

## **‘VENTILATOR ASSOCIATED PNEUMONIA IN MAJOR PAEDIATRIC BURNS’**

To fulfill the requirements of Masters of Medicine (Plastic Surgery)

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## DECLARATION

The research reported is based on the independent work of the candidate. Neither the whole work nor any part of it has been, is being, or is to be submitted for another degree to any other university. The literature review and the discussion have been reproduced in part from a review article published by the author. The appendix on the preventative modality 'Noninvasive Ventilation in Major Burns' has been referenced in the manuscript; it has been accepted for publication. The results have not been reported or published prior to the candidate's registration for the MMed (Surgery) degree.

University of Cape Town

## OUTLINE

A – PROTOCOL

PAGE 5

B – LITERATURE REVIEW

PAGE 14

1. Background
2. Prevention
3. Diagnosis
4. Treatment
5. Conclusions
6. Figures
7. References

C – JOURNAL READY MANUSCRIPT

PAGE 30

1. Abstract
2. Background
3. Materials and Methods
4. Results
5. Discussion
6. Conclusion
7. Figures
8. References

Appendix 1- Department of Surgery Research Committee approval letter

Appendix 2 – University of Cape Town Human Ethics Research Committee approval letter

Appendix 3 - ‘Noninvasive Ventilation in Major Burns’

Appendix 4 – Burns Journal submission guidelines

University of Cape Town

A - APPLICATION TO CONDUCT RETROSPECTIVE DESCRIPTIVE STUDY:

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## 1. Background

Severe burns are one of the most devastating forms of trauma. In South Africa, burn injuries are the third commonest external cause of fatal injuries up to the age of 15 years and the main cause under the age of 4 years. In the Cape Town region, at least six in 10 000 children are seriously burnt every year, and as many as 15 in 10 000 toddlers and infants.<sup>1,2</sup>

A number of advances have been made in recent times with regard to fluid resuscitation protocols, dressings, infection control strategies and antimicrobials, surgical techniques, intensive care and nutrition. There is now widespread recognition that specialist burns units or centres deliver the best care for these patients. As a result of these measures, mortality and morbidity rates have declined significantly over the last few decades.<sup>3-4</sup>

Significant thermal injuries induce a state of immuno-suppression; three quarters of all severe burn related deaths are as a consequence of infection, most notably burn wound infections, sepsis, pneumonia and urinary tract infections, many of which are nosocomial.<sup>4-8</sup>

There are a number of mechanisms for the development of pneumonia in the severely burnt. Pulmonary complications are common with inhalational injury, but burnt patients have more pulmonary complications even without direct lung injury. Atelectasis and hypostatic pneumonia are common due to altered ventilation and reduced lung expansion that may occur in patients with chest or abdominal burns. These patients may also have a high risk of aspirating, and respiratory physiotherapy with regular airway suctioning of upper airway secretions and expectoration of sputum may be critical to maintaining pulmonary function.<sup>5,9</sup>

Patients who require prolonged ventilation are also at risk of developing ventilator-associated pneumonia (VAP). Prior to 2007, VAP could only be diagnosed after 48 hours of mechanical ventilation. No minimum time of ventilation is now required to make the

diagnosis.<sup>10</sup> Despite this change in definition, there may still be some utility in considering patients in early or late groups, because causative organisms and their resistance patterns vary in relation to this.

In the paediatric intensive care setting, VAP is responsible for significant morbidity and mortality, and ranks as the second commonest hospital acquired infection. In fact, a large European trial in a variety of paediatric settings showed that VAP accounted for over half of hospital acquired infections in the PICU.<sup>11</sup>

The prevalence of nosocomial pneumonia in the ICU ranges from 10 to 65% and mortality rates exceed 25%. Those who develop VAP are twice as likely to die compared to those without VAP, and spend longer in intensive care. The nosocomial bacteria that cause VAP tend to be more resistant.<sup>11-15</sup>

There is a paucity of literature on VAP in children, and particularly within the context of major paediatric burns. International guidelines for the prevention and management of VAP have largely have been extrapolated from adult experience with VAP. Burns patients, and particularly paediatric patients with burns, are a special group, with peculiar demands and predispositions, and should be managed by burns surgeons, anaesthetists, specialist nursing staff, paediatric intensivists, physiotherapists and occupational therapists with special interest and experience in managing severely burnt children.

The intention of this study will be twofold:

1. To determine the incidence and epidemiology of VAP in this patient group in the setting of Red Cross War Memorial Children's Hospital.
2. To undertake a comprehensive literature review to determine strategies for the diagnosis, prevention and management of ventilator associated pneumonia in the context of paediatric burn injuries.

## 2. Materials and Methods

### 2.1 Study Setting

Red Cross War Memorial Children's Hospital (RXH) is a 288-bed state teaching hospital with tertiary and regional functions. It is predominantly a referral hospital but also houses 24-hour trauma and emergency units, both with overnight inpatient beds. It is the only paediatric inpatient facility for the central health districts of Cape Town. Its tertiary services, including an intensive care unit (PICU), receive referrals from southern, central and western parts of Cape Town, the southern half of the western Cape, other tertiary children's services in the province and other provinces and other African states. It serves children less than 13 years of age, the vast majority of whom are dependent on state services. Approximately 156 000 children attend the outpatient and emergency services each year, of whom about 18 000 are admitted.

The RXH has the largest dedicated paediatric burns centre in South Africa with 26 beds, admitting more than 1000 patients annually. The adjacent Paediatric ICU is a 30-bed facility. It is a combined medical and surgical ICU with specialist consultant intensivists and registrars with paediatrics, anaesthetics, emergency medicine and surgical backgrounds. Burns patients are admitted to the ICU only if they require ventilation, at the discretion of the admitting surgeon in consultation with the resident ICU staff and consultants.

### 2.2 Inclusion Criteria

Patients admitted with burn injuries who required ventilation in the Paediatric ICU at Red Cross War Memorial Children's Hospital (RXH) will be included in the study. The medical records from a five-year period (January 2005 to December 2009) will be collected.

### 2.3 Exclusion Criteria

The following patients will be excluded:

1. Patients ventilated for less than 48 hours.
2. Patients with incomplete notes

### 2.4 Study design

Patient data was obtained by review of patient records (demographics, clinical course) and laboratory data (chemistry, haematology, microbiology) from the hospital database.

The following criteria were recorded and analysed:

1. Demographic details
2. Aetiology of burn injury
3. Size of burn
4. Presence of inhalational injury
5. Incidence of pneumonia
6. Incidence of VAP (as diagnosed by the clinical team, irrespective of the method of diagnosis)
7. Microbiology of specimens collection
8. Method of specimen collection
9. Length of mechanical ventilation
10. Length of ICU stay
11. Mortality rate
12. Blood Transfusions
13. Re-intubations
14. Surgical episodes

Data will be recorded on a proforma designed using an Excel spreadsheet. Data will be collected in the form of categoric and continuous variables, and analysed where appropriate. The relationship between interventions and end-points will be evaluated. Descriptive statistics will used throughout. Significance is regarded as a p value of 0.05 using the student's t-test.

## 2.5 Patient Management

The Parkland Formula is applied to the resuscitation of all major burns victims. Enteral resuscitation and nutritional support is initiated as soon as possible. ICU admission is determined by the attending ICU registrar and consultant, and management within the unit based upon established, evidence-based protocols where available. For instance, a guideline for the diagnosis, prevention and treatment of paediatric ventilator-associated pneumonia was published in the SAMJ in April 2009. The South African Burns Society also publishes recommendations to guide the burns care professionals.<sup>3,9</sup> Standard burns management principles are practised in the unit, and early burn excision and grafting are adhered to as far as possible. Patients are managed with modern closed wound dressings and coverage strategies, including silver based products (Acticoat<sup>16</sup> and Aquacel Ag), and skin substitutes (Biobrane<sup>17</sup> and Suprathel) when indicated. The unit is currently setting up a deceased donor allograft skin bank to improve access to cadaver skin.<sup>18</sup>

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## B – LITERATURE REVIEW

### VENTILATOR ASSOCIATED PNEUMONIA IN MAJOR BURNS

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## Abstract

Major burns victims are particularly susceptible to pneumonia, especially ventilator-associated pneumonia (VAP). VAP remains a prominent cause of morbidity and mortality, despite improvements in intensive care and burns surgery in recent times. Length of ventilation, type and size of burn (especially inhalational burns) are related to the incidence of VAP. Other risk factors (number of re-intubations, theatre visits) are also important.

Effective preventative strategies should be adhered to, and protocols should be implemented to aid in the diagnosis and treatment of VAP. Clinical criteria, radiology, and broncho-alveolar lavage should be used to determine the causative organism, and there should be a low threshold for the early initiation of empiric therapy, based on the prevailing resistance patterns in the unit. Major burns should be managed in centres where there is ready access to multi-disciplinary resources and expertise.

