiotics, investigations and surgical costs.

Discussion

The care for patients with diabetic foot problems is an increasingly heavy economic burden. Diabetic foot patients are estimated to have a healthcare expenditure 3 times that of the general population, with hospitalisations costs accounting for 73% of increased cost.³ Our study attempts to evaluate the cost of inpatient treatment of patients with diabetic foot problems in our institution and the contributing factors to higher cost of treatment.

The largest cost component was that of hospital stay, SGD (\$) 381,765.30, which was 36.5% of total cost of treatment. These findings are similar to other studies which show that the major cost in treating diabetic foot ulcers is inpatient care, accounting for 74 to 84 percent of total costs.^{4,5}

In our study, the following factors were found to be associated with higher cost of treatment: critical limb ischaemia, major amputation, multiple admissions and high dependency/ICU stay. Critical limb ischaemia is a risk factor for higher costs due to higher rates of amputation, postoperative complications, revisions, and length of hospitalisation.⁶⁻⁸ Patients undergoing major amputation had

Table 3. Mean Cost of Each Cost Component for Each Type of Treatment Per Year

Type of Treatment	Mean Cost of Hospital Stay SGD (\$)	Mean Cost of Dressings SGD (\$)	Mean Cost of Antibiotics SGD (\$)	Mean Cost of Investigations SGD (\$)	Mean Cost of Surgery SGD (\$)	Mean Cost of Dialysis SGD (\$)	Mean Cost of Allied Healthcare SGD (\$)	Mean Total Cost SGD (\$)
Conservative	\$567.31	\$140.07	\$195.60	\$373.07	NA	\$23.05	\$31.63	\$1328.14
Minor surgery	\$1277.50	\$672.64	\$547.73	\$720.24	\$486.07	\$40.49	\$88.49	\$3833.16
Minor amputation	\$1615.26	\$1404.83	\$883.93	\$601.59	\$397.57	\$103.90	\$154.41	\$5161.49
Major amputation	\$3845.65	\$947.38	\$1448.95	\$1249.11	\$1192.74	\$618.09	\$421.71	\$9695.20
All patients	\$1790.06	\$771.19	\$1265.82	\$731.56	\$511.68	\$188.96	\$169.02	\$4907.25

NA: Not applicable

a total cost of treatment 7.3 times that of non-operatively treated patients. This could be accounted for by major amputation patients having longer hospital stays, increased requirement for high dependency/ICU care and multiple readmissions.

Prior to the formation of the NUH multidisciplinary team for diabetic foot problems, the mean total cost of treatment per patient in 2002 was SGD (\$)8847.20.⁹ This has decreased to SGD (\$)4907.30 per patient, a decrease of nearly 50%. A coordinated outpatient and inpatient multidisciplinary approach is needed to manage these patients and prevent hospital admissions and major amputation. When such an approach is used, an estimated 45% to 85% of all amputations can be prevented.¹⁰⁻¹³

Limitations

This was a retrospective study with possible selection bias as patients not treated by the multidisciplinary team were not studied. This study also only used total hospital bills and did not take into account the effect of government subsidies.

Conclusion

This study demonstrates the high cost of treating diabetic foot problems in the inpatient setting, with costs of hospital stay being the largest cost component. Critical limb ischaemia, major amputation, multiple admissions and high dependency/ICU stay were found to be risk factors for high cost of treatment. A multidisciplinary approach to treatment of diabetic foot problems is needed to reduce costs and major amputation rates.

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Potential for Cefazolin as De-escalation Therapy for *Klebsiella Pneumoniae* Bacteraemia

Dear Editor,

Klebsiella pneumoniae causes the syndrome of liver abscess, meningitis and endophthalmitis associated with capsular serotype K1/K2, mucoid phenotype and aerobactin production as virulence factors.¹ Overall mortality from *Klebsiella pneumoniae* bacteraemia ranged from 19% to 55%.²

Chromosomally mediated SHV-1 beta-lactamase in *K. pneumoniae* could inactivate cefazolin in an inoculum-dependent manner.³ Cefotaxime and ceftriaxone were superior to cefazolin in murine pneumonia.⁴ A Taiwanese study comparing cefazolin with extended-spectrum cephalosporins in *K. pneumoniae* found more metastatic complications in the cefazolin group.⁵ However, cefazolin was superior to ceftazidime in bactericidal activity in vitro against *Escherichia coli* and *K. pneumoniae*.⁶ In *K. pneumoniae* bacteraemia, mortality with monotherapy with first-generation cephalosporin was 6%, second-generation 11% and third-generation 19%.² Narrow-spectrum cephalosporin was used effectively for *K. pneumoniae* liver abscess in Taiwan.⁷

In this retrospective study, we evaluated the clinical efficacy of culture-guided de-escalation to cefazolin 2 g 8-hourly, compared the clinical and microbiological outcome of culture-guided use of cefazolin versus ceftriaxone, and determined independent risk factors for 30-day mortality in patients with *K. pneumoniae* bacteraemia.

