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Transpyloric Feeding
Thrombosis in the Newborn

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The Paediatric Quiz

Thrombosis in the Newborn
H. Ebrahim, L. Naidoo, H.R. Mackanjee

Answer to the Quiz

Instructions for Authors
Are the symptoms really signs of allergy?

Nasal congestion/sneezing, itchy/watery eyes and nose:

- **65%** of patients diagnosed as having allergic rhinitis and prescribed antihistamine may not be allergic.¹ ²

Wheezing, coughing, breathing problems:

- **90%** of children and **60%** of adults with asthma have allergy.³ ⁵

Dry skin, pruritus, scratching:

- **30%-70%** of infants and young children with eczema have underlying allergy.³ ⁶

Rule in or rule out allergy early – add a Phadiatop® blood test to increase certainty

Phadiatop® measures IgE antibodies to a well-balanced mixture of common inhalant allergens. These tests help you to:

- differentiate IgE mediated atopic allergy from other allergy-like symptoms⁷–¹³
- identify patients that need Specific IgE testing for allergen identification and continued allergy care⁷–¹³

References:

Editorial

An Explosion in Medical Malpractice Litigation

It is a great pleasure and an honour to be the new editor of The Paediatric Quarterly Journal. As the new Head of Department of the Department of Paediatrics and Child Health at the University of KwaZulu-Natal, it is great to be part of an enthusiastic and great team of colleagues. I would first like to thank Professor Prakash Jeena, who has worked tirelessly as the previous editor of the journal; I am taking over the journal from a position of strength.

We are now working in a climate where there is increasing litigation; with medical practitioners being increasingly sued for medical errors and negligence. This has resulted in the Minister of Health Dr. Aaron Motsoaledi describing a medical malpractice litigation “crisis” at a recent medico-legal summit in Pretoria. The minister highlighted that the crisis we are faced with is “not a crisis of public healthcare. It is a crisis faced by everybody in the healthcare profession - public and private”.

The cost of medical malpractice claims has skyrocketed and the number of claims increased substantially. This has resulted in malpractice insurance rates sky-rocketing in the last five years to between 300% and 500% in some specialties. This unfortunately includes paediatricians with neonatologists being included in the “big-four” (obstetrics and gynaecology, neurosurgery, neonatology, and orthopaedics) of the highest specialties targeted.

We therefore need to practice defensive medicine and most importantly keep abreast of new and better treatments and techniques to look after our patients. One of these obviously involves continuous medical education.

In this edition of the journal we have two interesting cases in paediatric surgery, both of which hold relevance to paediatricians. The role of radiography and checking of correct placement of feeding tubes is highlighted in the paper by Itzikowitz et al. The other review by Daan Den Hollander involves the management of the child with burns, an occurrence which paediatricians are unfortunately continuously faced with. Ebrahim et al have written a comprehensive overview on thrombotic disorders in the neonate.

There is also an interesting quiz highlighting an important congenital dermatological problem in the neonate.

In future, the editions of this journal will also be available on our UKZN paediatrics website at http://paediatrics.ukzn.ac.za. I hope you enjoy this first edition of the journal for 2015.

Enjoy reading!

Prof Refiloe Masekela

Editor-in-Chief
PhD
Head of Department
Department of Paediatrics and Child Health
Nelson R Mandela School of Medicine
University of KwaZulu-Natal
Private Bag X1
Congella
Durban
4013

e mail: Masekela@ukzn.ac.za
Early management of the Burned Child – The Role of the Paediatrician

Daan den Hollander FCS(SA)
Clinical Director, Burns Unit, Inkosi Albert Luthuli Central Hospital and Honorary Lecturer
Department of Surgery, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban

Abstract

Burns are a common reason for admission to a paediatric ward and paediatricians may be called upon to assist in the early management of these patients. The assessment and resuscitation of the child with a major burn is reviewed. The mainstay of resuscitation in these patients is replacement of ongoing fluid losses as guided by the child’s vital signs and urine output, as well as providing dextrose-containing maintenance fluids.

CASE

Thuthukile (not her real name), a 15 month old girl, got burned when she ran into her grandmother while the latter was carrying a pot of boiling hot water. She sustained burns to the anterior chest, the left arm, both thighs, lower legs and the back. She presented to a peripheral hospital and as there were no beds available in the hospital, she was only admitted to the ward after 36 hours in the emergency department. No information is available about the management of the child during this period.

On admission to the ward, the responsible medical officer assessed the burn wound as a partial thickness burn of 40% of the total body surface area (TBSA). The patient had a blood pressure of 80/50 mmHg, a heart rate of 202 beats per minute, and had cold and cyanosed extremities. Urea and electrolytes (U&E) done at admission showed a urea of 3.8 mmol/l, creatinine of 45 umol/l, bicarbonate of 11.5 mmol/l and base deficit of -9. Lactate was 3.4 mmol/l and the pH was 7.39. The full blood count was clotted. The child was resuscitated with two aliquots of 20 mls/kg of Modified Ringers Lactate (MRL). After completion of these fluids, the intravenous line ‘tissued’ and the medical officer was unable to set up a new one. He then requested a paediatrician to assist with vascular access.

By the time the paediatrician had succeeded in establishing vascular access (dorsum of the foot, scalp vein), a repeat full blood count became available which showed a haemoglobin level of 11 g/dl, a leucocyte count of 0.86 x 10³/l and a platelet count of 170 x 10³/l. The urea had increased to 9.4 mmol/l and creatinine was 59 umol/l. The child’s temperature was 38.0°C. The paediatrician considered that the child was septic and started her on a dopamine infusion, despite the fact that the urine output had normalized. Later that day dobutamine was added. The patient was then discussed with the burns unit. Advice was given on fluid management of the patient, and the patient was accepted for admission after completion of resuscitation.