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## Background

Severe burns are one of the most devastating forms of trauma. In South Africa, burn injuries are the third commonest external cause of fatal injuries up to the age of 15 years and the main cause under the age of 4 years. In the Cape Town region, at least six in 10 000 children are seriously burnt every year, and as many as 15 in 10 000 toddlers and infants.<sup>1,2</sup>

A number of advances have been made in recent times with regard to fluid resuscitation protocols, dressings, infection control strategies and antimicrobials, surgical techniques, intensive care and nutrition. There is now widespread recognition that specialist burns units or centres deliver the best care for these patients. As a result of these measures, mortality and morbidity rates have declined significantly over the last few decades.<sup>3-4</sup>

Significant thermal injuries induce a state of immuno-suppression; three quarters of all severe burn related deaths are as a consequence of infection, most notably burn wound infections, sepsis, pneumonia and urinary tract infections, many of which are nosocomial.<sup>4-8</sup>

There are a number of mechanisms for the development of pneumonia in the severely burnt. Pulmonary complications are common with inhalational injury, but burnt patients have more pulmonary complications even without direct lung injury. Atelectasis and hypostatic pneumonia are common due to altered ventilation and reduced lung expansion that may occur in patients with chest or abdominal burns. These patients may also have a high risk of aspirating, and respiratory physiotherapy with regular airway suctioning of upper airway secretions and expectoration of sputum may be critical to maintaining pulmonary function.<sup>5,9</sup>

Patients who require prolonged ventilation are also at risk of developing Ventilator-Associated Pneumonia (VAP). Prior to 2007, VAP could only be diagnosed after 48 hours of mechanical ventilation. No minimum time of ventilation is now required to make the diagnosis.<sup>10</sup> Despite this change in definition, there may still be some utility in considering

patients in early or late groups, because causative organisms and their resistance patterns vary in relation to this.

In the paediatric intensive care setting, VAP is responsible for significant morbidity and mortality, and ranks as the second commonest hospital acquired infection. In fact, a large European trial in a variety of paediatric settings showed that VAP accounted for over half of hospital acquired infections in the PICU.<sup>11</sup> The prevalence of nosocomial pneumonia in the ICU ranges from 10 to 65% and mortality rates exceed 25%. Those who develop VAP are twice as likely to die compared to those without VAP, and spend longer in intensive care. The nosocomial bacteria that cause VAP tend to be more resistant.<sup>11-15</sup>

There is a paucity of literature on VAP in children, and particularly within the context of major paediatric burns. International guidelines for the prevention and management of VAP have largely been extrapolated from adult experience with VAP. Burns patients, and particularly paediatric patients with burns, are a special group, with peculiar demands and predispositions, and should be managed by burns surgeons, anaesthetists, specialist nursing staff, paediatric intensivists, physiotherapists and occupational therapists with special interest and experience in managing severely burnt children.

## Prevention

Much has been written in the critical care literature about the prominent role that VAP plays in respect of mortality and morbidity in the ICU. Burns victims have the highest relative risk of any category of ventilated patients. Several studies have demonstrated that the incidence of VAP in burns patients is more than 22 per 1000 ventilator days, more than double that seen in either surgical or medical cohorts. The rate in our paediatric unit is as high as 30 per 1000 ventilator days.<sup>5-8</sup> VAP usually results from pathogens colonizing the lower respiratory tract and parenchyma by sustained micro aspiration. A number of factors in the burns patient facilitate the development of pneumonia. (Table 1)

Strategies to prevent VAP in burns patients have largely been adapted from studies focusing on other patient groups. Many of these have been incorporated into so-called 'care bundles' for ventilated patients. Table 2 lists some of the preventative strategies.

Daily interruptions and weaning protocols are now fundamental tenets of good adult ICU care. The role in children is less well established, but the principal of reducing ventilation duration to shortest possible is obviously paramount.<sup>9,11,16</sup> Adaptations to the endotracheal tube have been examined in an attempt to reduce the incidence of VAP. The NASCENT trial, for instance, showed a 35.9% risk reduction when a silver impregnated endotracheal tube was used.<sup>17</sup> Techniques to continuously aspirate subglottic secretions have been shown to be effective and should be implemented.<sup>17,18</sup> At present intermittent open suctioning techniques are the norm in ICU's in developing countries.

Stress ulcer prophylaxis and early enteral nutrition are now well-established in both burns care and in the ICU scenario. However, they may also be responsible for raising the pH and gastric bacterial colonization, which predisposes to VAP. Gastritis is rare in the well-resuscitated child burn victim and many units may choose not to make use of stress ulcer prophylaxis. Sucrulphate may be a sensible alternative to other agents that raise gastric pH.

In addition, postpyloric feeding rather than gastric feeding, may reduce the incidence of VAP.<sup>9,19</sup> Placing the patient in the semi-recumbent position is effective and easily applied in the adult patient, but may prove difficult in the paediatric population where there may be marked size differences between patients.<sup>9</sup>

Meta-analyses have showed a significant reduction in the incidence of pneumonia with the use of selective decontamination of the GIT.<sup>20,21</sup> Prophylactic antibiotics may also be justified in certain circumstances, but applied with an awareness of the prevailing resistance patterns.<sup>22</sup> Chlorhexidine mouthwash is a cost-effective and easily applied strategy for reducing VAP.<sup>23,24</sup> Contact precautions and hand hygiene are now well-established tenets of critical care, and adherence to these and other elements in the ventilator care bundles need to be regularly reviewed.<sup>25</sup>

Burns patients frequently require blood transfusions during their course of treatment. A restrictive policy should be adhered to, as each unit of blood received is associated with a 13% increased risk of infection, presumably by exacerbating the state of immunosuppression.<sup>26,27</sup> Intense insulin therapy and tight glucose control, despite initial optimism, needs to be re-evaluated in a major trial, and particularly in major paediatric burns. The consequences of hypoglycaemia are potentially catastrophic, and more significant than the potentiation of infection during periods of high normoglycaemia, or even hyperglycaemia.<sup>28,29</sup>

## Diagnosis

VAP remains one of the greatest challenges to the ICU clinician. This difficulty is illustrated by the fact that VAP represents the dominant indication for empiric antibiotic agents in the ICU. Scoring systems like the CPIS and the CDC criteria have been compiled to improve the accuracy by combining clinical, microbiological and radiological criteria. Scores of more than six are regarded as diagnostic. (Table 3)<sup>30-33</sup>

Scoring systems, however, have not been validated in paediatric burns victims, and a number of problems have been identified. For instance, the burn patient frequently exhibits pulmonary dysfunction due to inhalational injury, overwhelming systemic inflammation, pulmonary oedema and ARDS. Fever, sputum, leukocytosis or leukopaenia, deranged oxygenation, and abnormal chest radiographs may all be present in a burns patient without pneumonia.<sup>6,9, 30-34</sup>

The traditional 48 hours of ventilation required to make the diagnosis has now been removed from the definition of VAP.<sup>10</sup> The ventilator is recognized as a major risk factor for the development of pneumonia in the ICU. The spectrum of bacteria responsible (community acquired vs nosocomial) and the efficacy of preventative and therapeutic measures, make time an important component. VAP is a prominent cause of morbidity and mortality in burns patients, but patients who developed pneumonia prior to 48 hours of ventilation were also at high risk, particularly if they had large body surface burn wounds. Of the organisms responsible for VAP, *Acinetobacter baumannii* infections, in particular, have proved to be a virulent cause of ventilator associated pneumonia in our setting.<sup>6,9,11</sup> bronchoalveolar lavage, Protected specimen brush or non-bronchoscopic lavage are the best means of obtaining reliable quantitative cultures. By combining one of these techniques with clinical features of pulmonary infection, the sensitivity and specificity may be optimised.<sup>6,9,11, 34-38</sup>

## Treatment

Several studies have demonstrated that a delay in initiating appropriate antibiotics may result in increased morbidity and mortality. Consequently units should be aware of their local bacterial milieu and resistance patterns, so that appropriate empiric antibiotics choices can be made.<sup>6,9,11,37</sup> Pneumonias that occur early are more likely community acquired, most notably *Streptococcus pneumoniae* and *Haemophilus influenzae*. Later onset VAP's are more likely a consequence of MRSA and gram negative organisms like *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*.<sup>6</sup>

*Pseudomonas aeruginosa* remains the most invasive pathogen in our patients, but *Acinetobacter baumannii* is now also a major problem, not least because of growing resistance. Methicillin-resistant *Staphylococcus aureus* has not yet proved as significant a problem as experienced in other parts of the world. Because many of our patients are immunocompromised and malnourished prior to burn injury, several of our patients are particularly susceptible to fungal infections.