From 1 January 2008 to 31 December 2008, *K. pneumoniae* bacteraemia at Tan Tock Seng Hospital (TTSH), a 1400-bed university teaching hospital in Singapore, which was extended-spectrum beta-lactamase (ESBL)-negative on modified double disc synergy test (Becton-Dickinson, Sparks, Maryland, USA) and sensitive to ceftriaxone and ceftazidime was studied. Antimicrobial susceptibility was performed by disc diffusion per Clinical and Laboratory Standards Institute (CLSI) criteria. Ethics approval was granted.

Age, gender, comorbidities and Charlson's comorbidity score, source of bacteraemia, polymicrobial bacteraemia, Pitt bacteraemia score, therapeutic drainage, antimicrobial therapy, and antibiotic susceptibility of *K. pneumoniae* were extracted from medical records. Outcomes measured from the day of bacteraemia included 30-day mortality, duration

of hospitalisation, 7-day clinical response (resolution of symptoms and signs), 14-day microbiological response (where microbiology was repeated), and 30-day relapsed bacteraemia.

Empiric antibiotics were administered before blood culture and antibiotic susceptibility test results, and definitive antibiotic was given after these results. Antibiotics were determined by prescribers. Disseminated *K. pneumoniae* infection occurred with infective foci other than the suspected source within 48 hours of bacteraemia. Severe complications were metastatic infections, pulmonary complications, intensive care unit (ICU) admission or death more than 72 hours after active antibiotics and within 30 days of bacteraemia.⁵ Metastatic infections occurred with infective foci other than the initial source after more than 72 hours of active antibiotic.

Categorical variables were compared for statistical significance using the Pearson's chi-square or Fisher's exact test, and continuous variables were compared using the Mann-Whitney U test. Univariate and multivariate analyses incorporating all dependent variables with $P < 0.05$ on univariate analysis for 30-day mortality were performed using binomial logistic regression. Statistical analysis was carried out using PASW statistics 18 (SPSS Inc., Chicago, Ill.). A P value < 0.05 indicated statistical significance.

Of 147 patients reviewed, 13 patients were excluded (incomplete data in 4, blood clot specimen rather than bacteraemia in 1, no antibiotics given in 2, irretrievable medical records in 6). Of 134 patients, median age was 72 years (range, 19 to 98 years) and 78 (58.2%) were male. Median Charlson's comorbidity score was 4 (range, 0 to 11) and median Pitt bacteraemia score was 4 (range, 4 to 10).

Common sources of bacteraemia were hepatobiliary (46 [36.3%], of which 19 had liver abscess), urinary (40 [29.9%]) and respiratory (27 [20.1%]). Nine patients had polymicrobial bacteraemia (*E. coli* in 5, *Enterococcus faecium* in 2, and 1 each had *E. tarda*, *Enterobacter cloacae* and *Aeromonas* species respectively). Four patients had disseminated infection namely eye ($n = 1$), abdominal ($n = 1$), respiratory ($n = 1$) and urinary ($n = 1$) specimens. Nineteen (12.8%) patients needed drainage of their foci of infection, 18 patients underwent drainage and 7 had drainage within 3 days of bacteraemia. Other details are

shown in Table 1. In terms of active empiric antibiotic, 96.3% of patients received third-generation cephalosporins (75 [58.9%]) and beta-lactam/beta-lactamase inhibitors (24 [18.6%]); none received cefazolin. Notably, 5 (3.7%) patients did not receive any empiric therapy. Definitive therapy comprised cefazolin (47 [35.1%]), beta-lactam/beta-lactamase inhibitors (24 [17.9%]) and third-generation cephalosporins (20 [14.9%]). Seventeen (11.4%) patients did not receive definitive antibiotic as they died before bacteraemia was known. All patients who survived till blood culture results received active definitive therapy.

Complications included pulmonary complications (1 [0.7%]), ICU admissions (1 [0.7%]) and death (13 [9.7%]). Overall 30-day mortality was 23.1%. Eighteen of the 31 deaths occurred within 72 hours of active antibiotics. No metastatic infections occurred. Clinical response occurred in 79.1% and microbiological response in 92.9%. The median duration of hospitalisation was 10 days (range, 0 to 130 days). Two patients experienced relapsed *K. pneumoniae* bacteraemia; both received cefazolin as definitive antibiotic therapy for acute cholecystitis and pyelonephritis respectively.

Overall, independent risk factors of 30-day mortality were age, Pitt bacteraemia score and cancer.

Patients who received empiric third-generation cephalosporin had lower 30-day mortality (66.0% vs 32.3%, $P = 0.001$) versus other antibiotics; this was not significant upon multivariate analysis. In patients with early mortality, cancer, Charlson's score and empiric fluoroquinolone increased risk while empiric third-generation cephalosporin reduced risk; there was no independent risk factor of early mortality upon multivariate analysis (Table 2). Among patients with definitive therapy, cancer was the only independent risk factor associated with 30-day mortality. Empiric therapy with third-generation cephalosporin was independently associated with lower early mortality (Table 2).