The following morning both venous lines tissued, and the blood pressure dropped from 111/55 mmHg to 78/34 mmHg. The child’s blood sugar was 1.7 mmol/l. The paediatrician looking after the patient considered this a sign of shock despite the fact that the heart rate only increased from 170 to 176 beats per minute, and restarted the intropes. The urine output at the time was 3.9 mls/kg/hour. An arterial blood gas taken at the time showed a pH of 7.47, a lactate of 1.4 mmol/l and a base deficit of 5.9. The patient was then transferred to the burns unit.

On admission in the burns unit we saw a stable-looking child with 30% mainly superficial to moderately partial thickness burns. The inotropic medication was gradually discontinued and the child maintained systolic blood pressures of around 90 mmHg. The polyuria rapidly normalized after replacement of half the urinary output with MRL, in addition to paediatric maintenance fluids. A repeat U&E the following morning demonstrated that the urea had normalized to 1.4 mmol/l. The burns did not require grafting, and the child was discharged home after a week in hospital.

DISCUSSION

Thermal injuries are a common occurrence in South Africa and – as this case illustrates – paediatricians may be requested to partake in the early management of such patients, particularly in hospitals where there is no 24-hour surgical cover. A large part of the early management of burns is geared towards treatment of burn shock. The circulatory failure that occurs after major burns (i.e. more than 10-20% in a child, depending on the age) is the result of two mechanisms:

• Burned skin no longer retains moisture and large amounts of fluid and proteins leak through the burn wound. Burn wounds exudation is worse after partial thickness wounds as compared with full thickness wounds, as in the latter many of the skin vessels have been thrombosed, reducing the circulation through the burn.

• Coagulated proteins in the burn skin act as damage-associated molecular patterns (DAMPs) and incite a severe cytokine-mediated inflammatory reaction.\(^1\) With a burn greater than 20% total body surface area (TBSA) this inflammation ‘spills over’ into the general circulation evoking first a systemic pro-inflammatory response (SIRS), followed after 6-8 hours by a concomitant anti-inflammatory response (CARS). The SIRS reaction is responsible for widespread oedema formation in areas remote from the burn, adding to the circulatory failure. The CARS response is responsible for the susceptibility of burn patients to infection and sepsis.
Assessment of Size of Burn, Depth of Burn and Weight of the Child

Proper resuscitation of the burned child requires knowledge of the weight of the child as well as of the size and depth of the burn. If, because of haemodynamic or respiratory instability, a burned child cannot be weighed, the most accurate way of estimating the child’s weight is by extrapolation using the ‘Road-to-Health’ book. It is amazing how many mothers carry their children’s ‘Road-to-Health’ books with them, even when they rush out of the house with an injured child. In older children, or if the ‘Road-to-Health’ book is not available, a Broselow tape should be used.

Accurate assessment of the total area burned is one of the most difficult aspects of burn resuscitation for the doctor who does not do so all the time, as was illustrated in this case. Studies have shown significant inaccuracy in the assessment of % TBSA burned among health care workers, and inexperienced doctors have been known to ‘out’ by a factor 2 either way. 4, 5 This, of course, will have important consequences for the amounts of fluid that will be administered to the patient, who will run the risk both of under- and over-resuscitation. One way around this problem is to take photographs of the burn on a cell-phone and send these to a burn surgeon for evaluation.6 Although burn surgeons classify burns into superficial burns; superficial, moderate and deep partial thickness; and full thickness burns, these distinctions may be very difficult to make in a fresh burn. In fact, they are unnecessary at this stage, and it is only necessary to divide burns into:

• **Superficial burns:** this group includes both superficial and superficial to moderate partial thickness burns. These burns are characterized by redness and/or blistering.

• **Deep burns:** these burns include deep partial thickness and full thickness burns: they are characterized by a white, yellow or brown eschar (slough) which may range from semiliquid to leathery.

**Resuscitation of the Burn Patient**

There are two formulae in vogue for the calculation of fluid requirements in burns. Most doctors will be familiar with the Parkland or Baxter formula, which calculates the fluid loss as 4 ml/kg body weight for each %TBSA burned.7 The other formula is the Brooke’s formula, which estimated the fluid requirement as 2 ml/kg/%TBSA.8

Although originally the Brooke’s formula required a quarter of the resuscitation fluids to be supplied in the form of albumin, its designer Pruitt, later came to consider colloids in the resuscitation of burns as ‘expensive crystalloids’, and – as in the Parkland’s formula – nowadays the entire amount is given as a crystalloid solution.

Both the American as well as the South African Burns Association have recently recommended to start resuscitation with 3 ml/kg/%TBSA.9, 10 Burns resuscitation formulae, however, have severe limitations, as it is well recognized that the amount of fluid a patient requires after a burn is influenced by many other factors apart from surface area burned and weight, including the pre-existing status of hydration, the presence of an inhalation injury and intake of alcohol prior to the burn. A better approach to burn resuscitation, therefore, is to aim at restoration of the endpoints of resuscitation, although in trauma resuscitation many invasive endpoints of resuscitation may be pursued such as cardiac output or ventricular filling pressures. While these endpoints have not only been shown to be unhelpful in burn resuscitation, pursuing them may actually be harmful, as they can lead to overhydration resulting in pulmonary oedema and compartment syndromes (so-called ‘fluid creep’).9,11

Many burn surgeons therefore use simple clinical endpoints of resuscitation, such as heart rate and in particular urine output, supplemented with downstream indicators such as lactate and base excess. Urine output is the main endpoint of fluid resuscitation in burns, and an output between 0.5 and 1 ml/kg/hr should be aimed for, increasing or decreasing infusion fluids as required.9,10 The urine output of 2 ml/kg/hr, as advised in the paediatric advanced life support (PALS) course is outdated and now considered dangerous as it may lead to overhydration.

One of the most common errors in the fluid management of the paediatric burn patient is the omission of maintenance fluids. Maintenance fluids are required for two reasons:

• First, in contrast to adults, the resuscitation fluids administered in case of a moderate burn (e.g. 15-30%) are not sufficient to cover even the maintenance requirements of a small child. A 10 kg child with a 20% burn, would receive, according to the Parkland’s formula a total of 34 mls/hr of resuscitation fluid. This child, however, requires 40 mls/hr of maintenance fluid.

