Acquired infections in paediatric patients after cardiac surgery

By

Ilse Appel (FCPAEDS SA, Critical Care PAEDS SA)

Student Number: APPILS001

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Supervisors: Argent AC (MD; FCPAEDS SA; FRCPCH); Morrow BM (PHD)

Department of Paediatrics, University of Cape Town

TABLE OF CONTENTS

TITLE PAGE **Page 1**

TABLE OF CONTENTS **Page 2**

DECLARATION **Page 6**

ABSTRACT **Page 7**

ACKNOWLEDGEMENTS **Page 9**

LIST OF TABLES **Page 10**

LIST OF FIGURES **Page 12**

GLOSSARY **Page 13**

CHAPTER 1 **Page 16**

INTRODUCTION **Page 16**

BACKGROUND OF PAEDIATRIC CARDIAC SERVICES IN SOUTH AFRICA, A DEVELOPING COUNTRY'S PERSPECTIVE **Page 16**

IMPACT OF HOSPITAL ACQUIRED INFECTION (HAI) ON PAEDIATRIC CARDIAC PATIENT AFTER SURGERY **Page 17**

CHAPTER 2 **Page 19**

LITERATURE REVIEW **Page 19**

OBJECTIVES OF THE LITERATURE REVIEW **Page 19**

METHODS **Page 19**

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW **Page 19**

LITERATURE SEARCH STRATEGY **Page 19**

RESULTS OF THE LITERATURE SEARCH **Page 20**

SCOPE OF THE PROBLEM **Page 20**

Bloodstream infection (BSI) and other Hospital acquired infection (HAI): incidence and risk factors in postoperative cardiac patients **Page 21**

Risk factors for surgical site infections (SSIs) after paediatric cardiovascular surgery **Page 33**

Impact of delayed sternal closure on HAIs after paediatric cardiovascular surgery **Page 42**

Risk factors for nosocomial pneumonia including ventilator associated pneumonia (VAP) after paediatric cardiovascular surgery **Page 48**

Incidence and risk factors of urinary tract infections (UTIs) in postoperative paediatric cardiac patient **Page 54**

Immune and inflammatory responses after CPB **Page 57**

Genetic and malformation syndromes **Page 58**

Use of corticosteroids in postoperative paediatric cardiac patients **Page 62**

Red blood cell (RBC) transfusion in paediatric cardiac surgery patients **Page 67**

Perioperative antibiotic use in paediatric cardiac surgery patients **Page 68**

Diagnosis and treatment of HAIs **Page 71**

NEEDS FOR FUTURE RESEARCH **Page 77**

CHAPTER 3 **Page 78**

AIM **Page 78**

OBJECTIVES **Page 78**

MATERIALS AND METHODS **Page 78**

OPERATIVE MANAGEMENT OF PAEDIATRIC CARDIAC PATIENTS **Page 79**

PROTOCOLS FOR THE CARE OF POSTOPERATIVE CARDIAC PATIENTS ADMITTED TO THE PICU **Page 79**

CONSENT **Page 83**

DATA ANALYSIS **Page 83**

CHAPTER 4 **Page 84**

RESULTS **Page 84**

PATIENTS **Page 84**

COMORBID CONDITIONS **Page 85**

Genetic and congenital malformation syndromes in all patients admitted to the study **Page 85**

Other comorbid conditions in all patients admitted to the study **Page 85**

MEDICATIONS **Page 85**

CARDIAC CONDITIONS **Page 85**

INTRAOPERATIVE PROCEDURES AND EVENTS **Page 87**

POSTOPERATIVE EVENTS **Page 88**

INTRAVASCULAR CENTRAL LINES, URINARY CATHETERS, PACING WIRES, INTERCOSTAL DRAINS (ICDS) **Page 89**

MICROBIAL ISOLATES **Page 90**

INFECTIONS AND ANTIBIOTIC USE **Page 91**

ISOLATES IN PATIENTS WITH LIKELY HAI **Page 95**

Microbial isolates in all infections diagnosed in PICU following cardiac surgery **Page 95**