Pitt bacteraemia scores were comparable between patients with and without empiric third-generation cephalosporin, but there was a significant distribution of more severely ill patients in the third-generation cephalosporin group ($P = 0.041$). Patients with empiric third-generation cephalosporin had significantly less pneumonia, fewer severe complications >72 hours after active antibiotic and lower 30-day mortality and length of stay, and similar clinical and microbiological response, and relapse rates.

Between patients with definitive cefazolin ($n = 47$) and third-generation cephalosporin ($n = 20$), baseline characteristics were similar without statistically significant different patient outcomes (Table 3). Severe complications were 10.6% vs 15.0% ($P = 0.687$) and 30-day mortality

Table 1. Baseline Characteristics and Antibiotic Therapy of 134 Patients with *Klebsiella Pneumoniae* Bacteraemia with and without 30-Day Mortality

30-Day Mortality	No (n = 103)	Yes (n = 31)	P Value
Median age, years (range)	70 (19 – 98)	76 (47 – 96)	0.060
Male	62 (60.2)	16 (51.6)	0.396
Pitt bacteraemia score, median (range)	4 (4 – 9)	4 (4 – 10)	0.088
Charlson's comorbidity index, median (range)	4 (0 – 10)	5 (0 – 11)	0.014
Comorbidities			
Cerebrovascular disease	22 (21.4)	7 (22.6)	0.885
Dementia	11 (10.7)	3 (9.7)	1.00
Diabetes mellitus	51 (49.5)	14 (45.2)	0.671
Moderate to severe renal disease	15 (14.6)	6 (19.4)	0.520
Cancer	12 (11.7)	15 (48.5)	<0.0001
Source of bacteraemia			
Hepatobiliary	41 (39.8)	5 (16.1)	0.015
Intra-abdominal	5 (4.9)	3 (9.7)	0.320
Respiratory	14 (13.6)	13 (41.9)	0.001
Unknown	5 (4.9)	3 (9.7)	0.386
Urinary system	35 (34.0)	5 (16.1)	0.057
Others*	4 (3.9)	2 (6.5)	0.622
Disseminated infections	4 (3.9)	0 (0.0)	0.573
Antibiotic therapy			
Delayed active therapy >24 hours†	4 (3.9)	1 (3.2)	1.00
Active empiric therapy	99 (96.1)	30 (96.8)	0.865
No empiric therapy received	4 (3.9)	1 (3.2)	1.000
No definitive therapy received	0 (0.0)	17 (54.8)	<0.001
Empiric therapy			
Beta-lactam/beta-lactamase inhibitors	15 (14.6)	8 (25.8)	0.146
Third-generation cephalosporins	68 (66.0)	10 (32.3)	0.001
Fluoroquinolones	7 (6.8)	4 (12.9)	0.278
Carbapenems	4 (3.9)	4 (12.9)	0.083
Monobactam	1 (1.0)	0 (0.0)	1.000
Combination	4 (3.9)	3 (9.7)	0.352
Definitive therapy			
Beta-lactam/beta-lactamase inhibitors	22 (21.4)	2 (6.5)	0.065
Cefazolin	42 (40.8)	5 (16.1)	0.012
Third-generation cephalosporins	16 (15.5)	4 (12.9)	1.00
Fluoroquinolones	12 (11.7)	3 (9.7)	1.00
Others	11 (10.7)	0 (0.0)	0.067

All variables are expressed as number (percentage) unless otherwise stated.

*Others: 1 central nervous system, 1 otorhinolaryngological, 1 soft and skin tissue, and 1 line-related bloodstream infection.

†Delayed active therapy included both empiric and definitive antibiotic therapy.

Table 2. Independent Risk Factors of Mortality for Patients with *Klebsiella Pneumoniae* Bacteraemia

	30-Day Mortality aOR (95% ,CI)	P Value	Early Mortality (≤3 Days) aOR (95% ,CI)	P Value
All Patients (n = 134)				
Age (years)	1.061 (1.014 – 1.019)	0.01		
Pitt bacteremia score	1.969 (1.281 – 3.025)	0.002		
Charlson's score	0.934 (0.736 – 1.184)	0.571	1.330 (0.952 – 1.859)	0.095
Cancer	14.897 (3.097 – 71.665)	0.001		
Hepatobiliary source	0.336 (0.074 – 1.536)	0.16	3.554 (0.620 – 20.358)	0.155
Respiratory source	2.033 (0.483 – 8.550)	0.333		
Urinary source	0.354 (0.074 – 1.692)	0.193		
Empiric 3 rd generation cephalosporin	0.466 (0.155 – 1.402)	0.174	0.225 (0.040 – 1.249)	0.088
Carbapenems	0.750 (0.111 – 5.061)	0.768		
Empiric quinolones			7.392 (0.929 – 58.798)	0.059
Definitive Therapy (n = 117)				
Age (years)	1.037 (0.964 – 1.115)	0.330		
Male	0.425 (0.087 – 2.078)	0.290		
Charlson's score	1.191 (0.829 – 1.709)	0.344	1.311 (0.946 – 1.818)	0.104
Cancer	8.552 (1.243 – 58.837)	0.029	5.214 (0.929 – 29.283)	0.061
Intra-abdominal source	1.780 (0.223 – 14.214)	0.586		
Empiric 3 rd generation cephalosporin	0.220 (0.039 – 1.226)	0.084	0.152 (0.026 – 0.893)	0.037
Empiric quinolones	4.896 (0.501 – 47.852)	0.172	4.463 (0.540 – 36.912)	0.165