• Secondly, young children, in contrast to adults, do not experience a hyperglycaemic response after trauma, and as resuscitation fluids do not contain dextrose, a life-threatening hypoglycaemia may result if no maintenance fluids are administered. Although our child was given the correct amount of fluids, all was given as Modified Ringers Lactate, resulting in a dangerously low blood sugar of 1.7 mmol/l.

A controversial issue in the management of paediatric burns is whether at least part of the fluid requirements of a child should be given in the form of plasma. Despite Pruitt’s argument about ‘colloids’ being ‘expensive crystalloids’, many paediatric surgeons managing burns have continued to administer plasma to their patients, arguing that the massive exudation that takes place in more serious burns is responsible for the loss of humoral immunity to common pathogens such as gram-positive organisms.12 More recently it has been argued that in major burns (i.e. over 40-50% TBSA) providing at least part of the resuscitation requirements in the form of a synthetic colloid reduces resuscitation volumes and subsequent oedema, resulting in a decrease in complications such as burn wound progression and abdominal compartment syndrome.13,14,15

There may be a place for vasopressor support in a burn patient who remains hypotensive despite adequate fluid resuscitation. The first choice drug to achieve this aim is adrenaline. Although many paediatricians have a preference for dopamine in the child with septic shock, the effects are less reliable and it is associated with further increases in the inflammatory re-
Dobutamine (Dobutrex) is a vasodilatory agent and has no place in the management of hypovolaemic shock.

Further Management of the Burn Patient

1. Although most children that will have been burned are scalded, particularly in other mechanisms of burns (flame, electrical, chemical) it should be appreciated that the burn injury may be one of several injuries, caused by falling timber, violent muscle contractures or inhalation or absorption of toxic chemicals. If in doubt about the mechanism of injury, the doctor should perform a full advanced trauma life support (ATLS) primary and secondary survey.

2. All patients with burns requiring intravenous (IV) resuscitation fluids must have a urinary catheter passed to enable hourly monitoring of urine output.

3. All children with burns >15-20% should have a nasogastric tube passed. During the resuscitation phase the tube is left on free drainage but as soon as the child is stable and within 12-24 hours from the burn, nasogastric feeding should be started. Early feeding of the patient with major burns is associated with lower mortality.

4. Burns are painful and children with burns require analgesia. It has been established that young children are offered less adequate analgesia in the emergency situation than adults with the same injuries. An opioid titrated IV to effect is the safest method of providing analgesia in burned children.

5. There are myriad dressings available for burns and a Cochrane review from 2010 stated that there is very little evidence to determine the choice of dressing for superficial burns. However, silver sulfadiazine came out as inferior in all trials, and should thus be avoided in superficial burns. We prefer tulle gras with chlorhexidine (Bactigras®). An alternative is Aquacel®, which can be left in place until the wound has healed and the dressing sloughs off like a scab.

6. Deep burns require an antimicrobial dressing and most commonly silver-based dressings are employed. The cheapest and most widely available of such dressings uses silver sulfadiazine (SSD). Despite all the bad publicity that SSD has received in the past years, it is good to remember that the introduction of SSD, some ten years prior to the widespread adoption of early excision and grafting, was associated with a significant decrease in the mortality of moderate and major burns. The major drawback of SSD is its short half-life which necessitates dressing changes on a daily basis. If available, modern silver-containing dressings such as nanocrystalline silver should therefore be used instead.

Conclusion

The management of burn shock is fluids, although controversy remains as to what are the most appropriate fluids. In most burn patients enough fluids have been given when a sufficient urine output has been established and indicators of anaerobic metabolism are being corrected or have normalized. Transfer of a patient to a burns unit is most beneficial if the patient is referred early i.e. within the first 48 hours after injury. Although entry-criteria differ between burn units, a 40% burn would certainly have been accepted after a short (12-24 hour) period of resuscitation in all South African burn units.

REFERENCES

15. Dullhunty JM, Boots RJ, Rudd MJ, Muller MJ, Lipman J. Increased fluid resuscitation can lead to adverse outcomes in major-burn related patients, but low mortality is achievable. Burns 2008;34(8):1090-1097.

Correspondence: DaanHol@jalch.co.za
Transpyloric feeding – worth the risk?

R Itzikowitz1 MBChB
L Tooke2 MBChB, Dip PEC, Dip Obst, MMed(Paeds), FCPaeds, Cert Neonatology
1,2Neonatal Medicine and Department of Paediatrics, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa

CASE

Dichorionic twin boys were delivered vaginally at 33 weeks to a 28 year old human immunodeficiency virus (HIV) positive mother who was virally supressed on highly active antiretrviral therapy (HAART). Twin B was 1755 grams and required surfactant and continuous positive airway pressure (CPAP) post-delivery due to respiratory distress syndrome. Twin A was 1850 grams and well.

The infant received Penicillin and Gentamycin for 48 hours due to the mother’s spontaneous preterm labour and he was also started on Nevirapine prophylactically. Formula feeds were gradually increased at a rate of 24ml/kg/day, but the baby continued to experience recurrent non-bilious vomiting even after continuous gastric infusion was started. On day 9 of life, after surgical causes, sepsis and necrotising enterocolitis (NEC) were excluded, it was decided to insert a nasojejunal tube (NJT) with the abdominal x-ray (AXR) confirming the tube had passed through the pyloric sphincter (figure 1). This resulted in decreased, but not complete resolution of the vomiting.

On Day 12 of life, the NJT was dislodged and due to a marked increase in symptoms, it was re-inserted with little difficulty and the infant was not distressed.

However, the AXR post re-insertion showed the NJT in an unusual position in the chest (figure 2) and it was removed immediately.

The most likely explanation is a small oesophageal perforation leading to the NJT entering the mediastinal space.

