A review of the use of high flow nasal cannula oxygen therapy in hospitalized children at a regional hospital in the Cape Town Metro, South Africa

By

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DECLARATION

I, Elizabeth Hoffman, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abstract

Background: High-flow nasal cannula oxygen (HFNC) is a non-invasive alternative to nasal continuous positive pressure oxygen (CPAP) therapy for infants and children requiring respiratory support. There is a paucity of literature to support its use in children, with no published data from sub-Saharan Africa.

Objective: To describe the outcomes and adverse events of HFNC in the first year of its use in a level two (L2) general paediatric ward, compared with outcomes of a historical cohort when this intervention was unavailable.

Methods: This retrospective descriptive study included children aged <13 years who received HFNC in the first 12 months after its introduction (HFNC-availability group; *n*=66). Demographic data, clinical characteristics, and outcomes (death, treatment failure, length of HFNC, and HFNC-related adverse events) were assessed. A comparative description of children that required transfer to level 3 (L3) for respiratory support (more than available standard low-flow oxygen) in the 12-month period prior to HFNC availability (pre-HFNC group; *n*=54) was performed and outcomes were compared using standard descriptive and comparative statistics.

Results: The median age of the cohort was 5 months (interquartile range [IQR] 1.9–14.6). Sixteen children (13.3%) were malnourished, 10 (8%) were HIV infected, and 30 (25%) were ex-premature infants. The most common diagnoses were pneumonia, bronchiolitis, and asthma. Asthma, anaemia, and cardiac abnormalities were the most prevalent underlying co-morbidities. Two children died in each group. All 54 children in the pre-HFNC group were transferred to L3; 38 (70.4%) needed CPAP or invasive ventilation. In the HFNC-availability period, 85 children were assessed as needing more than standard low-flow oxygen therapy: 19 were immediately transferred to L3 where 17 (89.4%) received CPAP or invasive ventilation; 66 received HFNC at L2, 16 (24.2%) of these children required transfer to L3 for CPAP or invasive ventilation. The median duration of HFNC was 46.3 h (IQR 19.5–93.5) overall, and was 12 h (IQR 4-28) and 58.5 h (IQR 39.5–106) for those who failed or were successfully managed on HFNC, respectively. No HFNC-related serious adverse events were recorded at L2.

Conclusion: HFNC is a safe, effective, feasible option for non-invasive ventilation of children with respiratory illnesses in a resource-limited L2 setting. A greater proportion of children admitted with lower respiratory tract infections required support in the HFNC-availability group, but the intervention reduced the bed-

pressure on L3. Improved identification of HFNC failures and better adherence to the protocol is needed at L2.

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3. List of abbreviations:

ART	Antiretroviral therapy
CPAP	Continuous positive airway pressure
$ETCO_2$	End tidal carbon dioxide
FiO_2	Fraction (percentage) of inspired oxygen in volume being measured
HR	Heart rate
HFNC	High flow nasal cannula oxygen
HIV	Human immunodeficiency virus
ICU	Intensive care unit
IMCI	Integrated management of childhood illness
IPPV	Intermittent positive pressure ventilation
L2	Level two hospital (Regional hospital)
L3	Level 3 hospital (Tertiary hospital)
LBW	Low birth weight (<2500 g)
LFNC	Low flow nasal cannula oxygen
LRTI	Lower respiratory tract infection
nCPAP	Nasal continuous positive airway pressure
NP	Nasopharyngeal pressure
NIV	Non-invasive ventilation
OP	Oesophageal pressure
PARIS	Paediatric acute intervention study
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood sample
PICU	Paediatric intensive care unit
NSH	New Somerset Hospital
PEEP	Positive end expiratory pressure
PMTCT	Prevention of mother to child transmission
PTB	Pulmonary tuberculosis
RCT	Randomized clinical trail
RR	Respiratory rate
RSV	Respiratory syncytial virus
SaO_2	Oxygen saturation of arterial blood
SA	South Africa
SATS	South African Thoracic Society
TGI	Tracheal gas insufflation
WHO	World Health Organization

4. CHAPTER ONE: BACKGROUND AND LITERATURE REVIEW

Background

Acute severe lower respiratory tract infections remain a major cause of mortality and morbidity globally (13% mortality)[1,2] and in South Africa.[1] Pneumonia was shown to be the leading cause of death in a recent review of mortality among children under 5 years old in the Metro West geographical service area of the Western Cape Province; it accounted for 25% of all deaths.[3] Early and appropriate treatment of pneumonia can reduce morbidity and mortality.[4] Comprehensive guidelines have been developed, including recommendations contained in the Integrated management of childhood illness (IMCI) strategy and South African Thoracic Society (SATS) guidelines.[5] Appropriate and rational antibiotic use, supportive care and standard low-flow oxygen delivery (nasal prongs or face mask) form part of these guidelines.[5,6] However, in most resource-limited countries, mortality from severe pneumonia (related to hypoxia and respiratory failure) remains high despite implementation of guidelines.[6] Additional respiratory support, central to the care of critically ill children, is often unavailable or perceived as not being feasible or safe in resource-limited settings.[6,7]

The use of non-invasive ventilation (NIV), including nasal continuous positive airway pressure (CPAP) and high-flow nasal cannula oxygen (HFNC) within and outside the paediatric ICU, is growing.[8] The use of simple, self-made CPAP devices has been shown to decrease mortality (compared with the use of standard low-flow oxygen systems) in children with severe hypoxic pneumonia in a trial conducted in Bangladesh,[9] and researchers in Ghana showed that nurses can successfully and safely apply CPAP after receiving appropriate training.[10] Initially, HFNC was only used as an alternative to nasal CPAP to provide respiratory support to premature infants.[11] Now it is increasingly being utilized in infants and children with a variety of underlying reasons for respiratory distress.[12] Evidence from observational studies, mostly, indicates that HFNC may provide an increased level of respiratory support relatively safely, even outside the intensive care unit (ICU). Most studies to date have assessed HFNC use in children with bronchiolitis and have been conducted in developed countries.[12] Despite the increased use of HFNC in infants and children, there is a paucity of literature to support its use,[12] and no published data exist from South Africa or from sub-Saharan Africa.

Objectives

The objectives of the literature review were:

- To describe the impact of acute lower respiratory tract infection on paediatric morbidity and mortality in the research setting, in South Africa and globally.
- To review the mechanism of action of HFNC, including concerns regarding the provision of positive distending pressure.
- To review the experience and outcomes of HFNC use in infants and children.
- To review data on the complications related to HFNC, possible indicators of HFNC failure, and costs.

Literature search strategy and search results

PubMed and replicated searches (as allowed by the search format for HFNC studies) in Scopus, Web of Science, Cochrane and Africa wide via EBSCO were searched from inception until February 2017 using the following keywords:

- Children AND infants AND acute lower respiratory tract infection AND incidence AND developing countries
- Children AND acute lower respiratory tract infection AND hypoxia AND developing countries
- Under five child deaths AND western cape
- Children OR infants AND high flow OR high-flow nasal (cannula OR prong)

The searches were performed in 2017. The search was limited to children aged 0–18 years, regardless of study design. Preference was given to articles from the developing world. Related links and references in the selected articles were reviewed. Additional articles and guidelines were included which were recommended by either the supervisor or experts in the field.

The search strategy identified 107 articles: additional studies were included from reference list of these articles and from recommendations. A total of 114 full text articles were reviewed, and 48 articles were eventually referenced. The majority of the articles were from the latter part of the last decade, but 8 articles prior to 2007 were also included.

4.1. HFNC mechanism of action

Non-invasive ventilation, including nasal CPAP and recently HFNC, involves provision of ventilatory support without using an invasive artificial airway. CPAP is widely used for children with moderate or severe respiratory distress in ICUs in developed countries.[9]

HFNC provides heated (37°C), humidified (99% relative humidity), unblended or blended oxygen and air at flow rates of >1 L/min via nasal cannula.[14,15] Standard low-flow nasal cannulae provide dry, mostly cold, unblended oxygen at a flow rate of ≤1 L/min. Table 1 compares HFNC and nasal CPAP, both of which can provide unblended or blended oxygen and air that is heated and humidified.

Table 1. Main differences between HFNC and nasal CPAP

	HFNC	**Nasal CPAP**
Delivery mechanism	Nasal cannula	Nasal prongs/mask
Flow rate	>1 L/min (weight dependent) Range: 8 L/min (neonates) to 50 L/min (adults)	Variable
Positive distending pressure	Variable and unregulated	Variable and regulated

HFNC, high-flow nasal cannula; CPAP, continuous positive airway pressure.

HFNC likely works via the heating and humidification of inspired air, carbon dioxide wash-out of the nasopharyngeal space, reduction in upper airway resistance, and the provision of positive distending pressure. [14,16-19] Most physiological studies on how HFNC works are either observational studies performed in preterm neonates or laboratory-based simulation mode studies. Recently, 4 prospective observational/cohort studies were performed in infants and children.[25-28] The current paucity of data regarding the unregulated variable positive distending pressure provided by HFNC has raised clinical safety concerns.[12] Many modern HFNC devices now have pressure-limiting valves, but more robust physiologic studies are needed.[12]

4.1.1 Heating and humidification

Nasal mucosal drying, injury, infection, impaired clearance of secretions, bronchospasm, and patient discomfort can be overcome by heating and humidifying inspired air. This also allows for more comfortable provision of higher flow rates.[14] Warming and humidifying gases in the nasal passages requires energy.[16] Providing warm, humidified gases decreases the patient's metabolic demand and can be beneficial in patients with impaired pulmonary function. Hollerman-Duray *et al.* showed better growth in neonates treated with HFNC rather than nasal CPAP, ascribed to a reduction in energy needs in the HFNC group.[17]

4.1.2 Nasopharyngeal carbon dioxide wash-out

The presence of end-expiratory gas in the nasopharyngeal dead space at the beginning of inspiration reduces the efficacy of gas exchange. HFNC has a similar

action to tracheal gas insufflation which washes out the nasopharyngeal dead space. Tracheal gas insufflation has been shown to reduce inspiratory ventilation pressures, volume requirements and $PaCO_2$.[16]

4.1.3 Reduction in upper airway resistance

The large surface area of the nasopharynx increases inspiratory resistance. It is proposed that HFNC may improve inspiratory resistance by stenting the upper airway, similarly to CPAP.[16,18] HFNC also provides nasopharyngeal gas flow similar to or greater than the patient's own inspiratory flow, improving tidal volume and reducing work of breathing.[16]

4.1.4 The provision of positive end expiratory pressure (PEEP)

HFNC can produce PEEP[19] but the definitive pressures generated have not been consistently measured and show significant variation (in the limited studies published to date). Measuring nasopharyngeal, oesophageal, and tracheal pressures are ways of estimating the PEEP provided.[21] Initial HFNC physiology studies were done in preterm neonates in a neonatal ICU setting. Spence *et al.* showed an average PEEP of 4.8 cm H_2O at flows of 5 L/min in premature neonates,[19] while Sreenan *et al*. showed a relationship between the PEEP generated and infant weight.[22] Interestingly, Lampland *et al*. showed that end-expiratory oesophageal pressure was much lower than 6 cm H_2O even at flows of 6 L/min with a closed mouth,[23] and Saslow *et al.* showed no noteworthy increase in PEEP at flows of 3, 4, and 5 L/min in preterm neonates.[24]

Table 2 shows the HFNC physiological studies performed in infants and children outside the neonatal period. Important limitations of the studies are the small numbers of subjects,[25-29] technical problems (placement of pressure catheters),[29] and changes in PEEP possibly related to air leaks and mouth closure.[25]

Table 2. HFNC physiological studies performed in infants and children outside the neonatal period

Study	Setting and participants	Study Type	Outcomes	Findings
McGinley *et al*. 2009[26] *n*=12	Study ward Mean age 10.1 years All participants had obstructive sleep apnoea and were obese, receiving HFNC 20 L/min	Prospective cohort study	Sleep architecture Sleep disordered breathing Arousal indexes Inspiratory flow limitations Respiratory rate (RR) Inspiratory duty cycle	Decreased arousals Decreased obstructive episodes Reduced amount of inspiratory flow limitations leading to reduced RR and insp. duty cycle
Arora *et al*. 2012[25] *n*=25	Emergency department Mean age: 78.1 days/5.3kg	Prospective observational study	Nasopharyngeal pressure (NP) Vital signs Oxygen saturation Bronchiolitis severity score	Linear increase in NP pressure with flows up to 6 L/min. Significant differences between pressures in open and closed mouth states. PEEP was not affected by weight or sex A clinical severity score improved in subjects
Milesi *et al*. 2013[27] *n*=21	PICU Infants < 6 months old with acute RSV bronchiolitis on HFNC	Prospective observational study	Pharyngeal pressure (PP) and oesophageal pressure (OP)	Flow >2 L/kg/min generated a mean PEEP >4 cm H2O (measured at flows of 1,4,6, and 7 L/min Convincing reduction in respiratory rate from start to max flow rate.
Rubin *et al*. 2013[28] *n*=25	PICU Infants/children <18 years on HFNC Very heterogeneous	Prospective cohort study	OP Changes in pleural pressure, RR. Rate product (objective measure of effort of breathing)	Convincing reduction (25%) in effort of breathing with increase flow from 2 L/min to 8 L/min

	group with co-morbidities Mean age 6.5 months. Mean weight 6.4 kg			
Hough *et al*. 2014[29] *n*=11	PICU Infants with bronchiolitis on HFNC Mean age 3.17 ± 2.06 months. Mean weight 4.76 ± 1.39 kg.	Prospective observational study	OP Regional tidal volume (RTV) End-expiratory lung volumes (EELV) FiO_2 RR and oxygen saturation	Measured and compared 2 L/min vs 8 L/min: Increased end-expiratory pressure, not end-inspiratory pressure with flow 1.7 L/kg/min (by definition not continuous/CPAP)- may need higher flows to achieve. Increase EELV anterior lung, not posterior lung on HFNC No statistical significant difference in RTV Decrease in RR, nil difference in the other physiological parameters
Pham *et al*.[30] 2014 *n*=28	PICU 14 infants with bronchiolitis and 14 cardiac patients	Prospective study	Diaphragmatic electrical activity and oesophageal pressure off and then on HFNC at 2 L/kg/min	Significant reduction in oesophageal pressures and diaphragmatic activity as an estimate of the work of breathing. Decrease in respiratory rate

HFNC, high-flow nasal cannula; PICU, paediatric intensive care unit.