Many ICU's are still dependent on alternatives to invasive quantitative microbiological techniques like sputum cultures and tracheal aspirates. The results of these tests are relatively unreliable and treatment should be initiated and de-escalated with this in mind. If possible, empiric therapy should be limited to 48 hours: this period of use should not increase resistance.<sup>38, 39</sup> Antibiotics may safely be stopped once clinical features of infection have resolved. There is probably no difference in outcomes if an eight or fifteen day course of treatment is implemented, unless the organism responsible is *Pseudomonas aeruginosa* or *Acinetobacter*, where a longer course is necessary to reduce recurrence.<sup>39</sup> Table 4 lists some of the principles of antibiotic use for VAP.

Appendix

<b>Factor</b>	<b>Mechanism</b>
1. Intubation (especially pre-hospital/ emergency)	Bypass glottis barrier; pooling, leak of and inability to clear secretions
2. Cutaneous thermal injury	Bacterial Reservoir; systemic inflammation; immunosuppression
3. Prolonged ventilation	Sustained micro-aspiration; secretions; reintubation
4. Inhalational injury	Direct injury; exudate formation; poor mucociliary clearance; reduced lung compliance; ARDS; prolonged ventilation;
5. Transport out of ICU (e.g. theatre)	Reintubation; bacterial translocation
6. Blood transfusions	Immunosuppression

*Table 1. Factors predisposing the burns patient to pneumonia in ICU*

<b>Preventative Strategies</b>
1. Reduce the duration of ventilation
2. Postpyloric feeding
3. Chlorhexidine mouth wash
4. Reduce transfusions
5. Head elevation
6. Selective decontamination of the GIT
7. Staff factors – hand hygiene and barrier nursing
8. Silver endotracheal tubes and continuous aspiration

*Table 2. Strategies identified to prevent VAP*

	0	1	2
<b>Leukocytes (<math>10^9/l</math>)</b>	4 - 11	<4	>11
<b>Tracheal Secretions</b>	Absent	Non-purulent	Purulent
<b>Oxygenation (<math>PaO_2/FiO_2</math>)</b>	>240		<240
<b>Chest X Ray</b>	No infiltrate	Diffuse or patchy	Localised infiltrate
<b>Tracheal Aspirate</b>	< $10^3$	$10^3 - 100^3$	> $100^3$
<b>Temperature</b>	36.1 – 38.4	38.4 – 38.9	>39; <36

Table 3. The Clinical Pulmonary Infection Score

<b>Principles of therapy</b>	
1. Empiric antibiotics	Initiate early
	Broad spectrum
	New agent for patient
2. De-escalation	Preferably within 48 hours
	Adjust according to culture and sensitivity
	Monotherapy preferably
	Consider Linezolid as alternative to vancomycin for MRSA
	Consider colistin for carbapenam resistant <i>Acinetobacter species</i>
	Consider using aerosolized agents

Table 4. Principles of antibiotic use for VAP treatment

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C - JOURNAL-READY MANUSCRIPT

VENTILATOR ASSOCIATED PNEUMONIA IN MAJOR PAEDIATRIC BURNS

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## Abstract

More than three-quarters of deaths related to major burns are a consequence of infection, most notably pneumonia. A retrospective study was performed of children (under 13 years of age) with major burn injuries who were ventilated during their course of treatment, over a five-year period.

92 patients were included in the study; their mean age was 3.5 years and their mean total body surface area burn was 30%. 62% of the patients sustained flame burns, and 31% scalds. The mean ICU stay was 10.6 days (range 2-61 days) and the mean ventilation time was 8.4 days (range 2-45 days). There were 59 documented episodes of pneumonia in 52 patients with a rate of 30 infections per 1000 ventilator days. Length of ventilation and the presence of inhalational injury correlate with the incidence of pneumonia. Chest X-Ray remains the single most important factor used to diagnose pneumonia in the ICU, although organism culture, change in ventilatory requirements and clinical examination remain important. This unit has since validated the use of the Clinical Pulmonary Infection Score to aid in the diagnosis of VAP. 17.4 % of the patients died (n=16); half of these deaths may be attributed directly to pneumonia.

*Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Staphylococcus aureus* were the most prominent aetiological organisms; *Pseudomonas aeruginosa* and *Acinetobacter baumannii* were the leading causes of ventilator-associated pneumonia. Most of the organisms were identified by tracheal aspirate, although bronchoalveolar lavage was found to be more specific and sensitive at identifying the organism deemed responsible.

This study highlights the importance of implementing strictly enforced strategies for the prevention, detection and management of pneumonia in the presence of major burns.

## 1. Background

Severe burns are one of the most devastating forms of trauma. In South Africa, burn injuries are the third commonest external cause of fatal injuries up to the age of 18 years and the main cause under the age of 4 years. In the Cape Town region, at least six in 10 000 children are seriously burnt every year, and as many as 15 in 10 000 toddlers and infants.<sup>1,2</sup>

The modern treatment of burns has become a logical exercise in resuscitation, infection control, surgical wound care, pain relief, nutrition and psychological and physical rehabilitation. These methods are aided by technological advances in biological and synthetic skin substitutes, pharmacological amelioration of the hyper-metabolic response, and physical exercise programs. There is now widespread recognition that specialist burns units or centres deliver the best care for these patients. As a result of these measures, mortality and morbidity rates have declined significantly over the last few decades.<sup>3-4</sup>

Significant thermal injuries induce a state of immuno-suppression; three quarters of all severe burn related deaths are as a consequence of infection, most notably burn wound infections, sepsis, pneumonia and urinary tract infections, many of which are nosocomial.<sup>4-8</sup>

Pulmonary complications are common with inhalational injury, but burnt patients have more pulmonary complications even without direct lung injury. There are a number of mechanisms for the development of pneumonia in the severely burnt. Atelectasis and hypostatic pneumonia are common due to altered ventilation and reduced lung expansion that may occur in patients with chest or abdominal burns. These patients may also have a high risk of aspirating, and respiratory physiotherapy with regular airway suctioning of upper airway secretions and expectoration of sputum may be critical to maintaining pulmonary function.<sup>5,9</sup>

Patients who require prolonged ventilation are also at risk of developing ventilator-associated pneumonia (VAP), which is a nosocomial lower respiratory tract infection in ventilated patients. Prior to 2007, VAP could only be diagnosed after 48 hours of mechanical ventilation, but no minimum time of ventilation is now required to make the diagnosis.<sup>5,10</sup> Despite this change in definition, there may still be some utility in considering patients in early or late groups, because causative organisms and their resistance patterns vary in relation to this.

In the paediatric intensive care setting, VAP is responsible for significant morbidity and mortality, and ranks as the second commonest hospital acquired infection. In fact, a large European trial in a variety of paediatric settings showed that VAP accounted for over half of hospital-acquired infections in the PICU.<sup>11</sup> The prevalence of nosocomial pneumonia in the ICU ranges from 10 to 65% and mortality rates exceed 25%. Those who develop VAP are twice as likely to die compared to those without VAP, and spend longer in intensive care. The nosocomial bacteria that cause VAP tend to be more resistant.<sup>7,8,11</sup>

The application of preventative intensive care bundles has been paramount in reductions in VAP noted in this ICU over recent years. The timely diagnosis and treatment of VAP is critically important to limit significant morbidity and mortality.<sup>12</sup>

There is a paucity of literature on VAP in children, and particularly within the context of major paediatric burns. International guidelines for the prevention and management of VAP have largely been extrapolated from adult experience with VAP. Burns patients, and particularly paediatric patients with burns, are a special group, with peculiar demands and predispositions, and should be managed by burns surgeons, anaesthetists, specialist nursing staff, paediatric intensivists, physiotherapists and occupational therapists with special interest and experience in managing severely burnt children.

The intention of this study was twofold:

1. To describe the incidence and epidemiology of ventilator-associated pneumonia (VAP) in this patient group in the setting of Red Cross War Memorial Children's Hospital.
2. To undertake a comprehensive literature review to determine strategies for the cost-effective diagnosis, prevention and management of ventilator associated pneumonia in the context of paediatric burn injuries in resource-restricted settings.

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## 2. Materials and Methods

The RXH is a 288-bed state teaching hospital with tertiary and regional functions. It is predominantly a referral hospital but also houses 24-hour trauma and emergency units, both with overnight inpatient beds. It is the only paediatric inpatient facility for the central health districts of Cape Town. Its tertiary services, including an intensive care unit (PICU), receive referrals from southern, central and western parts of Cape Town, the southern half of the western Cape, other tertiary children's services in the province, other provinces, as well as other African states. It serves children under 13 years of age, the vast majority of whom are dependent on state services. Approximately 156 000 children attend the outpatient and emergency services each year, of whom about 18 000 are admitted.

The RXH has the largest dedicated paediatric burns centre in South Africa with 18 beds, admitting more than 1000 patients annually. The adjacent Paediatric ICU is a 20-bed facility. It is a combined medical and surgical ICU with specialist consultant intensivists and registrars with paediatrics, anaesthetics, emergency medicine and surgical backgrounds. Burns patients are admitted to the ICU if they require ventilation, at the discretion of the admitting surgeon in consultation with the resident ICU staff and consultants.