As the treatment of oesophageal perforation in neonates is usually conservative,1 the baby was treated with prophylactic antibiotics, and made an uneventful recovery. Feeds were re-initiated via nasogastric tube and gradually increased. Although vomiting persisted, this did diminish with time and the baby was changed to bolus feeds on day 24 and breast and cup feeds on day 30 of life. After 3 days of uneventful kangaroo-mother-care (KMC), the baby was discharged on day 33. Follow-up

Figure 1. X-Ray showing the NJT in the correct position, having passed through the pylorus

Figure 2. X-Ray showing the NJT in the mediastinum. Presumably it has perforated the oesophagus.
The feeding of preterm infants is an extremely important topic. Compared to term infants, preterm babies have more gastro-oesophageal reflux due to increased laxity in the lower oesophageal valve. Marked reflux has been reported to lead to increased levels of apnoea, bradycardia and aspiration, as well as poorer weight gain. Placing the enteral feeding tube through the pylorus therefore has the potential to decrease gastro-oesophageal reflux and its purported side effects. However, these transpyloric tubes are more difficult to place, require imaging to confirm their correct positioning and have potential other complications due to bypassing the gastric phase of digestion. There are also numerous case reports documenting complications such as intestinal perforation or pyloric stenosis following their use.

Two recent meta-analyses concluded that there is no evidence that routine transpyloric feeding has any benefits for preterm infants compared to gastric feeding. In fact, there is a higher risk of adverse events including gastrointestinal disturbances and one study demonstrated increased mortality in the transpyloric group. The meta-analyses did not show an increased risk of NEC, intestinal perforation or pyloric stenosis.

We recommend that transpyloric feeding should be used with extreme caution due to the potential adverse events for no proven benefit. We have not used this method of feeding since this incident.

REFERENCES


Correspondence: Lloyd.tooke@uct.ac.za

The Paediatric Quiz

The following photograph is that of a day 1 neonate.

**Question**

What is the Diagnosis?

For the answer and discussion, please go to page 13.
Abstract

Newborns are at particular risk for thrombotic emergencies secondary to the unique properties of their haemostatic system. Thrombotic complications are an important cause of morbidity and mortality. Prompt identification and appropriate management of thrombotic emergencies is critical in avoiding life-threatening complications. Treatment strategies have been extrapolated from adult literature but clinical experience from small-scale neonatal studies has resulted in therapeutic guidelines, which should be individualized for each neonate, taking into consideration age, risk factors and clinical status. In this case report, we describe a case of a patient with symptomatic thrombosis and the intervention thereof.

CASE

A 2.7 kg baby boy of term gestation was delivered at base hospital via caesarian section for foetal distress and meconium stained liquor grade 3. The mum was a 23 year old primigravida who was human immunodeficiency virus (HIV) positive on highly active antiretroviral therapy (HAART).

The neonate was referred to a tertiary level neonatal intensive care unit with meconium aspiration syndrome complicated by persistent pulmonary hypertension of the newborn (PPHN). The baby was treated for meconium aspiration syndrome and persistent pulmonary hypertension of the newborn (PPHN). The patient did have an umbilical vein catheter and an umbilical arterial catheter in situ, which were removed on day 5 of life.

During his stay in the unit, on day 13 of life, nursing staff reported difficulty in measuring the blood pressure in the lower limbs. It was noted that he had poor lower limb perfusion with impalpable lower limb pulses. The consideration was that this might be secondary to arterial occlusion from a thrombus.

An ultrasound doppler done in the unit revealed the presence of a thrombus in abdominal aorta. A computed tomography (CT) angiogram confirmed features suggestive of abdominal aortic occlusion at the level of origin of the superior mesenteric artery (see figure 1).

Thrombolytic therapy in the form of tissue plasminogen activator (tenecteplase) was administered to the patient. A dose of 100 iu/kg was given intravenously over ten seconds via a peripherally inserted central catheter. This dose was repeated after 24 hours. In addition, a work-up for thrombotic tendency was done. The patient was also commenced on aspirin therapy at a daily dose of 5mg/kg per os.

Further doppler examination showed improved flow patterns in the aorta after thrombolytic therapy. The patient’s perfusion improved and pulses were palpable. A follow up CT angiogram indicated re-canalisation of abdominal aorta distal to the previously mentioned occlusion at the infra-renal level (figure 2).

Figure 1. CT angiogram suggestive of abdominal aortic occlusion at the level of origin of the superior mesenteric artery.

Figure 2. CT angiogram after tenecteplase.
After 29 days at the tertiary neonatal unit, the patient was discharged to base hospital on aspirin and was due for follow-up at the neonatology clinic.

At follow-up, the patient was noted to be doing well, with good lower limb perfusion and palpable pulses. Repeat ultrasound doppler revealed good flow through iliac arteries.

**DISCUSSION**

**Background**

As survival of premature and sick newborns has improved, the frequency of complications associated with intensive supportive therapy and monitoring has increased. Clinically significant thrombosis is emerging as a serious complication in the intensive care of sick babies.

The incidence of neonatal thrombosis is said to be 2.4 per 1000 admissions to neonatal intensive care units in Canada, 5.1 per 100,000 births in Germany, and 14.5 per 10,000 neonates in Netherlands.\(^1\)

The unique developmental characteristics of the haemostatic system place the neonate at increased risk for thrombosis.\(^1\) There is an overall reduction in thrombin potential, along with altered fibrinolytic pathways. In addition, these developmental changes in the haemostatic system impact on treatment of neonatal thromboembolism.\(^2\)

Neonatal thrombosis is commonly associated with indwelling vascular catheters. Of note, autopsy studies shows 20-65 % of infants who demise with an umbilical vein catheter in place have associated thrombus.\(^2,3\)

**Unique physiological characteristics of the coagulation / thrombotic pathway in neonates:**\(^1,4,5\)

- In utero, coagulation proteins are synthesised by the foetus and do not cross the placenta
- Both the thrombogenic and fibrinolytic pathways are altered in the neonate
- At birth, concentrations of the vitamin K dependent factors (Factor II, Factor VII, Factor IX, Factor X) are reduced to about 50% of normal adult values and are further reduced in preterm infants
- Similarly, concentrations of the naturally occurring anticoagulants, are low at birth
- Plasminogen is the major protein involved in fibrinolysis
- Neonates have a decreased ability to generate thrombin
- Platelets are hypo-reactive
- Bleeding time shortened in neonates
- The haemostatic system matures during the early weeks and months of life

These factors, place the neonate at particularly high risk for developing thrombus.