Table 3. Comparisons of Patients who Received Definitive Therapy with Cefazolin and Third-Generation Cephalosporins in the Treatment of *Klebsiella Pneumoniae* Bacteraemia

Definitive Therapy	Cefazolin	Third-Generation Cephalosporins	P Value
Number	47	20	
Pitt bacteraemia score, median (range)	4 (4 – 7)	6 (4 – 7)	0.481
Source of bacteraemia			
Hepatobiliary	17 (36.2)	12 (60.0)	0.072
Intra-abdominal	2 (4.3)	2 (10.0)	0.364
Respiratory	5 (10.6)	0 (0.0)	0.312
Unknown	4 (8.5)	0 (0.0)	0.309
Urinary	16 (34.0)	6 (30.0)	0.747
Outcomes			
Severe complications >72 hours after active antibiotics	5 (10.6)	3 (15.0)	0.628
Clinical response at day 7	45 (95.7)	18 (90.0)	0.687
Microbiological response at day 14	8/10 (80.0)	1/1 (100.0)	1.00
30-day mortality	5 (10.6)	4 (20.0)	0.434
Median hospital length of stay, days (range)	13 (4 – 130)	15 (3 – 55)	0.426
Relapse of bacteraemia	2 (4.3)	0 (0.0)	1.00

All variables expressed as number (percentage) unless otherwise stated.

was 10.6% vs 20.0% ($P = 0.434$) for cefazolin versus third-generation cephalosporin groups.

A retrospective study of 107 cases of *K. pneumoniae* liver abscess suggested cefazolin was not as effective as third-generation cephalosporin in preventing severe complications but mortality was similar (8.5% vs 4.2%, $P = 0.42$); cefazolin was dosed at 1 g 8-hourly.⁵ One gram of cefazolin in humans achieved a mean serum level of 64 mcg/mL 1 hour after intramuscular administration.⁸ A similar mean serum level of 59.2 mcg/mL in murine pneumonia was associated with microbiological failure.⁴ In murine pneumonia, microbiological response to cefazolin occurred at a higher dose of 60 mg/kg with a mean serum level of 115.4 mcg/mL after 1 hour. We used 2 g 8-hourly of cefazolin for *K. pneumoniae* bacteraemia in our institution.

In 110 episodes of *K. pneumoniae* liver abscess (61% had bacteraemia), 86.3% received cefazolin for more than 3 days;⁹ 4.3% developed metastatic infections and mortality was 5.3%, similar to patients treated with extended-spectrum cephalosporin.⁵

Limitations of our study included its retrospective design and arbitrary treatment decisions by physicians. Our finding of effective cefazolin therapy was supported by an in vitro study⁶ and 3 human studies.^{2,7,9} With worsening antimicrobial resistance and diminishing antimicrobial pipeline, our data provides evidence for the culture-guided step-down use of an effective narrow-spectrum “old” antibiotic (cefazolin) for *K pneumoniae* bacteraemia.

Acknowledgement

The authors would like to thank Rou-an Tan for her assistance in data collection.

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Watch the Tongue

A 35-year-old male newly diagnosed with human immunodeficiency virus (HIV) infection (last negative test was 1.5 years ago) presented with an odd sensation on his tongue for a day without any dysgeusia. This was the first time he had experienced this. He received treatment for presumed tinea infection over his palms and soles a month ago. On examination, shallow, slimy erosions were noted over the left lateral border of the tongue (Fig. 1). There was no palpable cervical lymphadenopathy. Hyperpigmented papulosquamous patches were present over bilateral palmoplantar surfaces. The rest of the physical examination was unremarkable.

What is the diagnosis?

- A. Oral hairy leukoplakia
- B. Tongue carcinoma
- C. Fixed drug eruption
- D. Syphilis
- E. Kaposi's sarcoma

Discussion

The clinical picture demonstrates the appearance of serpiginous oral ulcers, classically described as bearing a “snail-track appearance” – a pathognomonic hallmark of lesions seen in secondary syphilis. The rapid plasma reagin titre for this patient was 1:128 and treponema pallidum particle agglutination assay was reactive confirming the diagnosis. Dark-field examination of the ulcer base was negative. Intramuscular benzathine penicillin G (2.4 MU weekly for 3 weeks) was commenced with resolution of his oral lesions when he was reviewed 2 weeks thereafter. The expedient response to the appropriate treatment further confirms the diagnosis.