Patients admitted with burn injuries who required ventilation in the Paediatric ICU at Red Cross War Memorial Children's Hospital (RXH) were included in the study. The medical records were collected from a five-year period (January 2005 to December 2009). Patients were excluded from study if they had incomplete notes, or were ventilated for less than 48 hours.

Patient data was obtained by review of patient records (demographics, clinical course) and laboratory data (chemistry, haematology, microbiology) from the hospital database. The following criteria were recorded and analysed: demographic details, aetiology of burn injury, size of burn, presence of inhalational injury, incidence of pneumonia, incidence of VAP (the

diagnosis as per the medical records, irrespective of the method diagnosis), microbiology of specimens' collection, method of specimen collection, length of mechanical ventilation, length of ICU stay and mortality.

Standard protocols were used during the emergency and acute phases of treatment, including the Parkland formula for fluid resuscitation, escharotomy if needed, early enteral nutritional support, topical wound care, early burn excision and grafting, and pain control. The South African Burn Society also publishes recommendations to guide burns care professionals.<sup>3,4</sup> Patients are managed with modern closed wound dressings and coverage strategies, including silver based products (Acticoat<sup>13</sup> and Aquacel Ag), and skin substitutes (Biobrane<sup>14</sup> and Suprathel) when indicated. The unit is currently setting up a deceased donor allograft skin bank to improve access to cadaver skin.

ICU admission was determined by the attending ICU registrar and consultant, and management within the unit was based on care bundles and established, evidence-based protocols<sup>9</sup>. Criteria for admission include: major burns exceeding 30% TBSA (total body surface area), extensive facial and neck burns (especially in small children), suspected or confirmed smoke or hot liquid inhalation, significant carbon monoxide poisoning, physical evidence of upper airway burns, potential for airway obstruction, high voltage electrical burns, depressed level of consciousness and hypoxic brain injury.

The clinical diagnosis of Ventilation Association Pneumonia (VAP) was based on published guidelines utilised by the ICU staff prior to 2010 and supplemented by additional criteria.<sup>15,16</sup>

Criteria used included: new and persistent radiographic evidence of focal infiltrates 48 hours or more after introducing mechanical ventilation; changes in ventilator or oxygenation parameters; the development of hypo- or hyperthermia; changes in white cell counts; cough; changes in chest signs; changes in the nature of endotracheal secretions and microbiological results from transtracheal aspirates and broncho-alveolar lavage.

Prior to 2007, VAP could only be diagnosed after 48 hours of mechanical ventilation. No minimum time of ventilation is now required to make the diagnosis.<sup>11</sup> Despite this change in definition, there may still be some utility in considering patients in early or late groups, because causative organisms and their resistance patterns vary in relation to this. For the purposes of this study, conducted in part prior to the changes, the old definition is applied.

Data were recorded on a proforma and then transferred to Excel (Microsoft Excel 2008 for Mac Version 12.3.0). Data were collected in the form of categoric and continuous variables, and analysed where appropriate using Epi-info (<http://www.cdc.gov/epiinfo>). The relationship between interventions and end-points were evaluated. Descriptive statistics are used throughout. Significance is regarded as a p value of <0.05 using the student's t-test.

Institutional and departmental approval was obtained to complete the study. The project number assigned by the Department of Surgery Research Committee was 2013/055, and by the Human Research Ethics Committee 358/2013.

### 3. Results

Over a five-year period (January 2005 to December 2009), 108 patients were admitted to the RXH Paediatric ICU with burn injuries. Sixteen patients were excluded from further study on the basis of either inadequate or incomplete records (n=5) or because the patient was ventilated for a period shorter than 48 hours (n=11).

The mean patient age was 3.5 years (range 4 months to 13 years, median 1.67 years). 59 % (n=54) of the patients were male and 41% (n=38) were female. The mean percentage total body surface area (TBSA) burnt was 30% (median 26%, range 3-90%). 72% of the patients (n = 66) had areas of full thickness burns.

Scald and flame burns were the commonest mechanisms of injury. 63% (n=58) of the patients sustained flame burns, 33% (n=30) scalds and 4 sustained other kinds of burns (contact, electrical or chemical). Twenty patients had documented evidence of inhalational burns (22% of the total group, 32% of the flame burn group).

Scald injuries occurred most commonly in the very young, with a mean age of 1.63 years (range 0.3-9 years), whereas the mean age of those who sustained flame burns was 5.12 years (range 0.25 – 13 years).

53 % (n=49) of the patients were admitted to the PICU within 12 hours of the injury. Patients who sustained flame burns were far more likely to be admitted early in their clinical course, with 57% (n=33) admitted in the first 12 hours and 84% (n=49) within the first 24 hours. Only 7% (n=4) of flame burnt children were admitted for the first time after 48 hours. As many as 36% (n=11) of scalds are only admitted to the PICU for the first time between 48 hours and one week after the injury.

57% (n=52) of the patients were diagnosed and treated for at least one episode of pneumonia during their clinical course (59 total episodes of pneumonia). Of those, 41

episodes (in 37 patients) met the criteria for ventilator-associated pneumonia (VAP). 18 of the episodes (in 15 patients) did not meet the unit's criteria for VAP, usually because they had manifested clinical features of pneumonia prior to 48 hours of ventilation (as per the previous definition of VAP). The rate of VAP was 30 infections per 1000 ventilator days. The average TBSA of patients who developed VAP was 31%, not significantly different from the rest of the group. 43% of the patients (n=40), despite being ventilated, did not develop pneumonia.

The mean number of re-intubations was 1.47 per patient (range 0-6). The mean ICU stay was 10.6 days (range 2-61 days), 14 days for those who died (range 2-46 days), and 15.4 days for those with VAP. The mean ventilation time was 8.4 days. (range 2 – 31 days, median 9 days). The mean number of ventilation days was at least three days longer in those with VAP compared to those without. The mean number of theatre visits was 5 (range 2 – 19). Length of ICU stay correlated with a significantly increased incidence of VAP ( $p < 0.05$ ). Selected results are compared between those with and those without VAP in Figure 1.

The investigative modality deemed most important when deciding to initiate antibiotics for pneumonia (as documented in the patient records) was chest x-ray findings (34%), organism culture (27%) and clinical examination (39%). The CPIS was inconsistently recorded during this period.

75 organisms were cultured and deemed responsible for pneumonia in 59 episodes in 52 patients during their stay in ICU. Broncho-alveolar lavage (BAL) identified the responsible organism in 16 of the 59 pneumonias, tracheal aspirates (34) and sputum the remainder. Antibiotics were more likely to be adjusted according to the BAL result than the alternative methods. Quantitative sampling and further clinical correlation were utilized in the cases of tracheal aspirates and sputum sample.

*Streptococcus pneumoniae* was the aetiological organism in 18 cases. Other important organisms in the whole group included *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Staphylococcus aureus*. VAP was caused by *Acinetobacter baumannii* in 13 cases. *Pseudomonas aeruginosa* (n=9), *Staphylococcus aureus* (n=9) and *Streptococcus pneumoniae* (n=7) were other prominent aetiological organisms. In two patients with VAP, viruses were responsible.

The other pneumonias (i.e. the group not classified as VAP) were caused by *Streptococcus pneumoniae* (n=13), *Haemophilus influenzae* (n=7), *Pseudomonas aeruginosa* (n=5), *Klebsiella pneumoniae* (n=4) and *Moraxella catarrhalis* (n=4). *Acinetobacter baumannii* was only cultured in one of these cases. *Streptococcus pneumoniae* infection was commonly associated with culture of other organisms such as *Moraxella catarrhalis* and *Haemophilus influenzae*. There was one case of Tuberculosis and two cases of viral pneumonias in this category. These cases were more likely to yield polymicrobial organisms. Figure 2 is a summary of prominent organisms in each category.

There is a significant degree of resistance in the PICU setting; Both *Acinetobacter baumannii* and *Klebsiella pneumoniae* demonstrate extended spectrum beta lactamase production in excess of 20%, and *Pseudomonas aeruginosa* cultured demonstrates a similar degree of carbapenam resistance.

Most patients (n=54, 91.5%) were receiving empiric intravenous antibiotics prior to organism identification. Bloodstream infections (positive blood cultures) were documented in 31 patients, with 43 organisms. In 9 cases (15%) of pneumonia the organism (with a similar sensitivity profile) was also cultured from the burn wound; most frequently this organism was *Pseudomonas aeruginosa*. In 16 episodes (27%) the causative organism was also cultured from the bloodstream.