**Risk Factors**

Central venous and arterial catheters are the most common acquired risk factors for developing a thrombus.\(^1\)

Deficiencies of protein C, S, anti-thrombin, and Factor V Leiden are amongst the common genetic causes for developing a thrombus. These deficiencies can be congenital or as a result of prematurity.\(^1,6\)

<table>
<thead>
<tr>
<th>Congenital risk factors</th>
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<tbody>
<tr>
<td>Deficiencies of protein C and S</td>
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<td>Deficiencies of anti-thrombin III, Factor V Leiden</td>
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<th>Maternal risk factors</th>
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<td>Oligohydramnios</td>
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<td>Prothrombotic disorder</td>
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<td>Preeclampsia</td>
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<td>Diabetes</td>
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<td>Intrauterine growth restriction</td>
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<td>Prolonged rupture of membranes</td>
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<td>Autoimmune disorders</td>
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<td>Emergent caesarian section</td>
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<td>Foetal heart rate abnormalities</td>
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<td>Instrumentation</td>
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<th>Neonatal risk factors</th>
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<td>Central catheters</td>
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<td>Congenital heart disease</td>
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<td>Sepsis</td>
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<td>Birth asphyxia</td>
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<td>Respiratory distress syndrome</td>
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<td>Dehydration</td>
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<td>Congenital nephritic / nephrotic syndrome</td>
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<td>Necrotizing enterocolitis</td>
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<td>Polycythemia</td>
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<td>Pulmonary hypertension</td>
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<tr>
<td>Surgery</td>
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<tr>
<td>Extracorporeal membrane oxygenation</td>
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<td>Medications (steroids, heparin)</td>
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**Table 1: Congenital and acquired risk factors for developing thrombosis in the neonate.**\(^6\)

**Clinical Manifestations**

The clinical presentation of thrombosis in neonates largely depends on site of occlusion and organ specificity. Postnatal thrombo-embolic events occur in the neonate in a number of locations, whether venous or arterial. Table 2 below describes the signs and / or symptoms according to location and vessel type.

**Investigations**

Baseline laboratory testing includes:

- Activated partial thromboplastin time (aPTT)
- Prothrombin time (PT) and international normalized ratio (INR)
- Plasma fibrinogen concentration
- Platelet count

The extent of workup is dictated by the presence of the inciting factor/s for thrombosis and the probability of underlying thrombophilia based on clinical evidence.\(^7\) Thrombosis must be confirmed before thrombolytic or anticoagulation treatment is initiated due to the risk of intracranial haemorrhage or other significant bleeding events.
Figure 3. Diagrammatic representation of the 3 pathways that make up the Classical Blood Coagulation Cascade.

Table 2. Symptoms and signs according to vessel and type / location.

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Type / Location</th>
<th>Symptoms and / or Signs</th>
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<tbody>
<tr>
<td>Venous</td>
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<tr>
<td></td>
<td>Inferior vena cava</td>
<td>Swelling of the lower limbs and lower body</td>
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<td></td>
<td>Superior vena cava</td>
<td>Swelling of the arm, neck, and head</td>
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<td>Renal vein</td>
<td>Flank mass, haematuria, or thrombocytopenia</td>
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<td>Intra-cardiac</td>
<td>New murmur, heart failure, or persistent sepsis</td>
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<td>Portal hypertension</td>
<td>Liver dysfunction and portal hypertension</td>
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<td>Cerebral venous sinus</td>
<td>Seizures, apnoea, and lethargy</td>
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<tr>
<td>Arterial</td>
<td>Ischaemic perinatal stroke</td>
<td>Seizures, lethargy, hypotonia, apnoea, poor feeding</td>
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<tr>
<td></td>
<td>Iatrogenic</td>
<td>Line dysfunction, extremity blanching and / or cyanosis, persistent thrombocytopenia, sepsis</td>
</tr>
</tbody>
</table>

Colour duplex doppler is the principal diagnostic modality used to detect thrombosis and is non-invasive. However, the limitation of doppler is it is operator dependant. Further precise diagnosis can be obtained by contrast angiography and CT scan.

Management

The management of patients with suspected or confirmed thrombosis is a challenging one. The literature on thrombolytic treatment for neonatal thrombotic disease contains reports of single cases and small series, with poor guidelines on management. Management involves an extrapolation from adult studies. The approach to the infant must balance risks and benefits. If it is an asymptomatic thrombus, management includes supportive care, monitoring and removal of an existing venous or arterial umbilical catheter. In terms of primary prophylaxis, low dose heparin by continuous infusion is used to prolong peripheral and umbilical catheter patency. If thrombus extends or is symptomatic, then
treatment with anti-coagulation and/or thrombolytic therapy is warranted.9

Treatment with anti-coagulation includes either unfractionated heparin or low molecular weight heparin. The mechanism of unfractionated heparin is to catalyse the ability of antithrombin to inactivate specific coagulation enzymes, in particular thrombin and Factor Xa. The studies of the use of unfractionated heparin in newborns are limited. Low molecular weight heparin is considered to be the anticoagulant of choice in neonates.9 This is due to lack of requirement of intravenous access, longer duration of anticoagulant effect as well as reduced monitoring requirements. Its mechanism of action is that it potentiates the inactivation of factor Xa by antithrombin. The major side effect with unfractionated heparin as well as low molecular weight heparin is bleeding.

The action of thrombolytic agents is mediated by the conversion of endogenous plasminogen to plasmin. Subsequent cleavage of fibrin results in clot breakdown. Thrombolytic therapy, for use in neonates should be reserved for limb, organ, and/or life-threatening thrombosis, including right atrial thrombosis. It is important to rule out contraindications to the use of thrombolytic therapy.