In summary, a few limited physiological HFNC studies done outside of the neonatal period do show increased PEEP with increased flow rates,[25, 27] possibly to a maximum of 6–8 L/min, likely influenced by mouth closure [25] and a reduction in respiratory rate and work of breathing in the small number of study subjects.[25, 27-29]

4.2. Experience in HFNC use in infants and children and outcomes

Initially HFNC was only used as an alternative respiratory support to nasal CPAP for premature infants,[11] but is now increasingly used in infants and children with a variety of causes for their respiratory distress[12] and in various settings. Most studies were performed in the PICU setting in developed countries; newer studies have shown promise for the use of HFNC in emergency departments,[46] during inter-hospital transport of ill children,[43] and in paediatric wards.[39] A recent guideline on high dependency care for children in the United Kingdom suggests that HFNC is an intervention that should be available to all children admitted to all inpatient facilities.[31] Despite the increased use of HFNC, there is a paucity of literature to support its use in children[12] and no published data are available from South Africa or from sub-Saharan Africa.

4.3.1 HFNC use in developing countries:

Review of the trial by Chisti *et al*.[9] in Bangladesh

The study by Chisti *et al*.[9] stands out as the only published data on HFNC use in children with severe pneumonia and hypoxia in a developing country. This open, randomised, single-centre clinical trial, comparing outcomes of children with severe pneumonia managed with bubble CPAP, HFNC (flow range: 2–12 L/min), or low-flow oxygen therapy (LFNC) was conducted at Dhaka hospital, Bangladesh. This is a large tertiary hospital (with mechanical ventilation available on site) closely connected to a research centre. Unfortunately, the trial was stopped at the second interim analysis, prior to reaching projected sample size (325 per treatment group), due to the marked difference in the number of deaths occurring between the treatment groups.

In total, 225 children aged <5 years with severe pneumonia (WHO criteria) and hypoxia (SpO_2 <90%) were randomized to 3 treatment groups. Exclusion criteria included preterm neonates; children with congenital cardiac disease, asthma, or

upper airway obstruction; and children meeting “treatment failure “criteria at presentation. The high incidence of co-morbidities (similar in each treatment group)—especially severe malnutrition (22%) and severe sepsis (8%)—makes the study particularly relevant to other developing countries where children present with similar co-morbidities. No commercial devices were used in the study. Both the bubble CPAP and HFNC devices were “self-made” with low cost and used available tubing and materials; hence, the interventions are feasible in resource-limited settings.

The primary outcomes included treatment failure (defined as 2 or more of following characteristics: severe hypoxia, signs of severe clinical distress, or respiratory acidosis on blood gas analysis) after at least 30 minutes of the intervention, intubation/mechanical ventilation (within the first 30 days), death (at any time during hospitalization), and leaving the hospital against medical advice. Secondary outcomes included length of hospital stay, nosocomial infections, isolation of *Mycobacterium tuberculosis* or another bacterial pathogen, and multi-organ failure in the first 7 days of respiratory support. Further analysis also assessed the time to resolution of hypoxia, normalization of the respiratory rate, and resolution of the signs of respiratory distress.

The study showed that mortality was significantly lower among children receiving bubble CPAP than among those receiving either LFNC or HFNC oxygen therapy, even after adjusting for all identifiable risk factors. The proportion of children that died was similar in the LFNC and HFNC groups. However, there was no significant difference between bubble CPAP and HFNC in terms of treatment failure. Although not statistically significant, children receiving HFNC had slightly shorter times to resolution of hypoxia and normalization of respiratory rates than those receiving LFNC. The relevance of this study is unquestionable for further research in advanced respiratory support for ill children in resource-limited settings.

The Children’s Oxygen Administration Strategies Trail (COAST)[49] is a multicentre (5 hospitals) RCT, currently enrolling (start February 2017-over 30 month period) in East Africa (Kenya).The trail will simultaneously evaluate 2 related interventions in children with pneumonia, namely liberal oxygen compared with so called permissive hypoxia (Sp02>80%) and high flow oxygen vs low flow delivery (current routine care).Primary outcome will be mortality at 48 hours. Outcomes and results will

contribute new knowledge not only to host response to oxygen strategies but outcomes ito of high flow vs low flow oxygen delivery will be very interesting.

4.3.2 HFNC use in developed countries

HFNC use in bronchiolitis

Viral bronchiolitis contributes significantly to infant mortality and morbidity in both the developed[32] and developing world.[1] Besides respiratory support and adequate nutrition effective treatment for bronchiolitis is limited.[33] The efficacy of breathing is reduced in infants with bronchiolitis who are uncomfortable and distressed.[20] The use of HFNC in children with bronchiolitis, as an alternative to CPAP, is an attractive option as it is well tolerated.[25, 27] Data related to HFNC use in bronchiolitis comes mostly from small observational studies; a recent review by Sinha *et al*.[20]concludes that more high quality randomized controlled trials (RCTs) using standardized methodology for bronchiolitis, directly comparing CPAP, HFNC, and standard low-flow oxygen delivery, are required.[20]

Randomized clinical trials

Hilliard *et al*.[34] compared HFNC to head box oxygen delivery in 19 infants with moderate to severe bronchiolitis (tertiary hospital setting). The primary outcome was SaO_2 at 8 h. The higher SaO_2 measurement observed in the HFNC group was not significant and likely reflected the higher inspired oxygen concentrations in the group at that time point. There was no difference in the time required to wean to nasal cannula oxygen or air, time to starting feeds, or in the duration of hospital stay.

Bueno Campana *et al*. [35] compared HFNC with nebulized hypertonic saline in 74 infants with moderate bronchiolitis in a regional hospital setting. The researchers did not demonstrate any difference in respiratory distress, as measured by the Respiratory Assessment Change Score, between the 2 groups at any time point during the 36 h post-randomization. Additional outcomes were a comfort score, length of stay, and rates of PICU admission. No difference was shown in these outcomes between the 2 groups. However, a recent study by Maquire *et al*. concludes that there is currently no robust evidence that hypertonic saline is an effective intervention in bronchiolitis. [33]

Published data from 2 new studies, Kepreotes *et al*.[36] (setting: paediatric emergency centres) trial and the PARIS (Paediatric Acute Respiratory Intervention

Study) trial,[37] are eagerly awaited. Both compared standard LFNC with HFNC therapy in infants with bronchiolitis. The PARIS study is a multi-centre RCT comparing standard low-flow nasal cannula oxygen with HFNC in infants aged <12 months with hypoxic bronchiolitis. Exclusion criteria are infants with an urgent need for respiratory support (including needing non-invasive or invasive ventilation, a low level of consciousness, and apnoea), cyanotic heart disease, basilar skull fracture, upper airway obstruction, craniofacial malformations, and infants who are already on home oxygen therapy. Infants will be recruited from general wards and emergency departments. The primary outcome is treatment failure (as determined by definitive criteria). The secondary outcomes include the number of infants requiring transfer to higher level of care (including admission to an on-site paediatric intensive care or transfer to a tertiary hospital) length of hospital stay (including ICU length of stay); intubation rates; associated healthcare costs for the respective therapy; length of oxygen therapy; and adverse events. Both developed and developing countries may find these study results very relevant to appropriate, safe, and cost-effective respiratory support for young infants with bronchiolitis.

Observational studies

The key limitation of most of the observational studies is the small number of study subjects. [25, 27, 30, 38-40] Moreover, all were single centre studies and the groups were poorly comparable. [38, 40]

Retrospective studies

PICU setting: McKiernan *et al*.[41] reviewed 115 infants (mostly <6 months of age) with bronchiolitis receiving HFNC (maximum flow rate: 8 L/min).They showed a statistically significant decrease in respiratory rate, need for intubation, and length of stay. Metge *et al*. [38] compared HFNC and CPAP in 34 infants with bronchiolitis caused by respiratory syncytial virus (RSV); a significant reduction in respiratory rate, heart rate, $PaCO_2$, and FiO_2 was demonstrated within groups, but not between groups.

Prospective studies:

PICU setting: The study by Arora *et al.*[25] showed a statistically significant reduction in severity scored in 25 infants with bronchiolitis receiving HFNC therapy in PICU.

Although predominantly a physiological study in a PICU, Milesi *et al*.[27] also showed a convincing reduction in respiratory rate from start to maximum flow rate in 21 infants with bronchiolitis due to RSV. Pham *et al*.,[30] in a small physiological, study showed a reduction in effort of breathing and respiratory rate in 14 infants with bronchiolitis.

General paediatric ward: Bressan *et al*.[39] prospectively reviewed 27 very young infants (mostly aged <2 months) with moderate-to-severe bronchiolitis receiving HFNC in a general paediatric ward. Primary outcomes were SpO_2, end-tidal carbon dioxide ($ETCO_2$), and respiratory rate (RR) measured for a baseline period of 1 h before and at specific time intervals within 48 h after initiating HFNC. They showed a statistically significant median SpO_2 increase changing from standard oxygen to HFNC. The median ETCO2 and RR decreased rapidly and significantly in the first 3 h of HFNC therapy and remained stable thereafter. There were no reported complications related to HFNC use and none of the patients required PICU admission.

Milani *et al*.[40] recently prospectively compared 36 infants aged <12 months with bronchiolitis who were treated with either LFNC or HFNC oxygen therapy in a general paediatric ward. Their exclusion criteria were premature infants, recurrent or chronic lung disease, heart disease, neurological problems, and those requiring admission to PICU. Improvements in RR, respiratory effort (measured at 30 min and 1, 24, and 72 h) and ability to feed occurred significantly more quickly in the HFNC group; this may explain the shorter length of hospital stay in the HFNC group. Limitations are summarized above.

HFNC use in respiratory distress due to other causes in children

Only a few studies on HFNC use in children with respiratory conditions other than bronchiolitis were identified. As reviewed, Chisti *et al*.[9] used HFNC in children with severe pneumonia. In a recent single-centre, randomised trial comparing HFNC with low-flow oxygen therapy after extubation in postoperative paediatric cardiac patients (aged <18 months), Testa *et al*.[42] showed higher partial pressure of oxygen/FiO_2 in the HFNC therapy group at each time point during the 48-hour study period. No difference in $PaCO_2$ value was shown at any time-point. In the low-flow oxygen group, 15% of patients needed non-invasive respiratory support; none in the HFNC therapy group required this.

A single-centre retrospective review showed a reduction in the need to intubate in an emergency department when HFNC is introduced early in children with pneumonia, asthma, bronchiolitis, and croup.[43] McGinley *et al*.[26] showed improved outcomes in children with obstructive sleep apnoea. Successful use of HFCN has been reported in case series/reports in patients with viral-induced wheeze and post-intubation stridor.[44, 45]

Sclhapbach *et al*.[46] analysed their experience of HFNC use during inter-hospital transport of critically ill children (aged <24 months). They assessed 793 children over an 8-year period. A comparison was made between the period prior (4 years) and during (4 years) the availability of HFNC for inter-hospital transport. During the period of HFNC availability, a third of children received HFNC therapy *en route*, and there was a significant decrease in the number of children requiring retrieval on invasive ventilation (14%). Retrieval rates on non-invasive ventilation declined from 7% to 2%. There was no statistically significant change in the number of retrieved children requiring intubation for respiratory reasons during the first 24 h after PICU admission.