Oral ulcerations occur in 30% of cases of secondary syphilis, although it may be the sole clue to the presence of infection, albeit rarely.¹ They have been reported anywhere within the mucosal surface of the oral cavity. The suspicion of syphilitic infection requires a high index of suspicion during the history taking and the diagnosis can be clinched with positive serological tests. Lesional histopathology is



Fig. 1. Linear, slimy and shallow ulcers are seen over the left posterolateral aspect of the tongue (as indicated by the asterix).

non-specific, often yielding an abundance of plasma cells against a milieu of epidermal psoriasiform hyperplasia, although spirochetes may be detected with the Warthin-Starry stain.

Of note, oral ulcers may manifest both as part of primary or secondary syphilis. A useful clinical pearl to distinguish the two is that the ulcers stemming from spirochetemia of secondary syphilis are multiple and maybe symptomatic, as compared to the oral chancres of primary disease which are usually painless and solitary.² The former also tend to occur concurrently with the typical cutaneous papulosquamous stigmata as seen in our case above.

It should be noted that there are a variety of oral manifestations of secondary syphilis. It may present as asymptomatic diffuse macular erythema involving the uvula, tonsils and palate (specific angina)³ while papular lesions arising over the hard palate, buccal mucosae or commissures have also been reported.⁴ Mucous patches and erythematous plaques (plaques fauchée) may occur over the labial mucosa, buccal mucosa, palate, or tongue.⁵

In addition to oral disease, cutaneous appearances of secondary leutic disease may either present as macular, papular, pustular or ulceronodular morphologies.⁴

Answer: D

Ulceronodular disease (lues maligna), a generalised syndrome of fever, headache, myalgia and a nodulo-vesiculopustular eruption over the face and scalp have been reported; it has a preponderance to occur in patients with HIV co-infection.⁶

Patients with syphilitic and HIV co-infection tend to have an aggressive course of leucic disease as alluded to, along with more rapid progression to tertiary disease if left untreated.⁷ Moreover, it is recommended that higher doses of penicillin be used in patients with HIV infection, as opposed to HIV-negative patients, to eradicate treponemal disease effectively;⁸ that is, 3 doses of intramuscular benzathine penicillin G 2.4 MU weekly for the former group instead of 1 dose (some physicians may opt for 2 doses) for the latter.

In summary, this article highlights that although there may be a myriad of aetiologies for oral ulcers in HIV-positive patients, being cognisant of the unique clinical appearance of certain infections such as those in syphilis can allow for prompt and accurate diagnosis.

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Blue Legs in a 60-Year-Old Gentleman

Case Report

A 60-year-old bread seller with a background history of diabetes mellitus, hypertension and a previous unidentified abdominal surgery (which may have been an abscess) was seen by the orthopaedic team for chronic right big toe ulceration. A wedge biopsy of the ulcer was done and showed acute-on-chronic inflammation with fungal organisms. However, the orthopaedic team noted an incidental finding of hyperpigmentation over his lower limbs and referred him to dermatology.

The patient noted a pruritic dark discolouration over his feet for the past 6 years and also had hyperpigmentation over his face. He denied applying anything on his skin. On examination of his lower limbs, he had dark bluish hyperpigmented patches on his legs and feet (Fig. 1). There was a similar but milder hyperpigmentation over his right and left periauricular regions and nails (Fig. 2).



Fig. 1. Bluish-grey hyperpigmentation over the legs and feet.

What is your diagnosis?

- A. Postinflammatory hyperpigmentation
- B. Drug-induced hyperpigmentation
- C. Alkaptonuria
- D. Haemochromatosis
- E. Addison's disease

A skin biopsy was done. Histopathological examination noted hyperkeratosis with dense infiltrates of predominantly lymphocytes and plasma cells in the upper dermis and periadnexal areas. There were collections of melanophages in the upper dermis, containing coarse granules of melanin (Fontana stain positive) admixed with iron (Perl's stain positive), associated with an interrupted band-like infiltrate of lymphocytes and plasma cells (Fig. 3). Eosinophilia was not a feature, distinguishing this from a drug-induced inflammatory reaction. There was no degeneration of the epidermis. The melanophages were CD68 positive, indicating their macrophage nature. They were negative for HMB45, indicating that they were not melanocytes. The overall impression was a lichenoid inflammatory reaction with postinflammatory hyperpigmentation.

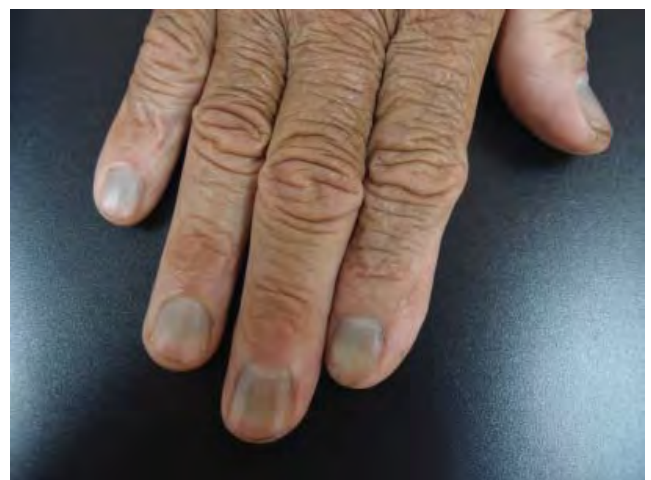


Fig. 2. Involvement of the finger nails.