Table 3. Absolute contra-indications to use of thrombolytic therapy.1,9

<table>
<thead>
<tr>
<th>Absolute contraindications include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• CNS surgery or ischaemia within 10 days</td>
</tr>
<tr>
<td>• Active bleeding</td>
</tr>
<tr>
<td>• Invasive procedures within 3 days</td>
</tr>
<tr>
<td>• Seizures within 48 hours</td>
</tr>
</tbody>
</table>

The drugs used in paediatrics are the same as those used in adult medicine, namely streptokinase (SK), urokinase (UK) and tissue-type plasminogen activator (t-PA).

Tenecteplase

Tenecteplase is an excellent anti-thrombolytic. It is a recombinant fibrin-specific plasminogen activator that is derived from native t-PA by modifications at three sites of the protein structure.11 It binds to the fibrin component of the thrombus (blood clot) and selectively converts thrombus-bound plasminogen to plasmin, which degrades the fibrin matrix of the thrombus. It is given intravenously or intra-arterially, and metabolised in the liver. Because of the potential for major bleeding, and the general lack of information, thrombolytic therapy should likely be reserved for newborns with life, organ, or limb threatening situations.9

Prior to thrombolytic therapy, both an ultrasound of the brain to determine if there is a pre-existing haemorrhage and coagulation screening tests to detect a concurrent coagulopathy are recommended.11,12

Decisions on use of treatment must be individualised.12 Neonates remain the highest risk group for thrombosis. Appropriately designed and controlled clinical trials still needed to guide the management of thrombo-embolism in neonates and improve outcomes. The judicious use of anti-thrombolytic agents has the potential of revolutionising management of thrombosis of the neonate.
Conclusion and Recommendation

Current recommendation in the management of acute thrombosis in the newborn should include the use of tenecteplase after due consideration of its risk profile.

REFERENCES


Correspondence: hassinaebraham6@gmail.com

ANSWER TO THE QUIZ ON PAGE 8

Answer

Giant Congenital Melanocytic Nevus

DISCUSSION

C ongenital melanocytic nevi (CMN) are collections of melanocytes that are arranged in nests in the epidermis, dermis or in other tissue and are present at birth or develop within the first year of life or even the first 2 years of life.1,2 Although CMN develop during intrauterine life, the occurrence of these late congenital nevi may be explained by the insufficient initial production of melanin and/or by the small size of the nevus early on, hindering its detection.1

Melanocytes (pigment producing skin cells) are found in utero at about 40 days gestation and are of neuroectodermal origin.3 Congenital melanocytic nevi (CMN) originate between the 5th and 24th weeks of gestation.14 It is thought that a morphological error occurs in the neuroectoderm during embryogenesis, leading to accelerated proliferation of melanoblasts, the precursor cells of melanocytes.1,5,6

Nevi will be larger and deeper when this process starts during the embryonic or early foetal periods. The later the onset of cell proliferation, the smaller the melanocytic lesion will be.1,6 Small CMN and acquired nevi, therefore arise after melanoblasts have reached the epidermis (which occurs around the 10th week in utero, when cell differentiation begins). If melanocytes located in the dermal-epidermal junction begin to multiply shortly before birth, the result would be a small CMN. If proliferation begins after birth, it would produce an acquired melanocytic nevus. Thus, the common origin between acquired nevus and small CMN would explain the clinical and histopathological similarity of these lesions reported in some studies.1

CMN present as macular, papular or plaque-like, roughed, warty or cerebriform pigmented lesions. The pigmentation of nevi can range from tan to dark brown and depends on the concentration and kind of melanin, a natural pigment produced from the amino acid tyrosine in the skin (in the basal layer of the epidermis).1,7 Nevi are important because they may be associated with severe complications such as malignant melanoma, affect the central nervous system (neurocutaneous melanosis) and have a major psychosocial impact on the patient and his or her family due to its unsightly appearance.1,5,7

About 1% of live births present with CMN and large or giant melanocytic nevi (GCMN) occur in approximately 1 in 20 000 newborns. The variety “garment-like” of GCMN is even rarer with an incidence of 1 : 500 000.1,8,9

Nevi can vary in size from small to large or giant covering almost the entire body.1 According to the definition, the diameter of a giant CMN must exceed 9 cm (20 cm in adulthood) or 2% of body surface area.7 Attempts to classify CMN according to their size derive mainly from the fact that the risk of complications is proportional to the diameter of the nevus. Over the last few decades, various criteria have been used by
different authors to define a CMN as giant. However, the classification proposed by Kopf et al is the most accepted. Kopf et al proposed an arbitrary classification of CMN according to their largest diameter in adulthood, dividing them into small (<1.5 cm), medium (from 1.5 cm to 19.9 cm) and large or giant (>=20 cm).

More recently, Ruiz-Maldonado suggested a modification to this classification, defining medium CMN as those with an average size between 1.5 cm and 10 cm, large as those between 11 cm and 20 cm and giant nevi as those more than 20 cm in diameter. Lesions typically grow proportionately with the individual and most commonly are categorized according to assumed adult size. Allowing for expected proportionate growth, CMN measuring approximately 9 cm in diameter on the head or 6 cm on the body in neonates qualify as large CMN (LCMNs). One way of obtaining an estimate of the size of CMN in adult life is multiplying the diameter of the lesion in the infant by a numerical factor that varies according to the location of the nevi (see table 1).

<table>
<thead>
<tr>
<th>CMN location on infant</th>
<th>CMN diameter at birth (cm)</th>
<th>Factor#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>11.8</td>
<td>1.7</td>
</tr>
<tr>
<td>Hands, feet, torso, forearms, hips</td>
<td>7.2</td>
<td>2.8</td>
</tr>
<tr>
<td>Thighs</td>
<td>5.9</td>
<td>3.4</td>
</tr>
<tr>
<td>Legs</td>
<td>6.1</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Table 1. Estimated size of CMN in adulthood based on its diameter in infancy. CMN: Congenital melanocytic nevus.

*Diameter in which the nevus would reach at least 20 cm in adulthood.

#Factor that should be multiplied by the CMN diameter in infancy to obtain its estimated size in adulthood.