4.4. HFNC Complications

4.4.1 Air leaks

In a case series, Hedge *et al*.[47] described 2 cases of pneumothorax and 1 case of pneumomediastinum occurring in children receiving HFNC**.**

4.4.2 Gastric distension

Abdominal distension has been reported in 2 patient reports.[42]

4.4.3 Infection

In 2005, an outbreak of infection with *Ralstonia* spp. occurred in children in the USA; it was linked to the use of the Vapotherm 2000i HFNC therapy system. The device was recalled and changes were made. After reintroduction, no further problems were reported. [48]

Summary

Acute severe lower respiratory tract infections remain a major cause of mortality and morbidity in South Africa[1] and globally (13%).[1, 2] Interest in, and use of, non-invasive ventilation for respiratory support, including nasal CPAP and HFNC within and outside the paediatric ICU, is growing.[7, 8] The literature search shows that there is paucity of robust literature and evidence to support the use of HFNC in children outside the PICU setting and in conditions other than bronchiolitis.[12] More clarity is needed on the mechanism by which HFNC provides PEEP, which appears variable. A brave, contextually relevant study from Bangladesh showed no difference in "treatment failure" outcomes (defined as 2 or more of following characteristics: severe hypoxia, signs of severe clinical distress, or respiratory acidosis on blood gas analysis) in severe pneumonia comparing bubble CPAP with HFNC, but mortality rates were higher in this setting in the LFNC and HFNC groups, indicating potential risk for harm associated with these modalities. HFNC had no impact on mortality compared with LFNC therapy.[9] Awaited data from 2 new RCTs comparing HFNC with standard LFNC will be important. Deductions from mostly observational studies show that HFNC reduces the RR and effort of breathing in infants with bronchiolitis, appears safe (with very few reported complications), and is well tolerated. Commercial HFNC devices, deemed safer, are expensive. Guaranteeing that an appropriate, cost-effective form of respiratory support is delivered in a safe environment and that children requiring escalation of respiratory support are identified early are key to utilizing a resource/intervention effectively, especially in a resource-limited environment. Therefore, more research is needed to ensure the safe use and implementation of HFNC therapy.

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5. CHAPTER TWO: PUBLICATION-READY MANUSCRIPT

Title page

A review of the use of high flow nasal cannula oxygen therapy in hospitalized children at a regional hospital in the Cape Town Metro, South Africa

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All analyses were performed at the paediatric wards, New Somerset Hospital, Cape Town, South Africa.

Keywords: High flow nasal cannula oxygen therapy, Infants and children, South Africa

Abstract

Background. High-flow nasal cannula oxygen (HFNC) is a non-invasive alternative to nasal continuous positive pressure oxygen (CPAP) therapy for infants and children requiring respiratory support. There is a paucity of literature to support its use in children, with no published data from sub-Saharan Africa.

Objective. To describe the outcomes and adverse events of HFNC in the first year of its use in a level two (L2) general paediatric ward, compared with outcomes of an historical cohort when this intervention was unavailable.

Methods. This retrospective descriptive study included children aged <13 years who received HFNC in the first 12 months after its introduction (HFNC-availability group; *n*=66). Demographic data, clinical characteristics, and outcomes (death, treatment failure, length of HFNC, and HFNC-related adverse events) were assessed. A comparative description of children that required transfer to level 3 (L3) for respiratory support (more than available standard low-flow oxygen) in the 12-month period prior to HFNC availability (pre-HFNC group; *n*=54) was performed and outcomes were compared using standard descriptive and comparative statistics.

Results. The median age of the cohort was 5 months (interquartile range [IQR] 1.9–14.6). Sixteen children (13.3%) were malnourished, 10 (8%) were HIV infected, and 30 (25%) were ex-premature infants. The most common diagnoses were pneumonia, bronchiolitis, and asthma. Asthma, anaemia, and cardiac abnormalities were the most prevalent underlying co-morbidities. Two children died in each group.

All 54 children in the pre-HFNC group were transferred to L3; 38 (70.4%) needed CPAP or invasive ventilation. In the HFNC-availability period, 85 children were assessed as needing more than standard low-flow oxygen therapy: 19 were immediately transferred to L3 where 17 (89.4%) received CPAP or invasive ventilation; 66 received HFNC at L2, 16 (24.2%) of these children required transfer to L3 for CPAP or invasive ventilation.

The median duration of HFNC was 46.3 h (IQR 19.5–93.5) overall, and was 12 h (IQR 4-28) and 58.5 h (IQR 39.5–106) for those who failed or were successfully managed on HFNC, respectively. No HFNC-related serious adverse events were recorded at L2.

Conclusion. HFNC is a safe, effective, feasible option for non-invasive ventilation of children with respiratory illnesses in a resource-limited L2 setting. A greater proportion of children admitted with lower respiratory tract infections required support in the HFNC-availability group, but the intervention reduced the bed-pressure on L3. Improved identification of HFNC failures and better adherence to the protocol is needed at L2.

INTRODUCTION

Acute severe lower respiratory tract infections continue to be a major cause of mortality and morbidity globally (13%)[1,2] and in South Africa.[1] Reid *et al*. showed that pneumonia (25%) was the main cause of death in children under 5 years of age in the Metro West health district of the Western Cape Province in South Africa.[3] In many middle-to-low income countries with resource limitations, the number of child deaths resulting from severe pneumonia (related to hypoxaemia and respiratory failure) remains high, despite implementation of international and local guidelines.[4] Additional respiratory support, important in the care of critically ill children, is often unavailable or is perceived as being neither feasible nor safe in resource-limited settings.[4,5] The use of non-invasive ventilation for respiratory support, including nasal continuous positive airway pressure (CPAP) and high flow nasal cannula (HFNC) within and outside the paediatric intensive care unit (PICU), is increasing.[5,6] There is limited evidence to support the use of HFNC in children outside the PICU setting and in conditions other than bronchiolitis.[7]

The probable mechanisms of action of HFNC includes heating and humidification of inspired air, nasopharyngeal carbon dioxide wash-out, reduction in upper airway resistance, and the provision of positive distending pressure.[8, 9-12] The current paucity of data regarding the variable positive distending pressure provided by HFNC remains controversial and has raised clinical safety concerns[7]; many modern HFNC devices now have pressure-limiting valves. However, more robust physiological studies are needed. [7]

A pioneering, contextually relevant study from Bangladesh showed that outcomes in terms of "treatment failure" (defined as 2 or more of following characteristics: severe hypoxia, signs of severe clinical distress, or respiratory acidosis on blood gas analysis) were no worse in patients with severe pneumonia who received HFNC compared with bubble CPAP, but mortality rates were higher in the LFNC and HFNC groups, indicating potential risk for harm associated with these modalities [13].Results from The Children's Oxygen Administration Strategies Trail (COAST)[20], a multicentre (5 hospitals) RCT, currently enrolling (start February 2017-over 30 month period) in East Africa (Kenya) will be very interesting. The trail will simultaneously evaluate 2 related interventions in children with pneumonia, namely liberal oxygen compared with so called permissive hypoxia (Sp02>80%) and high flow oxygen vs low flow delivery (current routine care).Primary outcome will be mortality at 48 hours. Outcomes and results will contribute new knowledge not only

to host response to oxygen strategies but also outcomes ito of high flow vs low flow oxygen delivery will be very interesting. Various observational studies have shown that HFNC reduces respiratory rates and the effort of breathing in infants with bronchiolitis, has very few reported complications, and is well tolerated.[7] Awaited data from two new upcoming randomized trials comparing HFNC with standard LFNC in bronchiolitis will be important.

Commercial HFNC devices and circuits are expensive. Guaranteeing that a clinically effective and cost-effective form of respiratory support is delivered in a safe environment and that children requiring escalation of respiratory support are identified early, are crucial to the appropriate utilization of a new intervention, especially in a resource-limited environment. Consequently, more research is needed to document efficacy and safety in various clinical scenarios.

The donation in 2015 of two commercial HFNC devices to the general paediatric ward of New Somerset Hospital (NSH), a level 2 (L2) hospital in the Metro West sub-district of Cape Town, afforded the pragmatic opportunity to review this new intervention. Prior to the availability of on-site HFNC, all children that might require additional respiratory support (HFNC, CPAP, or intermittent positive pressure ventilation [IPPV]) were transferred by ambulance to the level 3 (L3) children's hospital that has dedicated high care and PICU facilities. The objectives of this study were to document the first year of experience using HFNC by describing the demographic and clinical characteristics of children who qualified (by protocol) and were initiated on HFNC oxygen therapy on site, and to evaluate their response to the intervention.

METHODS

Study design and participants

This was a retrospective descriptive study of hospitalized children < 13 years of age managed with HFNC oxygen therapy in the general paediatric ward of NSH during the first 12 months of its availability (1 August 2015 to 31 July 2016). A comparison was made with children < 13 years of age who required transfer for additional respiratory support for respiratory distress in the 12 months prior to the availability of HFNC oxygen therapy at the same institution (1 August 2014 to 31 July 2015).

The children commenced on HFNC oxygen according to departmental guidelines were identified from the ethics-approved NSH High Flow Nasal Cannula Registry (R051/2015). The children transferred to tertiary care for respiratory support in the preceding year were identified from existing routine morbidity and mortality records of the Department of Paediatrics at NSH. The Research Ethics Committee of the University of Cape Town granted ethical approval for this study (approval no. R051/2015) and waived the need for informed consent due to the retrospective nature of the study and the use of routine clinical data.

Setting

NSH is a 330-bed secondary level (L2) hospital, i.e. there are specialists on site, but no sub-specialty service is offered. The paediatric population served comprises approximately 100 000 children, mostly from middle and lower socioeconomic backgrounds (many from informal housing areas). There is no PICU on site and children requiring advanced respiratory support need to be transported to a tertiary level (L3) hospital (where sub-speciality services and PICU facilities are available) that is approximately 30 minutes' away by road ambulance transport. Staffing (both nurses and doctor numbers) were the same in the 2 study periods. All children with respiratory distress requiring oxygen therapy would be monitored closely in the paediatric ward. Supportive care and feeding by nasogastric tube when children are moderately or severely distressed is standard care in the ward.

HFNC system and protocol

The HFNC equipment used at NSH is a Fisher and Paykel® system (Fisher & Paykel Healthcare Limited Auckland New Zealand) with a humidifier, and age and weight appropriate Fisher and Paykel® nasal cannula. The NSH HFNC oxygen guideline was adapted for local use from the Royal Children's Hospital Melbourne guideline.[14] Starting flow rates were based on the weight of the child: < 10 kg: 2 L/kg/min and >10 kg: 2 L/kg/min for the first 10 kg plus 0.5 L/kg/min for each kg above 10 kg with max flow 50 L/min. The decision to commence HFNC always involved a senior paediatrician. Both nurses and doctors working in the ward received basic training in the use of the device and the children receiving HFNC had

hourly observations performed, including pulse oximetry, and measurement of the respiratory rate (RR) and heart rate (HR).

The guideline's suggested indications for HFNC include use in children with moderate-to-severe respiratory distress with hypoxaemia (SpO_2 < 90%) despite standard low-flow oxygen (provided by nasal prong or face mask) due to common childhood respiratory illnesses (community-acquired pneumonia [CAP], bronchiolitis, and asthma exacerbations). Absolute contra-indications for HFNC use include the need for immediate invasive respiratory support and infants or children with non-patent nasal passages.

Children receiving HFNC were monitored and reviewed both 30 min and approximately 2 h after being initiated on HFNC to determine whether transfer and/or additional support was required. No improvement in the RR and HR (> 20% reduction not achieved), the inability to wean the FiO_2 to < 40%, or worsening respiratory distress indicated treatment failure and the need to transfer the child for advanced respiratory support.

Data collection and definitions

The medical folders of identified patients were drawn from the medical records department, reviewed, and relevant data entered into an electronic data capture sheet (Microsoft Access®). Any results and details not recorded in the medical folder were searched for through the electronic National Health Laboratory Service and Clinicom platforms.

The data collected comprised patient demographic information (sex, age), diagnosis, underlying co-morbidity, gestational age at birth, birth weight, and nutritional and human immunodeficiency virus (HIV) status. HIV status was classified as uninfected, exposed but uninfected, and infected. Due to the small number of HIV-infected children, no distinction was made according to whether these children were taking combined antiretroviral treatment (cART), were pre-cART, or had defaulted cART, or according to their immunological or virological status. The nutritional status of each child was determined by the weight-for-age z-score (WAZ score) and the weight-for-height/ length z-score (WHZ). These z-scores were calculated using the "zanthro" function of Stata®/IC 13.0 statistical software, with the World Health Organization (WHO) 2007 UK term and preterm growth charts

used for reference (Birth: British 1990 Growth Reference, reanalysed 2009; Postnatal: WHO Child Growth Standards; 4-20 years: British 1990 Growth Reference). Hence, prematurity was taken into account in the calculation of the z-scores. Malnutrition was defined as a WAZ score <-2. The method of delivery of standard low-flow oxygen support received by transferred children in the pre-intervention group was collected.