17.4% (n=16) of the patients died. 63% (n=10) of those who died had sustained flame burns, whereas 25% (n=4) had sustained scalds and one each had electrical and chemical burns. The average TBSA of those who died was 46.8% (range 8 -90%, median 35%), significantly different from the mean TBSA of the whole group, which was 30% (range 3-90 %, median 26%) (p<0.05).

Half (n=8) of the deaths can be attributed to pneumonia. Six of these patients had VAP (causative organisms were *Klebsiella pneumoniae* in one case and *Acinetobacter baumannii* in three cases). Seven of the patients died of overwhelming *Pseudomonas aeruginosa* sepsis. Multiorgan dysfunction and head trauma comprised the remaining causes of death. One patient manifested features of fluid creep, and required laparotomy for abdominal compartment syndrome and fasciotomies for unburnt limbs.

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#### 4. Discussion

Many of the severely burnt children who are admitted to hospital and die, will die in the intensive care setting of complications of either burn wound infections or pneumonia. There is a notable absence of literature related to VAP in the paediatric burns setting, especially from the developing world, despite the recognition that burns is a significant independent risk factor for VAP.<sup>6,7</sup>

Nevertheless, much has been written in the critical care literature about the prominent role that VAP plays in respect of mortality and morbidity in the ICU. Burns victims have the highest relative risk of any category of ventilated patients. Several studies have demonstrated that the incidence of VAP in burns patients is more than 22 per 1000 ventilator days, more than double that seen in either surgical or medical cohorts. The rate in this study was 30 episodes per 1000 ventilator days, which would be in keeping with the literature.<sup>5-8</sup>

VAP usually results from pathogens colonizing the lower respiratory tract and parenchyma by sustained micro aspiration, and less commonly from haematogenous spread of infection. Burnt patients have a number of specific risk factors for developing VAP including the detrimental systemic effects and contamination of the burn wound itself, inhalation injury, as well as the prolonged mechanical ventilation and ICU stay.

The diagnosis of VAP remains one of the greatest challenges to the PICU clinician, but especially in the burnt patient where systemic inflammatory responses and lung injury are prevalent. Although there are a number of proposed definitions, we have adopted for this study a clinical diagnosis of a nosocomial lower respiratory tract infection which occurs in mechanically ventilated patients 48 hours or more after initiating ventilator support, combined with radiological features and microbiological evidence.<sup>5,9</sup>

Scoring systems like the Clinical Pulmonary Infection Score (CPIS) have been compiled to improve the accuracy by combining clinical, microbiological and radiological criteria. Scores of more than six are regarded as diagnostic. (Figure 3) <sup>16-18</sup> The CPIS has recently been validated at this hospital in the general pediatric ICU population and every ventilated patient is now allocated a score on a daily basis. This has resulted in a significant reduction in the incidence of VAP. <sup>12</sup>

Scoring systems have not been validated in the pediatric burns victims; a number of problems have been identified with their application in this context. The burn patient frequently exhibits pulmonary dysfunction due to inhalational injury, overwhelming systemic inflammatory response, pulmonary oedema and ARDS. Fever, sputum, leukocytosis or leukopaenia, deranged oxygenation, and abnormal chest radiographs may also all be present in a burns patient without pneumonia <sup>5-7</sup>

VAP is a prominent cause of morbidity and mortality in our burnt patients, but can be preceded by prior lung pathology. Fourteen of the cohort had evidence of pneumonia prior to 48 hours. These patients are also at high risk, particularly if they had large body surface burn wounds. To accommodate this frequent scenario, the traditional definition of 48 hours required for the diagnosis of VAP, has been revised. The latest guidelines state that there is no minimum period. This takes into account contributing factors such as inhalation injury, pre-hospital and emergency intubation, pre-existing reactive airway disease, the different spectrum of bacteria responsible (community acquired versus nosocomial) and the efficacy of preventative and therapeutic measures. Of the organisms responsible for VAP, *Acinetobacter baumannii* infections, in particular, have proved to be a virulent cause of VAP in our setting.

Establishing the diagnosis of VAP in a burnt patient can be difficult and the presence of the systemic inflammatory response to the burn and co-existing pulmonary dysfunction

contribute to the diagnostic dilemma.<sup>18</sup> Bronchoalveolar lavage, protected specimen brush or non-bronchoscopic lavage are the best means of obtaining reliable quantitative cultures. By combining one of these techniques with clinical features of pulmonary infection, the sensitivity and specificity may be optimized.<sup>6,9,11</sup>

Strategies to prevent VAP in burns patients have largely been adapted from studies focusing on other patient groups. Many of these have been incorporated into so-called 'care bundles' for ventilated patients.

Daily interruptions of sedation and daily spontaneous breathing trials may facilitate early extubation.<sup>5</sup> Its role in children is less well established, but the principal of reducing ventilation duration to shortest possible is obviously paramount. The reason for intubation was seldom formally documented, but in our setting it was frequently related to the magnitude of the burn, significant and progressive facial and or cervical swelling, inhalational injury below the larynx and deterioration of airway patency. The latter was based on history and clinical findings and corroborated through direct vision or fibre-optic laryngoscopy.

There is insufficient data to support either oral or nasal intubation methods in paediatric practice although oro-tracheal tubes are more prone to accidental extubation.<sup>9</sup> Adaptations to the endotracheal tube have been examined in an attempt to reduce the incidence of VAP. The NASCENT trial showed a 40% risk reduction when silver impregnated endotracheal tube was used.<sup>19</sup> Techniques to continuously aspirate subglottic secretions have been shown to be effective in adults, but are not verified in children, and therefore are not applied in this unit<sup>9,20</sup>

Noninvasive ventilatory (NIPPV) strategies are being utilised with increasing efficacy. This is unlikely to be appropriate for most severely burnt children requiring ventilator support because compliance is seldom adequate. Nevertheless, the principle of limiting invasive

endotracheal intubation and ventilation must be considered whenever possible. The principles of non-invasive ventilation are outlined in appendix 3. Recently, NIPPV helmets have been designed for this purpose and may be applied in older children.<sup>21</sup>

Stress ulcer prophylaxis and early enteral nutrition are now well-established in both burns care and in the ICU scenario. Gastritis is rare in the well-resuscitated child burn victim and stress ulcer prophylaxis should not be routinely used as data to support its use is lacking.<sup>9</sup> In addition, postpyloric feeding rather than gastric feeding may reduce the incidence of VAP.<sup>9</sup> Whenever possible, it is the practice of this unit to place a nasojejunal tube for early enteral feeding during the process of resuscitation. There have been a number of benefits to this strategy, not least in the perioperative period, when physiological feeding methods may be continued despite pending theatre visits and procedures. Placing the patient in the semi-recumbent position is effective and easily applied in the adult, but may prove difficult in the paediatric population where there may be marked size differences between patients. Wedge shaped mattresses of various sizes and objects placed under the legs of the bed have been inconsistently applied.<sup>9</sup>

Meta-analyses have showed a significant reduction in the incidence of pneumonia with the use of selective decontamination of the GIT in adults.<sup>22,23</sup> The routine use of prophylactic antibiotics should be discouraged in children, especially in the context of high levels of antibiotic resistance.

Chlorhexidine mouthwash has been a routine, easily applied and cost-effective strategy for reducing VAP.<sup>24,25</sup> Contact precautions and hand hygiene are now well-established tenets of critical care, and adherence to these and other elements in the ventilator care bundles need to be regularly reviewed.<sup>26</sup> With the open structure of our paediatric ICU, the regular use of alcohol based hand wash, gloves and aprons have been important simple measures to improve infection control. Maintaining low nurse-to-patient ratios in the ICU is equally

important, but may be more difficult to apply in resource restricted settings. The care bundles introduced in the ICU and applied to all children with burns consist of: elevating the head of bed, oral hygiene, limiting sedation, early weaning and extubation, correct positioning of ventilation and enteral tubing and the avoidance of saline use during suctioning.

Burns patients frequently require blood transfusions during their course of treatment. A restrictive policy should be adhered to, as each unit of blood received has been associated with a 13% increased risk of infection, presumably by exacerbating the state of immunosuppression.<sup>27,28</sup> Prior to major surgery, we transfuse our patients to a Haemoglobin of 10g%, and make regular use of packed cells for transfusion, and adrenaline-containing solutions for infiltration ('clysis') during surgery.