Answer: B

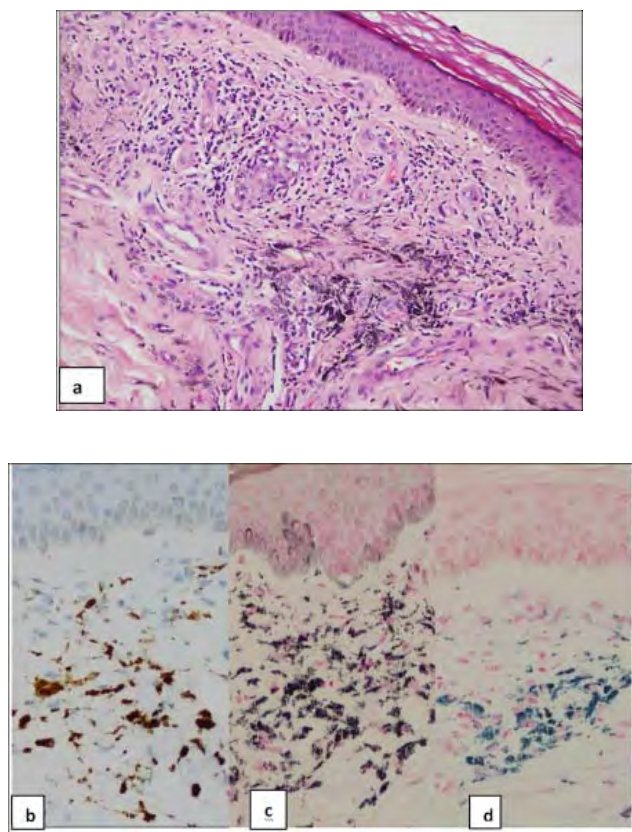


Fig. 3. Photomicrographs showing (a) hyperkeratosis of the epidermis and dense collections of melanophages in the upper dermis, containing coarse granules of dark pigment associated with infiltrates of lymphocytes and plasma cells. H&E x 200; (b) The melanophages are immunopositive for CD68. IHC CD68 x 400. (c) Pigment in melanophages and basal layer of epidermis stain positive for melanin. Masson Fontana x 200; (d) Some pigment are positive for iron (blue). Perl's stain x 200.

On further history taking, the patient had been consuming ampicillin/sulbactam for the past 1 year and minocycline for the past 30 years. He was unsure of the reason why he had been originally prescribed the antibiotics, merely stating that the pills were used for an “infection”. His doctor had prescribed him with minocycline 30 years ago and since then, he had continued buying minocycline over-the-counter from the pharmacy on his own.

Discussion

Minocycline is a semi-synthetic second generation tetracycline which binds to the 30S ribosomal subunit, blocking transfer RNA binding to the messenger RNA-ribosome complex and thus inhibiting bacterial protein synthesis. Minocycline-induced hyperpigmentation is a well known disfiguring side effect with prolonged usage of the antibiotic which may occur in up to 36% of patients.¹ Here, we present the case of an elderly gentleman who presented

with bluish hyperpigmentation over his legs, nails and face after use of minocycline for 30 years.

There are 3 recognised types of minocycline-induced hyperpigmentation. Type I minocycline-induced hyperpigmentation presents with blue-black or grey pigment on areas of scarring or acne-related inflammation on the face which stain iron and melanin extracellularly and within dermal macrophages. Type III presents with persistent diffuse muddy-brown discolouration in areas of sun exposure and there is non-specific increased melanin in basal keratinocytes and dermal macrophages staining for melanin. Mouton et al proposed a fourth type with circumscribed blue-grey pigmentation on the thorax within scar tissue which remained unchanged after 43 months of follow-up. This type was previously thought to be a variant of Type I. Histopathologically, pigment is present within dendritic cells and extracellularly throughout the dermis.²

Hyperpigmentation may also affect the nails, lips, oral mucosa, gingivae, teeth, bones, costal cartilage, postacne osteoma cutis, substantia nigra, atherosclerotic plaques, conjunctival cysts, sclera and breast milk.² In this case, the patient's clinical presentation is suggestive of type II minocycline hyperpigmentation which presents with blue-grey pigment on normal skin of shins and forearms, and which can also affect other sites besides the legs, namely the face and nails. The aetiology of minocycline-induced hyperpigmentation is postulated to be related to polymerised reactive metabolites, insoluble chelation products and lengthy treatment durations.²

The patient was advised to cease minocycline therapy. Topical clobetasone butyrate 0.05% and oral antihistamines were prescribed in view of the pruritus. On follow-up a year later, the hyperpigmentation had improved markedly upon discontinuing minocycline as advised with fading of the bluish discolouration over the legs and near-resolution over the upper shins and forefeet.