The baseline number of monthly admissions was available from routine departmental data on total admissions for acute respiratory tract infections in children aged < 5 years. Despite not including all ages we thought that this would be a reasonable approximation of total number of acute respiratory tract infections admissions given that 90% of our total cohort was < 5 years of age, and the older group were mostly children with asthma who would not be counted in the baseline data.

Data Analysis

The data analysis was performed using Stata®/IC 13.0 statistical software (Stata-Corp LP, TX77845, USA). Continuous data were tested for normality using the Shapiro-Wilks test, and are presented as the median (interquartile range [IQR]) or mean (standard deviation [SD]) for non-normally and normally distributed data, respectively. Medians and means were compared between groups using the Wilcoxon rank sum or Student's *t*-test, respectively. Categorical data are presented as the frequency and percentage, with the chi-squared or Fisher's exact test used for comparison between groups, as appropriate. For all tests p-value < 0.05 was considered significant.

Outcome measures

The primary outcomes when comparing the pre-intervention (pre-HFNC) and post intervention (HFNC) groups were to document the success of the intervention, defined as no need for escalation of respiratory support; the failure of the intervention, defined as needing further non-invasive (CPAP) or invasive (IPPV) respiratory support within 48 h of transfer; and death during admission. Secondary outcomes in the HFNC group were the length of time receiving HFNC and severe adverse events associated with HFNC use in a general ward.

RESULTS

In the first 12 months of on-site availability of HFNC in the general paediatric ward (1 August 2015 to 31 July 2016), 66 infants and children received HFNC oxygen therapy. In the pre-HFNC-availability period (1 August 2014 to 31 July 2015) during which only standard low-flow oxygen respiratory support (nasal prong oxygen or face mask oxygen) was available, 54 children required transfer to a L3 hospital for further respiratory support.

Demographic and clinical characteristics

The median age of the whole study cohort was 5 months (IQR 1.9–14.6), with a slight male preponderance (**Table 1**). Of the study population for whom nutritional data was available (106/120), 15.1% (16/106) were moderately or severely malnourished with more children malnourished in the pre-HFNC group (31.1%, 14/45) than in the HFNC group (3.3%, 3/61). A significantly greater proportion of children were HIV-infected or HIV-exposed in the pre-HFNC group than in the HFNC group. Among children with underlying comorbid conditions (*n* = 58), asthma and anaemia were the most prevalent, being present in 24.1% (14/58) and 17.2% (10/58) of these children, respectively, and 12.1% (7/58) had an underlying congenital cardiac abnormality. The most common diagnosis was pneumonia (*n* = 84 [70.0%]), followed by bronchiolitis, then asthma. Of those < 5 years of age, the majority of children (*n* = 82 [76.6%]) had pneumonia, whereas in the older age group (> 5 years) the majority (*n* = 11 [84.6%]) had asthma. A quarter of the study population comprised ex-premature infants.

Comparison of outcomes between the groups

Death during admission

There was no difference between the HFNC availability group and pre-HFNC availability groups in terms of the proportion of children who died, with 2 deaths (3.7% vs 3.0%, respectively) in each group. The children that died in the HFNC group were 4 and 13 months old. Both were HIV unexposed and uninfected, neither were malnourished, and both had an initial diagnosis of pneumonia. The 4-month-

old child had no underlying co-morbidities and was transferred within 12 h of commencing HFNC to the L3 hospital for invasive respiratory support where he died 8 weeks later of intractable respiratory failure secondary to severe bronchopneumonia. The 13-month-old child had significant underlying co-morbidities, with Down's syndrome, hypothyroidism, gastro-oesophageal reflux disease, and evidence of chronic lung disease. He received HFNC oxygen for 9 days during his stay and was weaned off successfully but unexpectedly died at the regional hospital after a 5-week hospital admission. The cause of death was aspiration.

Need for escalation of respiratory support

Figure 1 shows the study flow. In the pre-HFNC-availability group, 54/835 (6.5%) children admitted for acute lower respiratory tract infections (LRTIs) were assessed as needing transfer to the L3 hospital for possible additional respiratory support. Of the 54 children transferred, 38 (70.4%) required CPAP or IPPV within 48 h of transfer, or died, while 16 (29.6%) received HFNC or remained on nasal prong oxygen at the L3 hospital.

In the HFNC availability group, 85/604 (14%) of children admitted for acute LRTIs were assessed as needing more than standard low-flow oxygen therapy; 66 (10.9%) were initiated on HFNC in the general ward at NSH while 19 (3.1%) were assessed as needing more support than HFNC and were transferred directly to L3. Overall, 33 (5.5%) children admitted for acute lower tract respiratory infections were eventually transferred to L3. Of the 19 children assessed as requiring transfer to L3 without being offered on-site HFNC oxygen, the majority 17 (89.4%) received CPAP or IPPV at the referral facility, while 2 (10.5%) were managed with HFNC or nasal prong oxygen. Of the 66 children initiated on HFNC in the general ward, 50 (75.8%) were successfully managed and successfully weaned off HFNC and discharged home. The other 16 (24.2%) were assessed as not settling on HFNC and were transferred to L3 within 48 h of being on HFNC. At L3 they received either CPAP or IPPV, and 1 died after prolonged ventilation.

The HFNC group

Length of time receiving HFNC

The overall median duration on HFNC was 46.3 h (IQR 19.5–93.5 h). Of the 16 children who failed HFNC at NSH, the median duration on HFNC was 12 h (IQR 4–

28 h). Among those who were successfully managed on HFNC, the median time on HFNC was 58.5 h (IQR 39.5–106 h). Four children required HFNC for longer than 7 days (range: 9 days [231 hours] and 13 days [322 hours]); one of these patients died.

Serious adverse effects in HFNC group

No pneumothoraces, episodes of gastric or abdominal distention, mucosal injury, or infections were documented for any of the children receiving HFNC oxygen therapy in the general ward of NSH in the first 12 months of its use.

Of the infants who failed HFNC at L2 and were transferred to L3, most were boys (*n* = 12, 75%) and the median age of the 16 infants was 6.7 months; 10 (63%) were < 6 months old. The attending doctor's interpretation of the children's x-ray images showed that 15 of the infants had hyperinflation and either focal areas of opacification or changes consistent with bronchopneumonia. Fifteen had blood cultures performed (all results were negative) and 12 (75%) had a nasopharyngeal aspirate (NPA) done at L3. Two children's NPA specimens were negative and 10 (83%) tested positive for respiratory viruses; 5 were positive for adenovirus, 3 tested positive for both adenovirus and respiratory syncytial virus (RSV), one specimen was only RSV positive, and one was influenza virus positive. The vital sign monitoring data (HR, RR, $Fi0_2$, and oxygen saturation) of the 16 children that failed HFNC, recorded hourly at L2, were reviewed; no consistent pattern predicting failure was observed.

DISCUSSION

This is the first study from sub-Saharan Africa documenting the safe, effective use of HFNC in a general paediatric ward setting. We identified no complications and demonstrated an increased capacity of a L2 hospital to manage children who require more than standard low-flow oxygen respiratory support, reducing pressure on L3 services. Children who were initiated on HFNC oxygen at the L2 hospital and subsequently transferred to L3 were also less likely to require CPAP or invasive ventilation at L3.

Pneumonia was the predominant diagnosis in the overall study population reflecting current evidence that pneumonia is the leading cause of morbidity and mortality in

children in South Africa.[1] A significant proportion of the children in this study population had wasting and 25% were ex-premature infants.

Asthma, anaemia, and cardiac abnormalities were the most prevalent underlying co-morbidities. Unlike the study by Chisti et al., [13] in the present study an underlying cardiac abnormality was not a contraindication for the use of HFNC despite very limited evidence for its efficacy in paediatric cardiac patients, as shown by Testa *et al*.[15][14] One child with a cardiac abnormality died, but not whilst receiving the intervention. Although the numbers were small, HFNC was successfully used in 4 children with underlying congenital heart disease as respiratory support during an acute admission for pneumonia.

The proportion of HIV-infected children was significantly lower in the HFNC-availability group; this may reflect, although unlikely, the effectiveness of ongoing strategies to prevent perinatally acquired HIV infection in South Africa via PMTCT, and the early initiation of cART.

HFNC use did not appear to impact on the number of deaths in the two groups, a finding consistent with that reported by Chisti *et al*. [13] Mortality rates were very low for the groups (0.2 and 0.3 deaths/100 admissions), therefore this study was underpowered to make any meaningful conclusions with regard to the effect of HFNC on mortality.

Transferring children from L2 to L3 hospitals causes significant strain on limited resources, including the emergency medical services and L3 bed capacity. Whether a transfer is warranted and safe raises anxiety and concern among staff at the referring facility. A much higher proportion of children required additional respiratory support in the year when HFNC was available (14% vs 6.5%). It is possible that this was due to a very “bad respiratory season” (anecdotal). It is unlikely that this was simply due to availability of HFNC, as the intervention had been available at the L3 facility in the preceding years, and criteria were the same for both institutions as to requirements for additional respiratory support, and children identified as needing the intervention would have been transferred. The transfers would not have been accepted by the tertiary institute if deemed unnecessary, and all decisions were consultant led. In cases of severe acute asthma, it can be postulated that use of HFNC may be adjunctive to the use of intravenous medication and nebulised medication as per protocol, but this made up a small part of the sample. Therefore,

almost two-thirds of the children who would potentially have been transferred prior to the availability of HFNC at L2 were successfully managed at L2 in 2016, reducing staff anxiety about observing and transferring very ill children, and decreasing the strain on the emergency medical services and L3 bed capacity.

A significantly lower proportion of children transferred after receiving initial HFNC at L2 needed non-invasive or invasive respiratory support at L3 once transferred, compared with children transferred on/after receiving only standard LFNC oxygen. This supports study the findings of Wing *et al*.,[16][15] that that the introduction of HFNC reduced the need for intubation and reduced the need for non-invasive/invasive retrieval during inter-hospital transfer. Because we used retrospective data from the pre-HFNC-availability cohort, we do not have information on how long children were at the referring facility prior to transfer and whether this could have impacted on outcome. Fewer children requiring high care/PICU non-invasive or invasive ventilatory support at L3 also reduces the strain on L3 resources (high care and PICU bed capacity and nursing requirements), justifying availability at lower levels of care. In the HFNC-availability group, the majority of children assessed to need support more than HFNC (i.e., those who did not meet the requirements of the protocol for safe use of HFNC at L2) ultimately required either CPAP or IPPV at L3. These findings support the current clinical practice and substantiate the current protocol.

The NSH HFNC standard operating protocol indicates that if there is no objective response to HFNC oxygen, with reduction in HR and RR, this should be deemed a failure and necessitates transfer. The median time of receiving HFNC oxygen was 12 h; this may indicate that this protocol was not strictly adhered to, and an earlier decision to transfer may have been preferable. It could also reflect natural disease progression with some patients deteriorating early in the admission, requiring increased support (including positive end expiratory pressure) because of hypoxia.

The absence of any recorded serious adverse events related to the use of HFNC in our general paediatric ward is encouraging and concurs with the literature reporting few adverse effects.[15,17,18][14,16,17] This further supports use as an attractive option but requires strict adherence to protocol.

Although reviewed, detailed analysis of the group of children that failed HFNC at L2 was not done as we did not have the corresponding data from children who did not fail, for comparison. However, there appeared to be an association between the

doctors' assessment of RR at initiation of HFNC and the documented RR at transfer (these patients remained significantly tachypnoeic).

The high proportion of adenovirus positive NPAs in a group of infants with severe pneumonia needing more than HFNC supports the recently published study by Zampoli *et al*.[19][18] showing adenovirus as a potentially important cause of severe pneumonia necessitating ICU admission and resulting in persistent lung disease in young children in South Africa.

Study limitations

This study has several limitations. This was a retrospective design using an unmatched, historical comparator group. However, the criteria for additional respiratory support were the same and the staff was unchanged. Although the time period was similar (including one autumn/winter respiratory season in both groups) and the referral areas and admission criteria were the same, it seems that there were more admissions in the first group and that the severity of illness necessitating additional respiratory support was greater in the second group. The analysis of the group of children that failed HFNC at L2 was not detailed as we did not have corresponding data from children who did not fail, for comparison.

Conclusions and recommendations

HFNC is a safe, effective, feasible option for non-invasive respiratory support in a relatively resource limited setting as an adjunct in management of respiratory illnesses in children, with clinical improvement with reduced work of breathing and respiratory rates in those children who were successfully managed in a general paediatric ward. The lack of serious adverse events is encouraging but there is a need to refine recognition of early failures and to avoid delays in transfer. A detailed cost analysis was not done, but, despite the relative cost of disposables and equipment, broader cost reductions are anticipated: Decreased inter-hospital transfers, avoidance of L3 admissions and reduced bed pressure in a setting known to have a shortage of PICU and high care space.