Intense insulin therapy and tight glucose control, despite initial optimism, needs to be re-evaluated in a major trial, and particularly in major paediatric burns. The consequences of hypoglycaemia are potentially catastrophic, and more significant than the potentiation of infection during periods of high normoglycaemia, or even hyperglycaemia.<sup>29,30</sup>

Probiotics have been identified as a potentially useful adjunct to the VAP bundle. Proposed mechanisms have included: to increase mucous production and the barrier function of the gut; competition with pathogens for epithelial adherence; an up-regulating effect on the secretion of host cell antimicrobial peptides; direct pathogen killing and immunomodulation and induction of lymphoid cells. There has been inconclusive evidence due to variability across studies with respect to probiotic strain, dosing, duration, route of administration, and diagnostic criteria for VAP. As such, we require more rigorous multi-centre studies to justify use of this strategy at this time.<sup>31</sup>

Several studies have demonstrated that a delay in initiating appropriate antibiotics may result in increased morbidity and mortality. Consequently units should be aware of their

local bacterial milieu and resistance patterns, to guide appropriate antibiotics choices.<sup>6,9,11</sup> Pneumonias that occur early are more likely community acquired, most notably *Streptococcus pneumoniae* and *Haemophilus influenzae*, and are more likely to be susceptible to antibiotic therapy. This is in contrast to later onset VAP's, more likely a consequence of *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and gram-negative organisms (*Escherichia Coli* and *Klebsiella pneumoniae*).<sup>6</sup>

Of great concern has been the identification of viruses contributing to the severity of VAP. Before April 2009, viral isolation and identification techniques were suboptimal and dependent on cell cultures or antigen detection. This could explain the low yield of viral respiratory pathogens amongst our patients in this study. In future, viral identification should become an integral investigation in burnt children on mechanical ventilation.<sup>32</sup>

We are still dependent on alternatives to invasive quantitative microbiological techniques, like sputum cultures and tracheal aspirates. The results of these tests are relatively unreliable and treatment should be initiated and de-escalated with this in mind. If possible, empiric therapy should be limited to 48 hours: this period of use should not increase resistance.<sup>5,6,33,34</sup> Antibiotics may safely be stopped once clinical features of infection have resolved.

There is probably no difference in outcomes if an eight- or fifteen-day course of treatment is implemented, unless the organism responsible is *Pseudomonas aeruginosa* or *Acinetobacter baumannii* where a longer course is necessary to reduce recurrence.<sup>35</sup>

Figure 4 outlines a broad diagnostic and therapeutic algorithm for VAP.

Weaknesses inherent in retrospective studies are applicable here. In an attempt to eradicate bias, members of the paediatric intensive care team were not involved in the analysis of the results and the interpretation of the data. Results were recorded based on

the medical records of the patients included, and the applicable laboratory data. Errors and omissions in record keeping may not reflect the comprehensive nature of the patient's care. Nevertheless, we believe that this study reflects the susceptibility of burns patients to VAP, as well as demographic information, highlights some of the prominent risk factors and emphasizes the strategies required to diagnose and manage VAP in resource-restricted settings. Prospective trials are required in this setting to eradicate confounding variables to clearly demonstrate the efficacy of strategies used to prevent, diagnose and treat VAP in paediatric burn patients.

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## 5. Conclusions

Major burns victims are particularly susceptible to pneumonia, especially ventilator-associated pneumonia. VAP remains a prominent cause of morbidity and mortality, despite improvements in intensive care and burns surgery in recent times. Length of ventilation and the type and size of burn (especially inhalational) correlate with the incidence of VAP. Other risk factors (number of re-intubations, theatre visits) are also important.

Effective preventative strategies should be adhered to, and protocols should be implemented to aid in the diagnosis and treatment of VAP. Clinical criteria, radiology, and broncho-alveolar lavage should be used to determine the causative organism, and there should be a low threshold for the early initiation of empiric therapy, based on the prevailing resistance patterns in the unit. Major burns should be managed in centres where there is ready access to multi-disciplinary resources and expertise.

## 6. Figures

	<b>Pts with VAP (n= 37) (41 episodes)</b>	<b>Others (n = 55)</b>	<b>Significant (P&lt;0.05)</b>
<b>Ventilator Days</b>	11.2	8	*
<b>Length of Stay</b>	15.4 days	7.4 days	*
<b>Theatre Visits</b>	6.5	5	
<b>TBSA</b>	31%	28%	
<b>Mortality</b>	8 (21.6%)	8 (14.5%)	*

Figure 1. Comparison of results comparing VAP, and those not diagnosed with VAP

<b>Prominent organisms cultured in VAP group</b>	<b>Prominent organisms cultured in the other group with pneumonia (usually early onset)</b>
<i>Acinetobacter spp</i> (13) <i>Pseudomonas aeruginosa</i> (9) <i>Staphylococcus aureus</i> (9) <i>Streptococcus pneumoniae</i> (7)	<i>Streptococcus pneumoniae</i> (13) <i>Haemophilus influenza</i> (7) <i>Pseudomonas aeruginosa</i> (5) <i>Klebsiella pneumoniae</i> (4) <i>Moraxella catarrhalis</i> (4) Viruses (2) <i>Acinetobacter spp</i> (1) Tuberculosis (1)

Figure 2. Prominent organisms cultured in those diagnosed with VAP, and those with pneumonia not diagnosed with VAP.

	<b>0</b>	<b>1</b>	<b>2</b>
<b>Leukocytes (<math>10^9/l</math>)</b>	4 – 11	<4	>11
<b>Tracheal Secretions</b>	Absent	Non-purulent	Purulent
<b>Oxygenation (<math>PaO_2/FiO_2</math>)</b>	>240		<240
<b>Chest X Ray</b>	No infiltrate	Diffuse or patchy	Localised infiltrate
<b>Tracheal Aspirate</b>	< $10^3$	$10^3 - 100^3$	> $100^3$
<b>Temperature</b>	36.1 – 38.4	38.4 – 38.9	>39; <36

Figure 3. The Clinical Pulmonary Infection Score (CPIS)

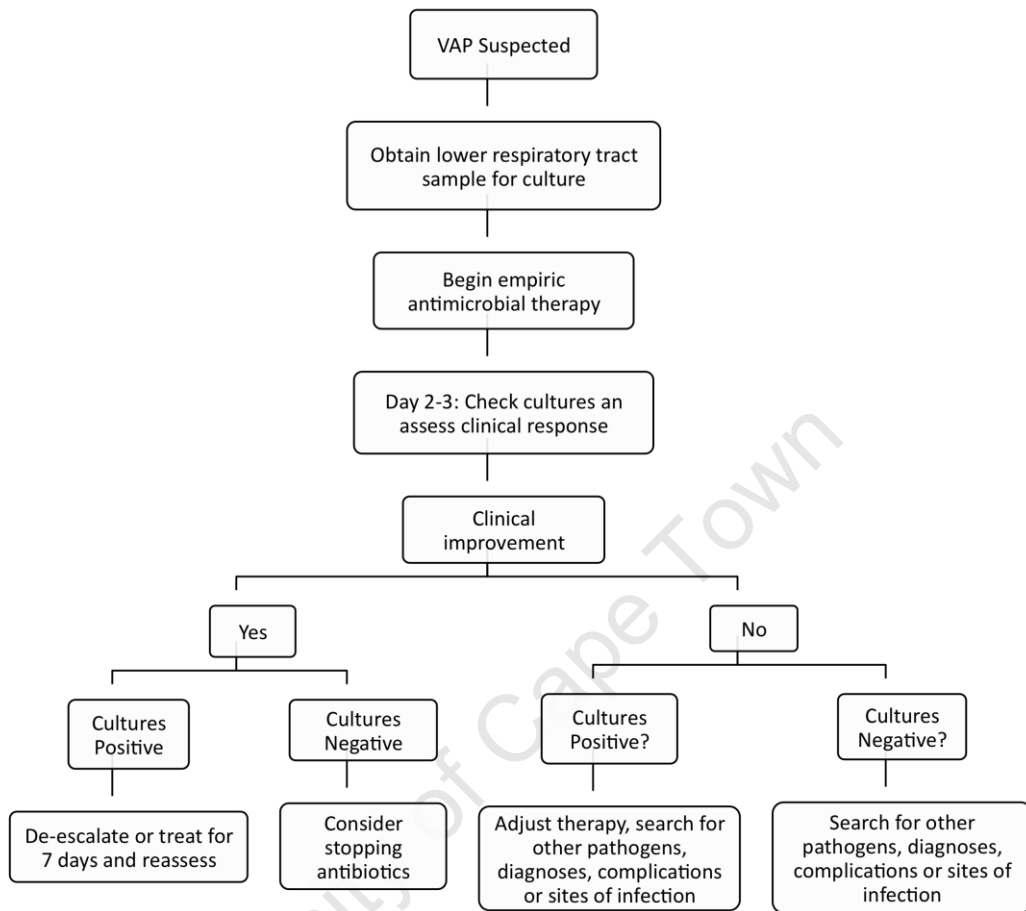


Figure 4. Algorithm for diagnosis and therapy

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D - APPENDICES

Appendix 1- Department of Surgery Research Committee approval letter

Appendix 2 – University of Cape Town Human Research Ethics Committee approval letter

Appendix 3 - Noninvasive Ventilation in Major Burns (reference 23 in journal-ready manuscript)

Appendix 4 – Burns Journal submission guidelines

University of Cape Town

Appendix 1.