Besides that, sun protection should be advised. Q-switched laser therapy has been used to treat minocycline-induced hyperpigmentation, with the Alexandrite 755 nm more effective than the Nd:YAG infrared 1064 nm and the Ruby 694 nm.³ Type I and II minocycline-induced hyperpigmentation was found to have better response to laser therapy compared to type III.³

In this patient's case, he had continued buying minocycline from the pharmacy. He was unsure regarding the reason the medication was initially prescribed and was unsure whether he should continue taking the medication. As such, it is important for prescribers to educate the patients regarding the indications and the duration of treatment for medications prescribed in order to prevent adverse effects and complications from misuse of medications. Patients should also be advised to follow up with their doctors

instead of self-medicating.

Conclusion

Minocycline-induced hyperpigmentation is an important adverse effect to consider while choosing antibiotic therapy in clinical practice. Prolonged minocycline use can be a cause of blue-grey pigmentation over the lower limbs, and may also affect the face, teeth, nails and sclera. Patients should be advised to cease the drug, use sun protection and Q-switched laser therapy, in particular with the Alexandrite 755 nm, may be offered. Prescribers should educate and counsel patients regarding the indications and duration of medications so that patients will use their medications as prescribed.

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The Syndrome of 'Hard Swellings'

A 63-year-old Chinese hawker presented with episodic left-sided dull abdominal pain over several years, associated with increasing abdominal distention and early satiety. She also had very occasional dyspnoea. Physical examination revealed bilateral ballotable renal masses. A slightly raised fibrous plaque was noted on the left side of her forehead. Her full blood count, renal panel, liver panel and electrocardiogram showed normal results. Computer tomography showed cystic pulmonary parenchymal changes (Fig. 1), renal cysts and large bilateral renal angiomyolipomas (Fig. 2a). The renal angiomyolipomas showed areas of vascularity with contrast enhancement, and their poorly enhancing areas had Hounsfield unit of -80, consistent with fat (Fig. 2b). She declined further evaluations and follow-up appointments despite repeated counselling and sought herbal remedies on her own. She was admitted 3 years later for a stroke. Magnetic resonance imaging showed subependymal nodules and white matter tubers in the brain (Fig. 3).

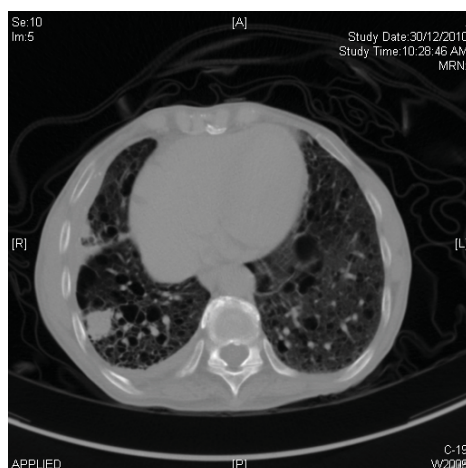


Fig. 1. Computer tomography scan showing cystic pulmonary parenchymal changes consistent with lymphangioleiomyomatosis.

What is the genetic disorder in this patient?

- A. von Hippel-Lindau disease
- B. Birt-Hogg-Dubé syndrome
- C. Tuberous sclerosis complex
- D. Multiple endocrine neoplasia type 1
- E. Multiple endocrine neoplasia type 2

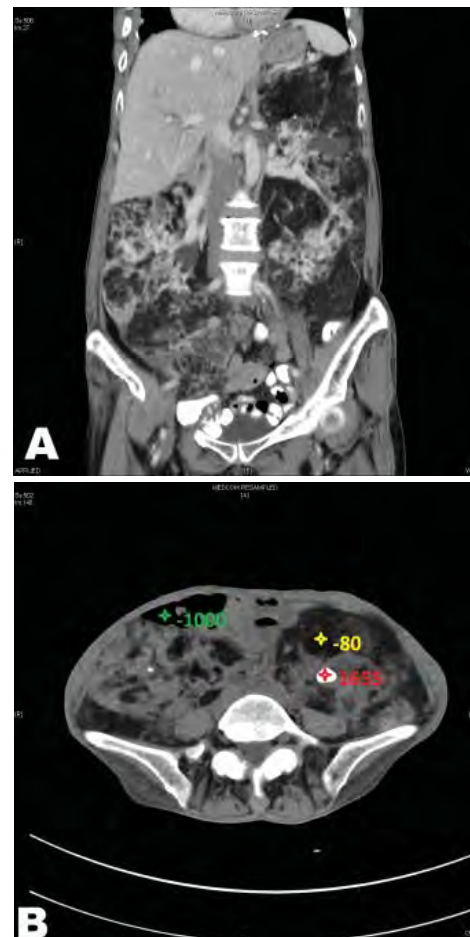


Fig. 2. Computer tomography (CT) scan of the patient. At A, the contrast-enhanced CT shows large bilateral renal angiomyolipomas, with displacement of bowels. At B, non-contrast CT shows a Hounsfield unit of -80 (yellow) in a poorly enhanced area of the left renal angiomyolipoma, consistent with fat. The Hounsfield unit of a left renal stone (red) and that of bowel gas (green) are also shown.