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Figure Legend

Figure 1. Participant flow

[a] Number of admissions for children ≥ 5 years old not available (89% of the overall cohort was <5 years old).
NP, nasal prong; HFNC, high flow nasal cannula; L3, level 3 hospital; NSH, New Somerset Hospital; CPAP, continuous positive airway pressure; IPPV, intermittent positive pressure ventilation.

Table 1: Demographic and clinical characteristics

		Total (*n*=120)	**Pre-HFNC-availability group** (*n*=54)	**HFNC-availability group** (*n*=66)	***P***
Age, months		5.0 (1.9; 14.6)	3.2 (1.4; 13.2)	6.4 (2.5; 14.9)	0.057
Age <5 y		107 (89.2)	47 (87)	60 (90.9)	0.49
Sex	Male	68 (56.7)	32 (59.3)	36 (54.6)	0.60
	Female	52 (43.4)	22 (40.7)	30 (45.4)	
Nutritional status	WAZ[a]	-0.98 ± 1.96	-1.38 ± 1.90	-0.65 ± 1.97	0.04
	WAZ <-2[a]	37 (30.8)	23 (42.6)	14 (21.2)	0.01
	HAZ[b]	-0.53 (-1.57; 0.28)	-0.53 (-1.56; -0.02)	-0.48 (-1.57; 0.57)	0.69
	HAZ <-2 [b]	22/114 (19.3)	9/48 (18.8)	13/66 (19.7)	0.90
	WHZ	-0.60 (-1.38; 0.86)	-1.17 (-2.09; 0.60)	-0.23 (-0.88; 0.92)	0.002
	WHA <-2	16/106 (15.1)	14/45 (31.1)	3/61 (3.3)	<0.001
HIV status	Exposed	23 (19.2)	13 (24.1)	10 (15.2)	0.02[†]
	Infected	10 (8.3)	8 (14.8)	2 (3.0)	
	Uninfected	87 (72.5)	33 (61.1)	54 (81.8)	
Co-morbidities	Anaemia	10/58 (17.2)	3/29 (10.3)	7/29 (24.1)	0.14[†]
	Asthma	14/58 (24.1)	5/29 (17.2)	9/29 (31.0)	
	CLD	4/58 (6.9)	3/29 (10.3)	1/29 (3.5)	
	HIV infected	10/58 (17.2)	8/29 (27.6)	2/29 (6.9)	
	Cardiac	7/58 (12.1)	5/29 (17.2)	2/29 (6.9)	
	Probable TB	4/58 (6.9)	1/29 (3.5)	3/29 (10.3)	
	Other	9/58 (15.5)	4/29 (13.8)	5/29 (17.2)	
Prematurity		30 (25)	18 (33.3)	12 (18.2)	0.057
Diagnosis	Pneumonia	84 (70)	42 (77.8)	42 (63.6)	0.13[†]
	Bronchiolitis	23 (19.2)	6 (11.1)	17 (25.8)	
	Asthma	13 (10.8)	6 (11.1)	7 (10.6)	

Data presented as n (%) or median (interquartile range) unless otherwise stated.

[a] mean ± standard deviation; [b] total *n*=114, Pre-HFNC group *n*=48; [c] HFNC-group *n*=66; total *n*=106, Pre-HFNC group *n*=45; HFNC-group *n*=61

[†] Fisher's exact test.

HFNC, high flow nasal cannula oxygen therapy; WAZ, weight-for-age z-score; HAZ, height (or length) for age z-score; WHZ, weight-for-height (or length) z-score; SD, standard deviation; HIV, human immunodeficiency virus; CLD, chronic lung disease; TB, tuberculosis.

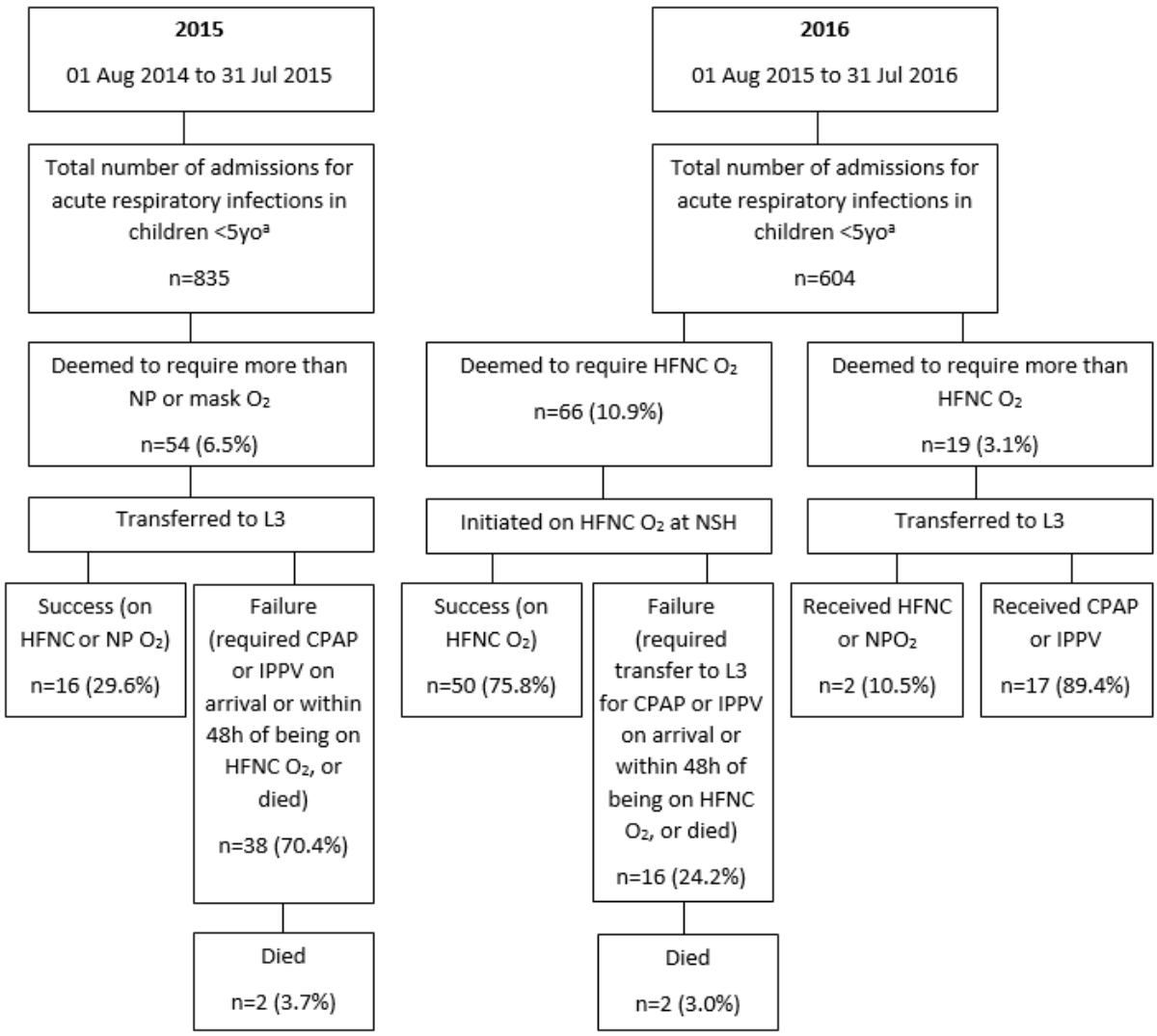
2015
01 Aug 2014 to 31 Jul 2015
Total number of admissions for acute respiratory infections in children <5yo[a]
n=835
Deemed to require more than NP or mask O_2
n=54 (6.5%)
Transferred to L3
Success (on HFNC or NP O_2)
n=16 (29.6%)
Failure (required CPAP or IPPV on arrival or within 48h of being on HFNC O_2, or died)
n=38 (70.4%)
Died
n=2 (3.7%)
2016
01 Aug 2015 to 31 Jul 2016
Total number of admissions for acute respiratory infections in children <5yo[a]
n=604
Deemed to require HFNC O_2
n=66 (10.9%)
Initiated on HFNC O_2 at NSH
Success (on HFNC O_2)
n=50 (75.8%)
Failure (required transfer to L3 for CPAP or IPPV on arrival or within 48h of being on HFNC O_2, or died)
n=16 (24.2%)
Died
n=2 (3.0%)
Deemed to require more than HFNC O_2
n=19 (3.1%)
Transferred to L3
Received HFNC or NPO_2
n=2 (10.5%)
Received CPAP or IPPV
n=17 (89.4%)

Fig. 1

Appendixes

APPENDIX 1: The protocol

APPENDIX 2: HREC approval letter

APPENDIX 3: HREC HFNC registry approval letter

APPENDIX 4: NSH SOP for use of HFNC

APPENDIX 5: Database data collection form

APPENDIX 6: Instructions to authors of chosen journal

APPENDIX 7: Turnitin report

MMED Protocol:

A review of the use of high flow nasal cannula oxygen therapy in hospitalized children at a regional hospital in the Cape Town Metro, South Africa.

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Master of Paediatrics

Supervisor: Dr Louise Cooke

Co-supervisor: Dr Mark Richards

Introduction

Acute severe respiratory infections remain a major cause of mortality and morbidity in South Africa[1], and globally (13%) [1-2]A recent review of under-5 deaths in children in the Metro West geographical service area of the Western Cape Province showed pneumonia (25%) was the leading cause of death followed by gastro-enteritis (10%), prematurity (9%) and injuries (9%)[3].

Early and appropriate treatment of pneumonia can reduce morbidity and mortality[4]. Comprehensive guidelines have been developed, including recommendations contained in the IMCI strategy and South African Thoracic Society (SATS) guidelines[5]. Both guidelines take into account the high prevalence of HIV infection in South Africa and its impact on childhood pneumonia. Appropriate and rational antibiotic use, supportive care and standard low flow oxygen delivery (nasal prongs or face mask) form part of these guidelines[5-6].

However, in resource-limited developing countries, mortality from severe disease (related to hypoxemia and respiratory failure) remains high despite implementation of guidelines. Advanced respiratory support is central to the care of critically ill children but is often not an option in resource-limited settings[7].

Recently there has been increased interest in, and use of, non-invasive ventilation (NIV) within and outside the pediatric ICU[8]. While there has been increased focus on non-invasive ventilation options (in multiple forms), there is a paucity of literature to support the use of this intervention in children, and more specifically in sub-Saharan Africa. Continuous positive airway pressure ventilation (CPAP) in various forms has been used in neonatal care across the world including developing countries for many years. Studies show the technology is much less expensive, has lower complication rates, and requires less technical skill than mechanical ventilation, making it an attractive option in resource-limited countries.[9-11]

Findings from research undertaken in Ghana showed that nurses in developing countries can successfully and safely apply CPAP after receiving appropriate training. The researchers found that CPAP decreases respiratory rate in children presenting with severe respiratory distress and was well tolerated and without complications[12].

Alongside CPAP the use of high flow nasal cannula oxygen (HFNC) devices in clinical settings is rapidly growing. These devices are being applied to patients across age groups in a variety of disease conditions. The mechanisms through which these devices affect the respiratory system and alter gas exchange are still under investigation but a growing body of evidence is supporting the mechanisms of action for HFNC to be five-fold:

1) HFT provides for washout of nasopharyngeal dead space, which contributes to establishing improved fraction of alveolar gases with respect to carbon dioxide as well as oxygen[13].

2) The distensibility of the nasopharynx provides significant resistance on inspiratory relative to expiratory efforts. HFT provides adequate flow rates to match inspiratory flow and thus markedly attenuates the inspiratory resistance associated with the nasopharynx, and thus eliminates related work of breathing[14].

3) The provision of adequately warmed and humidified gas to the conducting airways improves conductance and pulmonary compliance compared to dry, cooler gas[15].

4) The provision of adequately warmed and humidified gas through the nasal pharynx reduces the metabolic work associated with gas conditioning and,

5) High flow through the nasopharynx can be titrated to provide positive distending pressure for lung recruitment[16].

HFNC therapy can potentially improve outcomes such as reduced need for intubation and invasive ventilation.[17-19] HFNC is readily applied and is not resource or cost intensive. Staff can easily be trained in the application of HFNC therapy and in the care of children using this therapy. It may also reduce the length of intubation, as HFNC holds potential to transition between extubation and low-flow nasal cannula oxygen delivery. An additional advantage is that children requiring this therapy may be cared for outside of the pediatric intensive care unit (PICU) or centralized high care unit, reducing pressure on scarce resources. Other potential advantages in resource-limited services include reduced stress for parents when children require transfer, reduced demand on emergency paramedic services required for transfers, and reduced anxiety for the initial hospital staff related to difficult decisions regarding whether transfer for NIV is indicated.