UNIVERSITY OF CAPE TOWN

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**Department of Surgery**

**Departmental Research Committee**

**Professor Anwar Suleman Mall**

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13<sup>th</sup> May 2013

Dr Alan Rogers  
Department of Surgery  
Division of Plastic Surgery  
Groote Schuur Hospital  
University of Cape Town

Dear Dr Rogers,

**RE: PROJECT 2013/055**

**PROJECT TITLE:** Ventilator associated pneumonia in major paediatric burns

The above proposal was reviewed by the Department of Surgery Research Committee and I am pleased to inform you that the committee approved the study.

Please use the above project number in all future correspondence.

Yours sincerely

A handwritten signature in black ink, appearing to read 'Anwar Mall'.

**PROFESSOR ANWAR S MALL  
CHAIRMAN: RESEARCH COMMITTEE**

Appendix 2.

UNIVERSITY OF CAPE TOWN



Faculty of Health Sciences  
Human Research Ethics Committee  
Room E52-24 Groote Schuur Hospital Old Main Building  
Observatory 7925  
Telephone [021] 406 6338 • Facsimile [021] 406 6411  
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13 June 2013

**HREC REF: 358/2013**

**Dr A Rogers**  
**c/o Prof H Rode**  
Department of Plastic Surgery  
Surgery  
OMB

Dear Dr Rogers

**PROJECT TITLE: VENTILATOR ASSOCIATED PNEUMONIA IN MAJOR PAEDIATRIC BURNS**

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee 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 till the 30<sup>th</sup> June 2014**

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/research/humanethics/forms](http://www.health.uct.ac.za/research/humanethics/forms))

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

**Please quote the HREC. REF in all your correspondence.**

Yours sincerely

**PROFESSOR M BLOCKMAN**  
**CHAIRPERSON, FHS HUMAN ETHICS**

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki 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.

s.thomas

### Appendix 3

#### Noninvasive Ventilation in Major Burn Injuries

Dr A.D. Rogers

Prof. H. Rode

The Burns Unit, Divisions of Plastic and Paediatric Surgery, Red Cross War Memorial

Children's Hospital and the University of Cape Town, South Africa

Prof. D.M. Linton

Medical Intensive Care Unit, Hadassah Hospital and Hebrew University Medical School, Ein

Karem, Jerusalem, Israel

From:

Rogers AD, Rode H, Linton D. NIPPV in major burns. In Esquinas A. (Ed) Noninvasive ventilation in High Risk infections and mass casualty incidents. Elsevier - In press

#### Key Words

Burns

Ventilator Associated Pneumonia

Inhalational burns

Intubation

Extubation

Facial Burns

Noninvasive ventilation

Helmet

### Abbreviations

NIV – Non-invasive ventilation

NIPPV - Non-Invasive Positive Pressure Ventilation

ARDS – Acute Respiratory Distress Syndrome

VAP – Ventilator-Associated Pneumonia

CPAP – continuous positive airway pressure

PEEP – Positive End Expiratory Pressure

University of Cape Town

## Inhalational Burns, Intubation and Mechanical Ventilation

Severe burns are one of the most devastating forms of trauma. In South Africa, burn injuries are the third commonest external cause of fatal injuries up to the age of 15 years and the main cause under the age of 4 years. In the Cape Town region, at least six in 10 000 children are seriously burnt every year, and as many as 15 in 10 000 toddlers and infants.<sup>1-3</sup>

While the majority of paediatric burns are scalds sustained in the domestic setting, a greater proportion of the adult burns, and the more severe burns in children, are flame burns. These are most common in informal housing as a result of the use of paraffin stoves for cooking and heating; other prominent causes of flame burns in adults include accidents in the workplace, and as a result of epilepsy or interpersonal assault. Burn victims caught in enclosed spaces are frequently the most severely injured, and those who suffer smoke inhalation injury may have mortality rates over 30%.<sup>4,5</sup>

A number of advances have been made in recent times with regard to fluid resuscitation protocols, dressings, infection control strategies and antimicrobials, surgical techniques, intensive care and nutrition. There is now widespread recognition that specialist burns units or centres deliver the best care for these patients. As a result of these measures, mortality and morbidity rates have declined significantly over the last few decades.<sup>3,6,7</sup>

The main challenge to those managing major burns is now resisting the threat of overwhelming infection. Because significant thermal injuries induce a state of immunosuppression and the wounds themselves are exposed to micro-organisms prior to skin graft coverage, three quarters of all severe burn related deaths are as a consequence of infection. Besides burn wound infections, these may manifest as sepsis and pneumonia, many of which are nosocomial. There are a number of mechanisms for the development of pneumonia in the severely burnt. (Figure 1) Pulmonary complications are undoubtedly common with inhalational injury, but burnt patients have more pulmonary complications

even without direct lung injury. Atelectasis and hypostatic pneumonia are common due to altered ventilation and reduced lung expansion that may occur in patients with chest or abdominal burns. These patients may also have a high risk of aspirating, and respiratory physiotherapy with regular airway suctioning of upper airway secretions and expectoration of sputum may be critical to maintaining pulmonary function.<sup>3,8,9</sup>

The overwhelming systemic inflammation associated with a major burn may result in respiratory compromise itself, manifesting as Acute Respiratory Distress Syndrome (ARDS). Lower respiratory infection in the presence of major burn injury carries an additive mortality of 60%.<sup>5</sup>

Those who require prolonged ventilation are at risk of developing Ventilator-Associated Pneumonia (VAP). VAP is responsible for significant morbidity and mortality, and ranks as the second commonest hospital acquired infection. In fact, a large European trial in a variety of paediatric settings showed that VAP accounted for over half of hospital acquired infections in the PICU. The prevalence of nosocomial pneumonia in the ICU ranges from 10 to 65% and mortality rates exceed 25%. Those who develop VAP are twice as likely to die compared to those without VAP, and spend longer in intensive care. In addition, the nosocomial bacteria that cause VAP tend to be more resistant.<sup>10</sup>

The incidence of VAP in major burns in our setting is as high as 30 cases per 1000 ventilator days, more than double that in any other category of ventilated patients. A protocol has been implemented to reduce the incidence of VAP: some of these preventative strategies are listed in Figure 2. Undoubtedly the most effective strategy of all has been to reduce the length of ventilation.<sup>3</sup>

Critical to managing patients at risk is to reduce secondary insults inherent in management strategies. Endotracheal intubation and mechanical ventilation has been the mainstay of treatment for apparent or impending respiratory failure in major burns. In fact, more than

three-quarters of inhalational burn victims require some form of respiratory support.<sup>11</sup> Other than VAP, there are significant potential complications inherent in intubation and mechanical ventilation. During the process of intubation, up to 20% of patients experience a period of hypoxaemia, 10% are hypotensive, 7% have oesophageal intubations and 6% aspirate. Other complications include dental injury or inadvertent extraction, swallowing dysfunction, dysphonia and tracheal stenosis. Repetitive laryngeal barotrauma can result from suction catheter use for clearing secretions.<sup>12,13</sup>

Some authors have suggested that the features used to guide physicians have overstated the need for invasive ventilation, particularly in the hospital setting. Emergency intubation at the scene of the fire, with its higher complication risk, should be avoided wherever possible. The clinical features on history and examination, so-called soft signs (singled nasal hair, closed space fire and facial burns) and hard signs (stridor, hoarse voice and dysphagia), used to guide physicians to intubate and ventilate burn victims, may be less helpful than traditionally taught, in respect to their accuracy at determining the actual need for ventilation. This is particularly relevant in light of the risks involved and the possibility of an effective alternative to invasive airway management.<sup>12,14</sup>

In fire related deaths, the toxic products of combustion are probably more important a cause of morbidity than the airway thermal burn itself. The effects of direct thermal burns in the oropharynx are analogous to those changes occurring elsewhere in the body. Protein is denatured, activating the complement cascade, histamine, xanthine oxidase, and oxygen free radicals, which are responsible for further protein extravasation and oedema. Toxins and inhaled products interfere with the normally effective methods of clearance in the upper airways. In the trachea and bronchi, ciliated epithelium and mucus-secreting epithelium normally make up the 'mucociliary escalator', capable of removing inhaled particulate matter at a rate of up to 4 cm/hr. Mucosal necrosis and slough leads to impaired

clearance and airway obstruction. The presence of a cuffed endotracheal tube may itself further interfere with this mucociliary elevator. Bronchoconstriction and mucosal sloughing may result in atelectasis, with possible progression to pneumonia.<sup>12, 15, 16</sup>

### Non-invasive Ventilation in Major Burn Injuries

The International Consensus Conference in Intensive Care Medicine<sup>17</sup> defined NIPPV as any form of ventilatory support without the use of an endotracheal tube. Its goal is to decrease the work of breathing, optimize ventilatory exchange and avoid intubation. Typically, NIV is positive pressure ventilation with the use of a facemask attached to a ventilator. CPAP masks are widely used for improving oxygenation in hypoxaemic patients and to rest patients with chronic disorders like COPD or neuromuscular disorders. The benefits of noninvasive positive pressure ventilation (NIPPV) are most described for avoiding re-intubation (by more than 50%) after exacerbations of COPD. As a result, mortality and hospital length of stay have reduced. Recognising the benefits of NIV, clinicians have attempted NIV and adapted its use for managing acute reversible respiratory failure in addition to the traditional uses. NIV has seldom been used in the context of burns patients, but it has been shown to be an effective means of oxygenating awake and alert surgical and injured patients.