There is a slightly higher prevalence of GCMN in female patients with ratios ranging from 1.17:1 to 1.46:1. Although GCMN can affect any region of the body, it’s most frequent location is the torso or trunk, followed by the limbs and head (scalp and neck). Commonly, however, GCMN affects more than one body segment. Some peculiar locations led to the term “GCMN in garment” or “garment-like” which describes the “bathing trunk”, “stole” or “coat sleeve” distribution.

The textures of CMN vary and CMN may be with or without hair. In newborns CMN may have a lighter colour and present few or no hair follicles and occur as a macule or as an elevated lesion.

Giant CMN are commonly associated with benign melanocytic growths within the substance of the lesion, termed “proliferative nodules”. The presence of smaller pigmented lesions scattered over the skin surface, known as satellite nevi is common in individuals with GCMN, occurring in up to 78% of cases. These satellite nevi are present at birth or arise months to years later. Over time, GCMN can undergo a process of darkening or lightening, develop a more heterogeneous or homogeneous pigmentation, present with an increase in hair growth, acquire a more irregular surface or more rarely, spontaneously regress. Generally, however, lesions tend to become thicker over time.

Some cases of depigmentation have been reported around the nevus region (halo phenomenon), in the nevus and/or in skin areas distant from it. This depigmentation is interpreted as an autoimmune phenomenon, involving a response of the immune system to melanocyte antigens.

Although usually an asymptomatic lesion, patients with CMN may complain of pruritis, the mechanism of which is not fully understood. GCMN may also have important psychological consequences especially when lesions are very extensive and located in visible areas such as the face. Emotional or behavioural problems arise as a result of an impaired self-image caused by the presence of the nevus, the anxiety over the risk of complications such as melanoma, the discomfort caused by multiple invasive treatments and even by the unsightly appearance of surgical scars. Parents and other family members also often present with psychological symptoms associated with the difficulty in accepting the problem and dealing with its implications.

It is believed that the increased incidence of melanoma in individuals with GCMN, compared to those with acquired nevi and small CMN, is explained by the significantly larger number of melanocytic cells or by a different biological behaviour of melanocytes in GCMN. Changes in gene regulation associated with deoxyribonucleic acid repair mechanisms or tumour resistance to chemotherapy were observed in GCMN. There is also evidence of structural chromosomal abnormalities in the process of malignant transformation of these lesions.

Melanoma developing in large/giant CMN must be considered in patients with lesional changes, including the development of papules, nodules, erosions or colour variations, although all of these may represent normal progression of the lesion.

Large/giant CMN may be associated with limb hypoplasia, spinal dysraphism and myelomeningocele when in a lumbosacral manifestation or neurocutaneous melanosis (NCM) when located on the head or neck. Various malignant tumours and malformations have also been observed.

Table 2. Key pointers to melanoma transformation in large/giant CMN.

Neurocutaneous Melanosis

Neurocutaneous melanosis (melanocytosis) (NCM) is a rare congenital disorder in which the leptomeninges contains excessive layers of melanocytes and melanin. Large/giant CMN on the neck, head and posterior midline is a risk factor for development of the disease. The presence of more than 20 satel-
The risk of developing NCM is not exactly known but is assessed to range from 3% to 12% in the reviewed groups of patients with GCMN. Neurological manifestations of NCM depend on localization and extension of the lesions and usually occur before 2 years of age; less frequently symptoms appear in the 2nd and 3rd decade of life. The most characteristic CNS symptoms include increased intracranial pressure, seizures, motor deficits, aphasia, and hydrocephalus. In case of spinal localization, myelopathy, radiculopathy and bowel or bladder dysfunction may occur.

Prognosis in symptomatic NCM is poor but asymptomatic patients have a more unpredictable course. In the literature, most of the symptomatic patients died before the age of 10 years. The use of chemotherapy and radiation are not effective in modifying the course of the disease. Palliative treatments such as the use of shunts to reduce intracranial pressure and administration of anticonvulsants may be used.1

There may be associated other structural CNS malformations such as arachnoid cysts, choroid plexus papilloma, cerebellar astrocytoma, spinal dysraphism (associated with GCMN located in the lumbosacral region) and type I Arnold-Chiari (herniation of cerebellar tissue through the foramen magnum). Dandy-Walker malformation may be associated with NCM or occur in the absence of CNS involvement by melanocytic cells and is characterized by cystic enlargement of the fourth ventricle, aplasia or hypoplasia of the cerebellar vermis and an increase of volume of the posterior fossa with or without hydrocephalus.1

Histology

The histological characteristics may be heterogeneous within a nevus. Nevus cells (melanocytes) extend from the dermal-epidermal junction into the deep part of the skin and sometimes to subcutaneous tissue.7 Histologic findings of CMN may be the same as for acquired nevi or may show some differentiating features.

GCMN diagnosis is mainly clinical.7 Histologically, the benign proliferation of melanocytes in a nested pattern, which may extend through subcutaneous fat or within epithelial structures of adnexa, is diagnostic of large / giant CMN. Differentiation from other pigmented lesions may be aided by staining techniques with antibodies. Dermatopathology consultation may be appropriate for distinguishing abnormal histologic features in patients with large / giant CMN because misdiagnosis of benign CMN as a melanoma is not uncommon.2

Treatment

The clinical management of patients with small or intermediate CMN remains controversial. Most CMN may be safely followed up clinically, with or without photographic documentation. The decision to excise lesions and the timing of excision should be governed by an individualized assessment of factors such as appearance of the lesion (i.e. colour and presence of papules or nodules), technical ease of surgery and expected cosmetic result. Q-switched laser treatment of CMNs has been attempted but initially promising results have been tempered by recurrence.2

Treatment of GCMN remains a multidisciplinary challenge. The decision concerning the best way of management of the child with GCMN is complicated because it involves a multidisciplinary medical team without certainty of success in every patient.7 The treatment must be tailored individually for each case taking into consideration the age of the patient, size and location of the lesion, risk of repeated general anaesthesia, risk of melanoma, possibility of concomitant NCM, the presence of changes suggestive of malignancy on the nevus, possible functional impairments resulting from invasive procedures and the psychological impact (on the child and the parents) associated with the CMN or the surgical scars, often unsightly.1,7 Thus, treatment options include surgical or non-surgical procedures, psychological and / or clinical interventions.1

Surgical interventions also include various possibilities such as full thickness excisions, partial thickness excisions, dermabrasions, curettage and laser treatment, but there is no agreement about the best age at which to begin the surgery and the evaluation of which option at which age is best.7

The decision of whether or not a patient should undergo surgical treatment involves both the technical difficulties of performing such procedures (especially when considering the cosmetic motivations) and the uncertainties regarding its effectiveness as a prophylaxis against melanoma.