Complications and serious adverse events that have been described with HFNC use include abdominal distension, pneumothorax, undetected clinical deterioration, blockage with nasal secretions and pressure necrosis[20-21]

The recent donation of two HFNC devices to the general pediatric ward of New Somerset Hospital (NSH), a regional hospital in the Metro West sub-district of Cape Town afforded the pragmatic opportunity to review this new intervention.

We propose a retrospective descriptive study of all children initiated on HFNC in the first year of availability of the intervention at NSH.

Pimary aim will be to:

a) Describe the paediatric patients who qualified by standard protocol for HFNC oxygen, and their outcome

b) Describe the incidence of serious adverse events (SAE) associated with this new intervention at regional level and compare this with available local and international data.

Secondary aim is:

Compare the number of children transferred to tertiary care for further non-invasive/Invasive ventilation with the number of transfers in the year prior to availability of HFNC oxygen.

Our findings will inform our current local practice and potentially provide evidence to support introduction of this intervention in similar setting in South Africa and other resource limited settings

Purpose of Study:

We aim to document the first year of use of high flow nasal cannula(HFNC)oxygen support in hospitalized children younger than 13 years of age with respiratory distress at New Somerset Hospital(NSH), a regional level hospital in the Cape Town Metro, South Africa.

The study will aim to:

- Describe the paediatric patients who qualified by standard protocol for HFNC oxygen.
- Compare the number of children transferred to tertiary care for further non-invasive/Invasive ventilation with the number of transfers prior to availability of HFNC oxygen. (Was there a significant reduction in the need for transfer,indirectly reducing the load on tertiary services ,emergency medical services and caregiver distress related to transfer and access to the tertiary centre?)
- Describe the incidence of serious adverse events(SAE) associated with this new intervention at regional level and compare this with available local and international data.(Is the intervention safe?)

Background:

Methodology:

Study design:

A retrospective descriptive study of all children initiated on HFNC in the first year of availability of the intervention at NSH. A comparison will be made with children who required additional respiratory support and transfer in the year preceding inititation.

Study population:

The following children younger than 13 years of age will be included:

- All children commenced on HFNC oxygen according to standard indication and standard operating procedure(S.O.P) at NSH from 1 August 2015 to 31 July 2016.(Identified from the ethics approved NSH High Flow Nasal Cannulae Registry R051/2015).Sample size will be determined at end of study period(August 2016)-estimated 30-40 patients

- Chidren <13 years transferred to level 3 /tertiary care for respiratory support over a period of 12 months prior to the availability of HFNC oxygen therapy at NSH.(Patients identified from existing Morbidity and Mortality records in the Department of Paediatrics NSH).Sample size:approximately 50 patients.

Objectives :

Child:

Primary

Describe the paediatric patients who qualified by standard protocol/S.O.P for HFNC oxygen support by:

- Demographics: Age, Gender, Gestational age at birth/Birth weight
- Nutritional status(WHO classification – normal, moderate or severe malnutrition based on Z-scores)
- HIV status (HIV –exposed, uninfected, HIV negative, HIV infected on ARVs, HIV infected not on ARVs)
- Diagnosis
- Any underlying chronic illness
- Length of time receiving HFNC
- Outcome (demised, weaned successfully and discharged, transfer to L3, any SAE)

Secondary

Document the incidence and type of SAE and compare with available data(Local and international).

SAE include:

1. Gastric distension with/without aspiration
2. Nasal Pressure sores/necrosis
3. Blocked prongs secondary to secretions
4. Pneumothorax

Service/System

Primary

Compare the number of children transferred to tertiary care for further non-invasive/Invasive ventilation with the number of transfers prior to availability of HFNC oxygen at this regional hospital. (Was there a significant reduction in the need for transfer,indirectly reducing the load on tertiary services ,emergency medical services and caregiver distress related to transfer and access to the tertiary centre?)

Secondary

Study the incidence of SAE and compare with available data(international).This may indicate a need for improved training for health personal involved in children's care.

Methods:

Data collection:

The NSH HFNC registry data will be available to the principle investigator(PI).The folders of all identified patients will be requested and drawn from medical records at NSH and will be reviewed by the PI for additional data. Each entry will record :

- Age
- Gender
- GA at birth/Birth weight
- Current nutrition status(WHO Z-scores)
- HIV status
- Diagnosis
- Duration receiving HFNC
- Outcome: failed HFNC(transfer to level 3 hospital for further non-invasive(CPAP) or invasive support(intubation and IPPV), death, successful weaning
- Serious adverse events recorded while receiving HFNC oxygen therapy.
- Nutritional status(WHO classification – normal, moderate or severe malnutrition) Z-scores)
- HIV status (HIV –exposed, uninfected, HIV negative, HIV infected on ARVs, HIV infected not on ARVs)
- Diagnosis
- Any underlying chronic illness
- Length of time receiving HFNC
- Outcome (demised, weaned successfully and discharged, transfer to L3, any SAE)

Available existing morbidity data for the 12 month period preceding the study period will be reviewed recording:

- Number of children transferred for respiratory support over a period of 12 months prior to introduction of HFNC oxygen therapy.
- Number of children transferred for respiratory support over the period of 12 months since the introduction of HFNC oxygen therapy.

Data will be directly entered on an electronic data collection database(Microsoft Access).

Data will be analysed by a UCT statistician using appropriate descriptive and comparative statistics. Analysis will be using STATA®.

Ethics:

In order to maintain confidentiality each entry will receive a study number and the data collated onto the data collection forms will only bear this study number. The principle researcher however will retain a copy of folder numbers correlated with study numbers so that a folder could be located again through medical records should it be necessary.This will be an electronic list,kept in password encrypted folder.No published data will be linked to a specific patient.

HIV results will be obtained from the folders, for which consent (as per hospital guidelines) will have been obtained by the clinician involved in care and management and the parents duly counseled.

It will not be possible to obtain individual consent from the parents of each child involved because of the retrospective design, but management is not influenced or altered by the study. Consent for the use of medical records will be obtained from the hospital CEOs of NSH and Red Cross Hospital with application to waive individual consent.

Risks to participants: There are no risks to the participants as this is a retrospective study.

Benefits to participants: There are no direct benefits to the patients in this study. However management guidelines at the local institution may be improved depending on results

Reporting and implementation:

All results of data analysis will be reported back to the paediatric department of New Somerset hospital with the potential to improve future management.

Budget:

The study will be undertaken by the principal researcher as part of her MMED project under the University of Cape Town. There will be no personal compensation for the principal researcher or the supervisor. Only routine existing equipment available at New Somerset Hospital will be required.

Expenses related to printing and internet will be covered by funding through the postgraduate committee allocated to training registrars research projects (R5000/student). This will be managed from the supervisors entity for incidental costs. Statistical support will be from the University allocated statistician at no additional cost

Strengths and limitations:

The study is limited by its retrospective nature -the accuracy of recorded notes and the availability of the required folders from medical records may impact on data collection and validity.

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Appendices:

NSH HFNC SOP

NSH HFNC Registry

NSH M&M data base.

APPENDIX 2: HREC Approval Letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

27 July 2016

HREC REF: 534/2016

Dr M Cooke
Department of Paediatrics
Room 5.20, 5th Floor, ICH Building
SCAH

Dear Dr Cooke

PROJECT TITLE: A REVIEW OF THE USE OF HIGH FLOW NASAL CANNULA OXYGEN THERAPY IN HOSPITALIZED CHILDREN AT A REGIONAL HOSPITAL IN THE CAPE TOWN METRO, SOUTH AFRICA (MMeD-candidate- Dr E Hoffman) linked to 051/2015

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 July 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Yours sincerely

pp T Burgess
PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

APPENDIX 3: HREC HFNC Registry Approval Letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: nosi.tsama@uct.ac.za
Website: www.health.uct.ac.za/research/humanethics/forms

20 October 2015

REF NO: R051/2015

Dr M Richards
Paediatrics
ICH Building
Red Cross Children's Hospital

Dear Dr Richards

PROJECT TITLE: New Somerset Hospital High Flow Nasal Cannulae Registry

Thank you for submitting registry to the Faculty of Health Sciences Human Research Ethics Committee for review.

The HREC has **approved** the registration of your registry.

Please Note: All research, including that undertaken for a master's or doctoral degree, using registered databases, registries and repositories, requires submission as a new study. It requires an application form (FHS013) and a protocol which has undergone departmental review. The study will receive its own HREC REF number which will be linked to the main database or repository.

The registration of this database is valid until **30 October 2018.**

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS

Western Cape Government
Health

COMPONENT:
Child and Newborn Services
NEW SOMERSET HOSPITAL

Serving the Community

CLINICAL PROTOCOL/GUIDELINE

Protocol/Guideline Name: NASAL HIGH FLOW PRONG OXYGEN GUIDELINE

Date of first issue: 5 / 12 / 2014 **Revision 03 /11/ 2015**
Date for review: 5/12/2016

Main author: ML Cooke
Adapted for local use from:
Royal Children's Hospital Melbourne NHF Oxygen guideline

NASAL HIGH FLOW OXYGEN GUIDELINE

Preamble

Humidified high flow nasal prong (cannula) oxygen therapy is a method for providing oxygen and continuous positive airway pressure (CPAP) to children with respiratory distress. It is used for the same indications as the traditional method of CPAP using a nasopharyngeal tube. HFNP may reduce need for NCPAP/intubation, or provide support post extubation. At high flow of 2 litres per kg per min, using appropriate nasal prongs, a positive distending pressure of 4-8 cmH2O is achieved. This improves functional residual capacity thereby reducing work of breathing. Because flows used are high, heated water humidification is necessary to avoid drying of respiratory secretions and for maintaining nasal cilia function.

INDICATIONS

HFNP are used for the same indications as the traditional method of CPAP using a nasopharyngeal tube. At NSH the usual clinical scenarios would include:

- Respiratory distress from bronchiolitis or pneumonia or acute severe asthma
- Respiratory distress from congestive heart failure
- Respiratory support to children with neuromuscular disease

Although additional indications include apnoea and support of the very small baby with respiratory distress, at NSH we will limit use to children above 3 kgs and will be temporary in apnoea- babies with recurrent apnoea should be transferred to Red Cross, as should babies under 3 kgs with significant respiratory distress to be closer to ICU/additional respiratory support.

- High flow can be used if there is hypoxaemia (SpO2<90%) and signs of moderate to severe respiratory distress despite standard flow oxygen.

Contraindications:

- Blocked nasal passages/co anal atresia
- Trauma/surgery to nasopharanyx

EQUIPMENT

- Oxygen source WITH Flow meter(no blender or humidifier)
- Humidifier (Fisher and Paykel® MR850) with circuit tubing to attach to humidifier
    - Doctor will select if infant or adult pack depending on weight to match prongs
    - <12kg: infant, >12 kg adult
- 1 litre vacolitre bag of water for irrigation (for humidifier)
- Nasogastric tube
- Nasal cannula (prongs) to attach to humidifier circuit tubing (size to fit nares comfortably)
    - Infants and children **up to 12kg**: OPT316 Infant (max flow 20L/min) or up to 12.5kg: OPT318 Paediatric cannula (max flow 25L/min)
    - **Children >12 kg**: Adult cannula size S OPT542, size M OPT544, size L OPT546

.

SET UP OF EQUIPMENT

- Setup by attending doctor
- Select appropriate size nasal cannula and circuit/humidifier tubing for patient size(<14kg – paeds circuit and prongs, >14 kg – adult circuit and prongs)
- Hold bottom arrow down for 5 seconds to change from paeds to adult mode
- Connect nasal cannula to adaptor on circuit tubing, and connect circuit tubing to humidifier
- Connect oxygen tubing to back of humidifier from the wall(no blender or humidifier)
- Attach 1 litre "water for irrigation" bag to humidifier on machine and turn on to 34°C. The water bag must run freely and be placed as high as possible above the humidifier to achieve flow of water into the humidifier chamber. Do not fill from a bottle. The system is then ready for use.