NIV's principle benefit is obviously the avoidance of intubation and its concomitant complications. There are a number of additional benefits in avoiding intubation in the burns patient. Non-intubated patients maintain better oral hygiene and gut function (they may be able to continue with standard oral intake), critical components in the management of major burn victims; few other categories of critically ill patients undergo such profound catabolism. Non-intubated patients also communicate better and require minimal sedation. This is

important not least because burns patients can expect to be in hospital at least 1 day per percentage of body surface injured, usually translating to lengthy periods away from 'normal' society, making reintegration very challenging indeed. Further benefits are listed in Figure 3.

Ventilator associated pneumonia is the most feared complication of endotracheal intubation, particularly in the burns patient, who are inherently more susceptible to infection in light of the overwhelming systemic inflammation and because normal defence mechanisms are bypassed (skin, gut, sinuses, orotracheal). NIV has been shown to reduce the incidence of VAP, predominantly by reducing the period of ventilation and by maintaining intact airway protection mechanisms. Shorter ICU stays are also independently related to improved survival, and translate into significant cost benefits for the health system.<sup>18,19</sup>

Success with NIV has traditionally only been achieved under certain circumstances. The patient must be co-operative, able to protect his own airway, and have an intact cough reflex and adequate secretion clearance. Uncooperative patients may repeatedly remove their mask, ventilate out of sync with the ventilator or may not remove their mask in the event of vomiting, placing them at risk for aspiration. Haemodynamic instability has been a relative contraindication for the use of NIV. Patients who cannot obtain an adequate seal are also excluded, as in a patient with gastrointestinal trauma or obstruction requiring nasogastric intubation and who are at risk for vomiting. Aerophagia may also occur, particularly if the pressures used to ventilate are greater than 30mmHg, which would overcome the closing pressure of the lower oesophageal sphincter. This is obviously particularly important in those with underlying gastrointestinal dysfunction or stasis, as is often the case with major burns.<sup>12,20</sup>

There is a paucity of literature describing the use of NIV in burn victims with or without inhalational injury, but its use ought to be considered in selected patients who meet these criteria for its use. Inappropriate use of NIV in burn patients may be catastrophic. This patient population is already at greater risk for haemodynamic instability and respiratory infection than other cohorts, and analgesic requirements may result in levels of sedation mitigating against the use of NIV. Smailes was however able to reduce endotracheal re-intubation to 7 of 30 burns patients with respiratory dysfunction after extubation.<sup>21</sup> In another study, a 6-year review of the use of NIPPV as an adjunct to extubation, 104 extubated paediatric burn patients were studied, only fifteen percent of whom required re-intubation. Ten patients who experienced respiratory distress post-extubation received NIPPV support, of which four required re-intubation for worsening respiratory status, while six avoided re-intubation.<sup>22</sup>

More work has been done in trauma indications other than burns. In one study by Linton, patients with blunt chest trauma were treated with either intubation and ventilation or NIV with CPAP. The two groups had similar levels of PEEP/CPAP, patient age, incidence of rib fractures, flail chest, and pulmonary contusion. The CPAP group had a smaller number of tracheostomies, less ICU days, and fewer complications.<sup>23</sup> In a further study, Hurst reviewed victims of blunt chest (rib fractures, pulmonary contusion, and flail chest) and penetrating chest injuries and long bone fractures. CPAP was used in 33 alert patients with hypoxic respiratory failure. The mean duration of CPAP was 28 hours, and only two patients (6%) required intubation for failure of oxygenation but not ventilation.<sup>24</sup>

Extrapolated to the intubated burns patient, earlier extubation and NIV application may increase patient comfort, decrease sedation, ICU stay, morbidity, cost, and mortality. NIV

may prove to be a useful adjunct allowing early extubation, providing bridging ventilatory support until normal respiration returns. In the context of an acute major burn injury, it is rational to consider NIV (prophylactically) for the patient with high carbon monoxide blood levels, who is receiving significant fluid volumes, or who has history or examination features to suggest an inhalational injury, but who may not require intubation. Clearly this represents a paradigm shift from the traditional teaching of early intubation in at-risk patients, but one must be cogniscent of the fact that these patients are in the high care setting and are awake, alert and cooperative on initiation of NIV. The process of NIV would have been clearly discussed with them. Any deterioration may warrant intubation and mechanical ventilation, in a controlled environment.

On initiation of NIV, low levels of PEEP are applied, and once comfortable, the device is secured and set until the work of breathing (assessed by accessory muscle use, rate of respiration, tidal volume and patient comfort) is minimized. Arterial blood gases, pulse oximetry, and end tidal CO<sub>2</sub> should be monitored regularly.

One of the major criticisms of NIV has been related to patient intolerance, particularly in the context of facial burns. If the interface contributes to excessive pain, discomfort or claustrophobia for the patient, the benefits of NIV may be lost, and the patient more likely to require intubation and mechanical ventilation. Optimal use has required a firm seal to maintain the pressure administered. Certain devices have resulted in skin necrosis over the bridge of the nose or zygoma if worn for extended periods. Pressure sores occur in up to 10% of patients undergoing NIV; in patients with facial burns, this would be unacceptable. Duoderm (Convatec, USA) or a similar product may ameliorate these effects in some cases.

As a result of problems with facemask NIV, helmets (fig. 4) have been devised for this

purpose.<sup>12, 25</sup> Several studies have demonstrated its benefits, including improved comfort, ability to interact, while also reducing the likelihood of superadded cutaneous trauma where the equipment is secured, particularly in burns patients. Criteria for use are similar to standard NIV principles. While better tolerated, helmet NIV has been shown to be as effective as conventional face-mask NIV in reducing hospital stay, mortality, infectious morbidity (including pneumonia), as well as the requirement for invasive ventilation. Uncontrolled leaks are significantly less likely with helmets than with traditional facemask methods. The only concern relating to helmet NIV has been its inability to maintain PCO<sub>2</sub> levels, probably as a result of CO<sub>2</sub> re-breathing. Factors relating to patient-ventilator interaction may also need to be monitored more closely in patients using helmet NIV.<sup>12, 25</sup>

#### Key Major Recommendations

1. Non-invasive ventilation is an important potential means of avoiding intubation in the major burns victim,
2. NIV may also be utilised to maintain airway patency after extubation
3. It is important that patients considered for NIV meet the criteria for its use, and be monitored appropriately.
4. Transparent helmets have been designed and have shown to be as effective as traditional facemask interfaces; these may be more successfully applied in patients with facial burns.
5. Prospective, randomized studies may better elucidate the role of NIV in burn patients with inhalation injury.

## Figures

Factor	Mechanism
1. Intubation (especially pre-hospital/ emergency)	Bypass glottis barrier; pooling, leak of and inability to clear secretions
2. Cutaneous thermal injury	Bacterial Reservoir; systemic inflammation; immunosuppression
3. Prolonged ventilation	Sustained micro-aspiration; secretions; reintubation
4. Inhalational injury	Direct injury; exudate formation; poor mucociliary clearance; reduced lung compliance; ARDS; prolonged ventilation;
5. Transport out of ICU (e.g. theatre)	Reintubation; bacterial translocation
6. Blood transfusions	Immunosuppression

Figure 1. Factors predisposing the burns patient to pneumonia in ICU

Preventing VAP in Burns patients
1. Reduce the duration of ventilation
2. Postpyloric feeding
3. Chlorhexidine mouth wash
4. Reduce transfusions
5. Head elevation
6. Selective decontamination of the GIT
7. Staff factors – hand hygiene and barrier nursing
8. Silver endotracheal tubes and continuous aspiration
9. Non-invasive ventilation as adjunct to extubation

Figure 2. Strategies identified to prevent VAP

Potential benefits of NIV in Burns
1. Improved communication
2. Better oral intake and gut function
3. Oral hygiene
4. Avoid orotracheal injury and barotrauma
5. Reduced respiratory tract infections
6. Maintain protective mechanisms
7. Less sinusitis
8. Shorter ICU and hospital stays
9. Improved speech and swallowing after extubation

Figure 3 - The benefits of NIV



Figure 4. A hermetic plastic helmet with CPAP in use (Castar, Starned, Italy)

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