While there is no current evidence that the removal of the nevus has a prophylactic role against the onset of melanoma, prophylactic surgical excision would be justified based on the assumption that the melanoma may arise on the nevic lesion. However, 50% of melanomas found in patients with GCMN occur elsewhere. Therefore, the removal of the nevus does not guarantee protection against malignancy. Furthermore, the size of the lesion may prevent complete resection. The size of the lesions makes their removal often dependent on the use of tissue expanders (especially nevi locate on the head or neck), serial interventions, the use of skin flaps, grafts or a combination of more than one type of surgical procedure.1

The partial removal of GCMN by procedures such as dermabrasion, skin curettage, tangential excision (shave excision), chemical peels and laser treatment has mostly cosmetic purposes, since only the most superficial cells of the lesion are removed. The use of laser in the treatment of GCMN is controversial. Lasers that can be used for this purpose are ruby, Q-switched and carbon dioxide lasers. However, though they may improve the aesthetic appearance of some lesions and reduce the number of melanocytic cells, there is some concern that the nevus cells exposed to sub-lethal doses of energy may have a higher probability of malignant transformation. Repigmentation may also occur. Thus, it is recommended to consider using the laser only when an interventional approach is the choice and surgical treatment is not feasible.1

Despite the controversy about the treatment, it is a consensus that the only absolute indication for surgical intervention in GCMN is the emergence of a malignant neoplasm on the lesion. It is important to note that even patients whose nevus was completely removed must undergo lifelong, regular examina-
tions of all skin and general medical examination to facilitate the detection of any malignancy in its earliest stages.¹

**Prognosis**

Congenital nevi are clinically significant because of their association with malignant melanoma. The risk for melanoma in patients with small CMN is 2.6% to 8.1%. Overall, the neonatal risk seems minimal and the lifetime risk unclear because of limited studies on the natural history of CMN and the influence of factors such as family history or sun exposure.² The estimated lifetime risk for melanoma in patients with LCMN, which are mostly found on the posterior trunk but also located to the head, neck or extremities, is less disputed and ranges between 6% and 8%.² The risk for melanoma arising in GCMN is about 5 – 15%. Melanoma may develop in infancy or in childhood.³

Approximately half of these melanomas become manifest within the first 5 years of life with a peak of malignant transformation during the prepubertal years. Axial location confers a higher risk, whereas satellite nevi, which are common in patients with large / giant CMN and continue to develop over time, have not been associated with malignancy.³

When melanoma arises in GCMN, the prognosis is especially dismal. Trozak et al, observed that none of the 20 patients whose tumour was associated with GCMN was alive at the end of 5 years, whereas among 35 other individuals (smaller nevi) diagnosed with prepubertal melanoma, the survival rate in the same period was 34.3%.¹,³,¹⁵

Cutaneous melanoma associated with GCMN typically grows in the dermis, making it more difficult to detect in clinical examinations, unlike the malignant transformation that occurs in smaller or medium CMN which starts at the dermal-epidermal junction and rapidly changing the appearance of a nevus. In the case of GCMN it is often necessary that a large nodule develops or ulceration occurs before the diagnosis of cancer is made. The often rough or nodular surface of GCMN further complicates the early observation of the tumour.¹

The great extent of nevic lesions causes their lymphatic drainage to be performed by multiple channels and the presence of malignant cells in the deeper layers of the nevus facilitates tumour spread through the lymph and blood vessels of greater caliber, favouring the occurrence of early metastases. In 24% of cases, melanoma will already be metastatic at the time of diagnosis without the primary site being identified.¹

**REFERENCES**


**This Quiz was submitted by:**

Dr S Pather
MBCHB, DCH, FCPath(SA)
Head of Clinical Unit Paediatrics, R.K. Khan Hospital and Honorary Lecturer, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban

**Correspondence:** selvanpather@telkomsa.net
Background

The Paediatric Quarterly (abbreviated Paediatr. q.) (ISSN number 2073-7645) is a free quarterly paediatric journal for paediatricians, paediatric registrars, paediatric medical officers, paediatric surgeons and healthcare professionals with an interest in paediatrics.

Articles and case reports published in The Paediatric Quarterly must be of clinical interest and educational value to the target reader. Relevant paediatric case reports and articles are invited from medical officers, registrars and specialists in all institutions throughout South Africa, as well as abroad. Each article / case report will be peer reviewed by at least one of the editors.

Protection of identifying details of patients

Any article in The Paediatric Quarterly that contains personal medical information that identifies the discussed patient requires the parent’s or guardian’s explicit consent before we can publish it. If consent cannot be obtained because the parent cannot be traced then publication will be possible only if the information can be sufficiently anonymised.

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Ethical approval for case reports published in The Paediatric Quarterly is not routinely required, unless in the opinion of the editors, the nature of the case report is such that ethical approval is required. In such cases, the report will be returned to the author for obtaining of ethical approval prior to publishing.

Authorship and Acknowledgements

There must be agreement on authorship based on substantial contribution to the case report and discussion. All persons who in the opinion of the authors contributed significantly to the final published article must be acknowledged at the end of the article, and their contributions preferably stated.

All articles must have the full names, qualifications and designation of each author, as well as the complete contact details of the corresponding author. If any conflict of interests exist, this must be declared.

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The length of all articles submitted must be no more than 3500 words including content and legends of tables, diagrams and photographs. Case reports will only be published in The Paediatric Quarterly if they have not previously been published elsewhere.

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