PATIENT MANAGEMENT

- Insert NGT
- Clean cheeks with unisolve or friars balsam and ensure DRY
- Secure nasal cannula on patient using supplied granuflex "wiggle pads™", ensuring the prongs sit well into the nares **DO NOT CUT PRONGS SHORTER**
- attach to the cheekbones to avoid dislodgement
- prongs should not totally occlude nares- should occlude ½- 2/3 of nostrils
- if not sitting well, remove at VELCRO level(not granuflex off skin) and reattach
- let the prongs hang down loosely over chest, DO NOT PUT BEHIND EARS

START THE HIGH FLOW NASAL CANNULA SYSTEM AT THE FOLLOWING SETTINGS:

- **Flow rate** :calculated by prescribing doctor
- ≤10Kg 2 L per kg per minute
- >10Kg 2 L per kg per minute for the first 10kg + 0.5L/kg/min for each kg above that (max flow 50 L/min)
- ***Usually start off at 6L/min and increase by 2l/min every 1-2minutes up to goal flow rate over a few minutes to allow patient to adjust to high flow.***
- ***If weight between 3-5kg start at 4l/min, increase by 1l/min***
- **FiO2**
- Adjust wall flow rate and read concentration of oxygen being delivered off machine and adjust accordingly
- Start at 50-60% for bronchiolitis and respiratory distress
- Target range for SpO2 of 94%-98% (not in cyanotic congenital heart disease)
- If the child needs a neb put over the prongs

PATIENT MONITORING

Monitor patient for response

- Respiratory rate and Heart rate
- Degree of chest in-drawing
- SpO2

Within 2 hours it should be possible to reduce the FiO2 and clinical stabilisation should be seen

- The FiO2 required to maintain SpO2 in the target range should decrease to <40%
- The heart rate and respiratory rate should reduce by 20%
- Chest in drawing and other signs of respiratory distress should improve

Urgent review for transfer +/- intubation if any of the following occurs:

- The patient is not stabilising as described above
- The degree of respiratory distress worsens
- Hypoxaemia persists despite high gas flow
- Persistent requirement for >50% oxygen
- Note that on high flow if high FiO2 is used, oxygen saturation may be maintained in an infant despite the development of hypercarbic respiratory failure
- If there is rapid deterioration of oxygen saturation or marked increased work of breathing, a chest x-ray should be done to exclude a pneumothorax

PATIENT NURSING CARE

- Infants on high flow should preferably have a nasogastric tube
- Aspirate the NG 2-4 hourly for air if abdominal distension
- Oral and nasal care must be performed 2-4 hourly
- Note nasal prongs are in correct position and no pressure areas to nares
- Spare "wiggle pads™" available to change as required to ensure prongs secure
- Gentle suction as required to keep nares clear
- Check humidifier water level hourly
- Documentation: NHF(nasal high flow) chart
    - hourly : Flow rate, FiO2 & humidifier temp: off machine NOT wall flow meter
    - Document RR,HR, SpO2
- Once stable on high flow, the infant should be assessed by a doctor as to whether they can feed. Some infants can continue to breast feed or cup feed, but most require feeding via a nasogastric tube, at least for first 24 hours

WEANING OF HIGH FLOW NASAL CANNULA OXYGEN

Start weaning when the child's clinical condition is improving as indicated by:

- Decreased work of breathing
- Normal or improved respiratory rate
- Return to normal cardiovascular parameters

<u>For infants <10Kg</u>

- The first step is to wean the FiO2 to <40% (usually within the first 1-2 hours, as above)
- Reduce flow gradually by 1- 2l/min
- Once flow down to 5 L/min then change to standard low flow titrated oxygen (1 to 2L/min) or cease oxygen therapy if stable

<u>For children >10Kg</u>

- Wean FiO2 to 40%
- Once the indication for using high flow has resolved, and the patient is stable in 40% oxygen the flow can be weaned to 1-2 L/min with FiO2 of 100% then switch to via standard nasal prong therapy, or cease oxygen therapy

Generally there is no need for a prolonged weaning process, better to be on high flow, standard low flow or off oxygen therapy.

Keep HF nasal prongs in packet next to patient should they require use again

DO NOT THROW AWAY UNTIL PATIENT DISCHARGED

<u>Complications</u>

Gastric distension

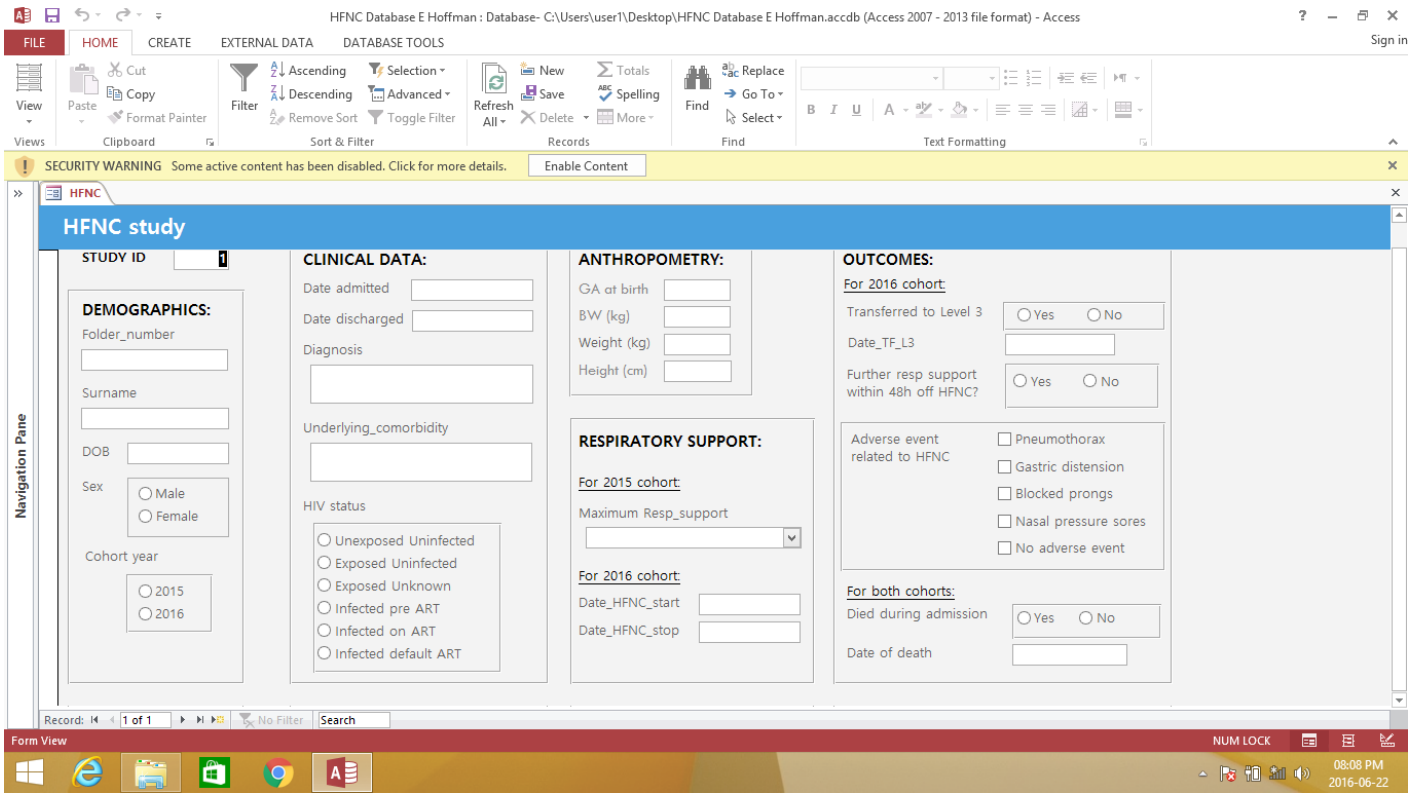
Pressure areas

Blocked HFNP due to secretions

Pneumothorax

STERILIZE WITH RED TUBING THAT IS PROVIDED WITH THE MACHINE according to instructions - 55MINUTE CYCLE,DO NOT SEND AWAY.PUT RED TUBE BACK IN BLACK BAG AFTER CYCLE COMPLETE

APPENDIX 5: Database Data Collection Form



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INSTRUCTIONS TO AUTHORS

Scope and policies

The *SAMJ* is a monthly, peer–reviewed, internationally indexed, general medical journal publishing leading research impacting clinical care in Africa. The Journal is not limited to articles that have 'general medical content', but is intending to capture the spectrum of medical and health sciences, grouped by relevance to the country's burden of disease. This will include research in the social sciences and economics that is relevant to the medical issues around our burden of disease.

The journal carries research articles and letters, editorials, clinical practice and other medical articles and personal opinion, South African health–related news, obituaries, general correspondence, and classified advertisements (refer to the section policies for further information).

Conflict of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an article. However, we aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

Manuscripts preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self–citations by referring to your own work in third person.

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word or RTF document format. Text must be single–spaced, in 12–point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, full affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and °C), e.g. '40 kg' and '20 cm' but '50%' and '19°C'.
- Please be sure to insert proper symbols e.g. ɲ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand–units, i.e. 4 000, 22 160.

- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format – this is the only exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.
- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.
  **NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.
- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'
- Use the latest approved gene or protein symbol as appropriate:
  - Human Gene Mapping Workshop (HGMW): genetic notations and symbols
  - HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
  - OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
  - Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424–433: standard human pedigree nomenclature.

Preparation notes by article type

- Research
- Editorials
- CME
- In Practice and Case reports
- Reviews
- Clinical trials
- Correspondence
- Obituaries
- Book reviews
- Guidelines

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain). –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author.
- Embed/include each table in the manuscript Word file – do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell–based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

    - ***Do not***: Use [Enter] within a row to make 'new rows':

- *Rather*:
  Each row of data must have its own proper row:

- ***Do not***: use separate columns for n and %:

- *Rather*:
  Combine into one column, n (%):

- ***Do not***: have overlapping categories, e.g.:

- *Rather*:
  Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and* ***not*** *with the use of reference manager software. Endnotes must not be used.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4–6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215–1217 **not** 1215–17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link).
  Authors are encouraged to use the DOI lookup service offered by CrossRef:
  - On the Crossref homepage, paste the article title into the 'Metadata search' box.
  - Look for the correct, matching article in the list of results.

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- Alongside 'url =' copy the URL between { }.
- Provide as follows,
  e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- Journal references: Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182
- Book references: Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96–101.
- Chapter/section in a book: Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457–472.
- Internet references: World Health Organization. The World Health Report 2002 – Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).

- Legal references

  - Government Gazettes:
    National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.
    In this example, 17507 is the Gazette Number. This is followed by :1514 – this is the notice number in this Gazette.

  - Provincial Gazettes:
    Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:
  South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:
  South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:
  South Africa. Traditional Health Practitioners Bill, No. B66B–2003, 2006.

- Green/white papers:
  South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:
  Rex v Jopp and Another 1949 (4) SA 11 (N)
  Rex v Jopp and Another: Name of the parties concerned
  1949: Date of decision (or when the case was heard)
  (4): Volume number
  SA: SA Law Reports
  11: Page or section number
  (N): In this case Natal – where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.

  NOTE: no . after the v

- *Other references* (e.g. reports) should follow the same format: Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person

must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

Manuscripts submission

To submit an article:

- Please ensure that you have prepared your manuscript in line with the SAMJ requirements.
- All submissions should be submitted via Editorial Manager
- The following are required for your submission to be complete:
    - Anonymous manuscript (unless otherwise stated)
    - Author Agreement form
    - Manuscript
    - Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.
- Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Submission Preparation Checklist 11.

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. Named authors consent to publication and meet the requirements of authorship as set out by the journal.
2. The submission has not been previously published, nor is it before another journal for consideration.
3. The text complies with the stylistic and bibliographic requirements in **Author Guidelines**.
4. The manuscript is in Microsoft Word or RTF document format. The text is single–spaced, in 12–point Times New Roman font, and contains no unnecessary formatting.
5. Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (preferably TIFF or PNG). These must be submitted individually as 'supplementary files' (not solely embedded in the manuscript).
6. For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.

7. Where possible, references are accompanied by a digital object identifier (DOI) and PubMed ID (PMID)/PubMed Central ID (PMCID).
8. An abstract has been included where applicable.
9. The research was approved by a Research Ethics Committee (if applicable)
10. Any conflict of interest (or competing interests) is indicated by the author(s).

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Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out

- **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
- **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
- **Conclusion:** must be supported by the data, include recommendations for further study/actions.

- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

CME (by invite only)

CME is intended to provide readers with practical, up-to-date information on medical and related matters. It is aimed at those who are not specialists in the field.

From January 2016, all CME articles will be printed in full in the *SAMJ*. Please try to adhere strictly to the guidelines on word count as we have a page limit for the print issue of the *SAMJ*. We reserve the right to place some tables and reference lists online if this is necessary for space.

In practice, this means that each CME topic usually covers two issues of the print issue of the *SAMJ*.

The guest editor, in consultation with the editor, is responsible for convening a team of authors, deciding on the subjects to be covered and for reviewing the manuscripts submitted. The suggestion is for 4 - 5 articles, although there is some room for flexibility contingent on discussions with the editor.

For queries about these guidelines please feel free to contact the CME editor, Dr Bridget Farham, by email (ugqirha@iafrica.com) or telephone (+27 (0)21 789 2331).

Review process

The guest editor reviews the articles and returns them to the CME editor for review and final approval.

Guest editorials

Guideline word limit: 1 000 words

- Include the guest editor's personal details (qualifications, positions, affiliation, e-mail address, and a short personal profile (50words)).
- If possible, include a photograph of the author(s) at high enough resolution for print. It is preferable to provide two guest editorials, one for each issue, so that the content of the articles in each issue is covered.