Answer: C

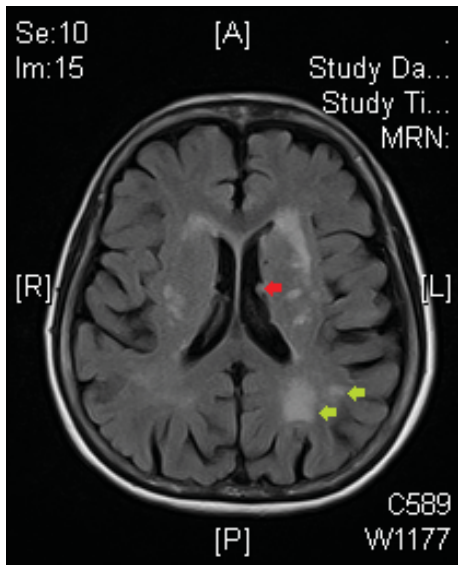


Fig. 3. Magnetic resonance imaging (T2 fluid-attenuated inversion recovery) showing subependymal nodule (red arrow) and subcortical tubers (green arrows).

Discussion

Tuberous sclerosis complex (TSC) is a rare autosomal dominant genetic disorder with multiple organ involvement. It has a population prevalence of about 1 in 12,000.¹ The name of the disease was derived from the Greek word ‘skleros’, meaning ‘hard’; and the Latin word ‘tuber’, meaning ‘swelling’. These ‘hard swellings’ refer to the thickened gyri found upon post-mortem examinations of the brains of TSC patients by French neurologist Désiré-Magloire Bourneville in 1880.

The mutations for TSC have been mapped to 2 tumour-suppressor genes, *TSC1* in 9q34, and *TSC2* in 16p13, encoding for the proteins hamartin and tuberin respectively. These 2 proteins function as a regulatory complex responsible for inhibiting the activity of mammalian target of rapamycin (mTOR), via inhibition of the small GTPase ras homolog enriched in brain (Rheb).² Since mTOR is involved in the signaling pathway leading to cell growth and proliferation, *TSC1* or *TSC2* mutation would result in the formation of various tumours.

The diagnosis of TSC can be made based on genetic or clinical diagnostic criteria. According to the 2012 International Tuberous Sclerosis Complex Consensus Conference, the identification of either a *TSC1* or *TSC2* pathogenic mutation is sufficient to establish a diagnosis of TSC, regardless of clinical symptoms.³ However, up to 25% of TSC patients have no identifiable mutations on conventional genetic testing, so a normal result does not

Table 1. Clinical Diagnostic Criteria for Tuberous Sclerosis Complex

Major Features	Minor Features
Hypomelanotic macules (3 or more, at least 5 mm diameter)	‘Confetti’ skin lesions
Angiofibromas (3 or more), or fibrous cephalic plaque*	Dental enamel pits (3 or more)
Ungual fibromas (2 or more)	Intra-oral fibroma (2 or more)
Shagreen patch	Retinal achromic patch
Multiple retinal hamartomas	Multiple renal cysts*
Cortical dysplasias* (tubers or cerebral white matter radial migration lines)	Non-renal hamartomas
Subependymal nodules*	
Subependymal giant cell astrocytoma	
Cardiac rhabdomyoma	
Lymphangioleiomyomatosis*	
Angiomyolipomas* (2 or more)	

*These features were found in our patient.

exclude TSC.³ The clinical diagnostic criteria for TSC is listed in Table 1, and a definite diagnosis of TSC can be established if a patient has 2 major features, or 1 major feature plus 2 or more minor features.³ While various benign tumours in the brain, lungs, kidneys, heart and skin are commonly found in TSC patients, none of them is pathognomonic for TSC. Our patient has at least 5 major features and 1 minor feature to support her diagnosis of TSC.

With its multiple organ involvement, the management of TSC should be based on a multi-disciplinary approach.⁴ Genetic counselling should be provided for newly diagnosed patients and their family members.⁴ Neurological and psychiatric assessment for any TSC-associated neuropsychiatric disorders (TAND) like seizures, intellectual disabilities, psychiatric disorders and occupational problems should be performed. Surgical resection of symptomatic or complicated subependymal giant cell astrocytoma may be necessary.⁴ Pulmonary function test should be considered in patients with lymphangioleiomyomatosis.⁴ An electrocardiogram is recommended even in adult TSC patients without cardiac symptoms to exclude conduction defects.⁴ An ophthalmological assessment is useful in detecting any visual field defects or retinal lesions.⁴ Dermatological consults should be made for symptomatic, disfiguring or rapidly growing skin manifestations; and similarly, dental consults should be made if enamel pits or oral fibromas lead to functional or cosmetic issues.⁴

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