Articles

Guideline word limit: 2 000 - 3 000 words

- Each article requires an abstract of ±200 words.
- The editor reserves the right to shorten articles but will send a substantially shortened article back for author approval.

Personal details

Please supply: Your qualifications, position and affiliations and MP number (used for CPD points); Address, telephone number and fax number, and your e-mail address; and a short personal profile (50words)and a few words about your current fields of interest.

In Practice

Guideline word limit: 2 000 - 3 000words

This section includes articles that would previously have been accepted into the Forum section, and case reports.

In practice articles are those that draw attention to specific issues of clinical, economic or political interest regarding medicine and healthcare in southern Africa. They are assigned to a topic:

Case report
Clinical practice
Clinical alert
Issues in medicine
Issues in public health
Healthcare delivery
Consensus/Position statement
Medicine and the environment
Medicine and the law
Cochrane corner

An In Practice article should follow the following format – sub-headings are not necessary, but may be used for clarity:

- Author affiliations and qualifications: to be the same as for Research. Provide all authors' names and initials, qualifications and full affiliations, and corresponding author.
- Short abstract: does not need to be structured, but should capture the essential features of the article
- Introduction: the reason for the article and the issue being addressed
- Recent research, discussion, local policy around the issue – include your own research where appropriate

- All statements should be referenced and, if opinion only, this should be stated
- Discussion: how this article adds to the discussion around a particular topic
- If a clinical practice or policy point is at issue, this needs to be emphasised, using a box with highlights if appropriate.

Essentially In practice is an opportunity for a more discursive approach to topics of clinical, economic or political importance in southern African health systems. It is not an opportunity to put forward unsubstantiated opinions!

Case reports

The *SAMJ* has recently started to accept case reports. The cases must come from Africa, preferably southern Africa unless the condition is common to all African countries, and must be either a completely new description of a clinical condition or result (use Google!) or a case that highlights important practice or management issues.

Please use the following format for case reports:

- Title of case: do not include the words 'a case report' in the title
- Summary/abstract: up to 150 words summarising the case presentation and outcome
- Background: why is this case important and why did you write it up?
- Case presentation: presenting features, medical, social, family history as appropriate
- Case management: should be according to best practice, and if not, please explain why
- Investigations, if relevant: save space by simply saying 'normal' if, for example, renal function was completely normal, rather than listing normal results, highlight the abnormal – or indeed the normal if this is clinically significant
- Differential diagnosis, if relevant
- Treatment, if relevant
- Outcome and follow-up
- Discussion – a VERY BRIEF review of similar published cases
- Teaching points: 3 - 5 bullet points
- References: as per the *SAMJ* house style
- Tables and figures: keep to a minimum. Use clinical images where relevant – we need hi-res versions for print, and identifiable persons must have a consent form
- Patient consent: please include a statement about patient consent to a written case report. This should be uploaded as a supplementary file.

Clinical trials

Guideline word limit: 4000 words

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The *SAMJ* therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Review articles

Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners.

Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important
- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.
- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
- Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 500 words

Letters to the editor should relate either to a paper or article published by the SAMJ or to a topical issue of particular relevance to the journal's readership

- May include only one illustration or table
- Must include a correspondence address.

Book reviews

Guideline word limit: 400 words

Should be about 400 words and must be accompanied by the publication details of the book. Provide a hi-res image of the cover if possible (with permission from the copyright holder).

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Guidelines

Guidelines should always be discussed with the Editor prior to submission.

Because of the intensive review process required to ensure Guidelines are independent, evidence-based and free from commercial bias, they are usually published as a supplement

to the *SAMJ*, the costs of which must be covered by sponsorship, advertising or payment by the guideline authors/association. We will provide a quote based on the expected length of the guideline and whether it is to appear online only, or in print, which must be accepted by the body putting the guidelines together before submitting the work to the SAMJ.

The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.

All guidelines should include a clear, transparent statement about all sources of funding and an explicit, clear statement of conflicts of interest of any of the participants in the guidelines about industry funding for lectures, research, conference participation etc.

All guidelines should be structured according to Agree II.

Please access this website before putting the guidelines together, download the Agree 11 instrument and use this to put the guidelines together.

All submitted guidelines will be sent to the local Agree II appraisal committee for review and must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed.

A structured abstract not exceeding 400 words (recommended sub-headings: *Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2.etc.) and summarised in a Table of Contents.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.

- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:
Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:
Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:
Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must* ***not*** *be used.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
  - On the Crossref homepage, paste the article title into the 'Metadata search' box.
  - Look for the correct, matching article in the list of results.
  - Click Actions > Cite
  - Alongside 'url =' copy the URL between { }.
  - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.

- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references

    - Government Gazettes:

    National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

    In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

    - Provincial Gazettes:

    Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

    - Acts:

    South Africa. National Health Act No. 61 of 2003.

    - Regulations to an Act:

    South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

    - Bills:

    South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

    - Green/white papers:

    South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

    - Case law:

    Rex v Jopp and Another 1949 (4) SA 11 (N)

    Rex v Jopp and Another: Name of the parties concerned

    1949: Date of decision (or when the case was heard)

    (4): Volume number

    SA: SA Law Reports

    11: Page or section number

    (N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.

    NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

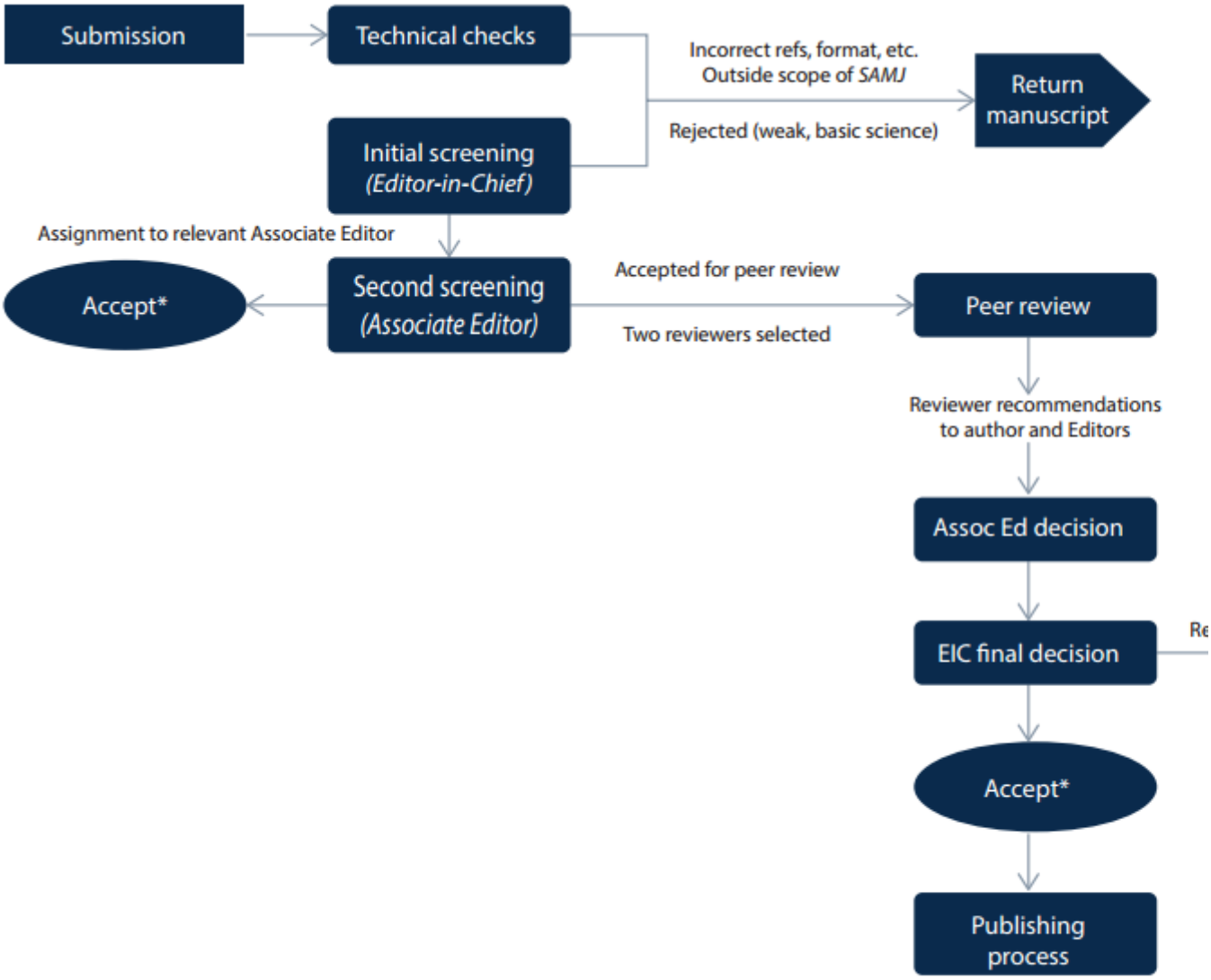
From submission to acceptance

Submission and peer-review

To submit an article:

- Please ensure that you have prepared your manuscript in line with the SAMJ requirements.
- All submissions should be submitted via Editorial Manager
- The following are required for your submission to be complete:
  - Anonymous manuscript (unless otherwise stated)
  - **Author Agreement form**
  - Manuscript
  - Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.
- Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Peer-review process



*Manuscripts accepted at this point are limited to Editorials, Correspondence, Obituaries, Book reviews, Abstracts, CME
**Some minor revisions may be requested

Production process

The following process should usually take between 4 - 6 weeks:

1. An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).
2. The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.
3. If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.
4. The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.
5. The CE will finalise the article and then it will be typeset.

6. Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proofreader.
7. The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.
8. The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

Changing contact details or authorship

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

Publication

Online v. print

The *SAMJ* is an online journal. The online version of the journal is the one that has the widest circulation, is indexed by bibliographic databases including PubMed and SciELO, and is accessible in academic libraries. A printed edition , containing material selected by the Editor is also published each month and distributed to the membership of the South African Medical Association.

Online

- The full text of all accepted articles is published in full online, open access, within 4 - 6 weeks of acceptance.
- Citation information of each article is based on its online publication.
- You may want to make use of the advantages of online publication e.g. specify web links to other sources, images, data or even a short video.

Print

- Not all articles will be selected for print.
- An article may be selected for print in a different month from that in which it was published online.
- Research articles will appear *in abstract form only*, if selected for a print edition.

Errata and retractions

Errata

Should you become aware of an error or inaccuracy in yours or someone else's contribution after it has been published, please inform us as soon as possible via an email to publishing@hmpg.co.za,including the following details:

- Journal, volume and issue in which published
- Article title and authors
- Description of error and details of where it appears in the published article
- Full detail of proposed correction and rationale

We will investigate the issue and provide feedback. If appropriate, we will correct the web version immediately, and will publish anerratum in the next issue. The correction will be indexed, as PubMed has a function for linking errata back to the original article. All investigations will be conducted in accordance with guidelines provided by the Committee on Publication Ethics (COPE).

Retractions

Retraction of an article is the prerogative of either the original authors or the editorial team of HMPG. Should you wish to withdraw your article before publication, we need a signed statement from all the authors.

Should you wish to retract your published article, all authors have to agree in writing before publication of the retraction.

Send an email to publishing@hmpg.co.za, including the following details:

- Journal, volume and issue to which article was submitted/in which article was published
- Article title and authors
- Description of reason for withdrawal/retraction.

We will make a decision on a case-by-case basis upon review by the editorial committee in line with international best practices. Comprehensive feedback will be communicated with the authors with regard to the process. In case where there is any suspected fraud or professional misconduct, we will follow due process as recommended by the Committee on Publication Ethics (COPE), and in liaison with any relevant institutions.

When a retraction is published, it will be linked to the original article.

Indexing

The *SAMJ* has an impact factor of 1.5.

Published articles are covered by the following major indexing services. As such articles published in the *SAMJ* are immediately available to all users of these databases, guaranteed a global and African audience:

- Index Medicus (Medline/PubMed)
- ExcerptaMedica (EMBASE)
- Biological Abstracts (BIOSIS)
- Science Citation Index (SciSearch)
- Current Contents/Clinical Medicine
- Scopus
- AIM
- AJOL
- Crossref
- Sabinet
- Scielo

Sponsored supplements

Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. Named authors consent to publication and meet the requirements of authorship as set out by the journal.
2. The submission has not been previously published, nor is it before another journal for consideration.
3. The text complies with the stylistic and bibliographic requirements in **Author Guidelines**.
4. The manuscript is in Microsoft Word document format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.
5. Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (PDF or jpeg). These must be submitted individually as 'supplementary files' (not solely embedded in the manuscript).
6. For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.
7. Where possible, references are accompanied by a digital object identifier (DOI).
8. An abstract has been included where applicable.
9. The research was approved by a Research Ethics Committee (if applicable)
10. Any conflict of interest (or competing interests) is indicated by the author(s).

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APPENDIX 7: Turnitin Report

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