PULMONARY POSTOPERATIVE INFECTION **Page 97**

ANALYSIS **Page 98**

UNIVARIATE DATA ANALYSIS **Page 98**

MULTIVARIATE DATA ANALYSIS **Page 101**

CHAPTER 5 **Page 102**

DISCUSSION **Page 102**

INTERVENTIONS INFLUENCING ICU INFECTION EPIDEMIOLOGY **Page 109**

BUNDLES OF CARE **Page 110**

ANTIMICROBIAL USE IN THE ICU **Page 110**

LIMITATIONS **Page 110**

CHAPTER 6 **Page 112**

CONCLUSION AND RECOMMENDATIONS **Page 112**

APPENDICES **Page 114**

APPENDIX 1. REFERENCES **Page 114**

APPENDIX 2. ETHICS APPROVAL **Page 121**

APPENDIX 3. DATA COLLECTION FORMS **Page 123**

APPENDIX 4. GUIDELINES FOR INFECTION INVESTIGATION IN THE PICU **Page 129**

APPENDIX 5. CDC DEFINITIONS OF INFECTIONS **Page 130**

APPENDIX 6. COMPLEXITY CATEGORIES OF CARDIOTHORACIC SURGICAL PROCEDURES **Page 146**

APPENDIX 7. SYSTEMS OF ASSESSING QUALITY OF CARE IN PAEDIATRIC PATIENTS FOR CARDIAC SURGERY **Page 147**

DECLARATION

I, Ilse Nadine Appel, 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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Signature: Ilse Appel

Date: 8 September 2015

Acquired infections in paediatric patients after cardiac surgery

Appel I; Morrow BM; Argent AC

Affiliations: Paediatric Intensive Care Unit, Red Cross War Memorial Children's Hospital and Division of Paediatric Critical Care and Children's Heart Disease, School of Child and Adolescent health, University of Cape Town.

ABSTRACT

Introduction:

Hospital acquired infections (HAIs) are an important cause of morbidity and mortality following paediatric cardiac surgery.

Aim:

To determine the incidence, risk factors for and outcome of postoperative HAIs in the Paediatric Intensive Care Unit (PICU) of the Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town.

Methods:

A prospective observational study of all postoperative cardiac patients admitted to PICU from September 2011 to March 2012. The definitions of laboratory confirmed blood stream infections (BSI), urinary tract infections (UTI), and surgical site infections were based on the Centres of Disease Control criteria. Ventilator associated pneumonia (VAP) was diagnosed using a modification of the Clinical Pulmonary Infection Score (CPIS).

Results:

110 patients (median age 19 months; 43% male) undergoing 126 surgical procedures were enrolled. Sixty HAIs occurred in 43 (39%) patients (68.3% pulmonary; 13.3% blood; 11.7% wound; 3.3% urine; 3.3% tissue). Nine (8.2%) patients died and their deaths were not related to HAIs.

Causative organisms for HAIs were gram negative isolates (57.3%), viral isolates (22.7%), gram positive isolates (16%) and fungal isolates (2.7%). The median (IQR) day postoperatively of first organism detected from any specimen was 3 (2 – 5) days. 36% of isolates were detected within 48 hours postoperatively.

Being underweight for age (adjusted odds ratio, OR: 2.77; 95% CI 1.04 – 7.36, p = 0.04), increased duration of days in hospital prior to surgery (OR 1.04; 95% CI 1.0 – 1.09; p =

0.04) and increased duration of arterial lines (OR 1.47; 95% CI 1.21 – 1.78; $p = 0.0001$) were identified as being independently associated with acquiring HAI on multivariate analysis.

Patients with HAI spent median (IQR) 6 (4 – 13) and 21 (9 – 38) days in PICU and hospital compared to 3 (2 – 5) and 9 (7 – 13) days in uninfected patients ($p < 0.0001$).

Conclusions:

The incidence of HAI in this population was high with identified associations and significant resource and clinical implications. Gram negative and viral isolates were most prevalent in HAIs.

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LIST OF TABLES

Table 1. Bloodstream and other hospital acquired infection rates in postoperative cardiac patients Page 23

Table 2. Surgical site infection rates Page 36

Table 3. Delayed sternal closure (DSC) Page 44

Table 4. Hospital acquired pneumonia infection rates and risk factors Page 50

Table 5. Rates of UTIs in postoperative cardiac patients Page 55

Table 6. Immune studies in postoperative surgery patients Page 60

Table 7. Use of corticosteroids in postoperative paediatric cardiac patients Page 63

Table 8. Perioperative antibiotic use in paediatric cardiac surgery patients Page 68

Table 9. Septic markers in postoperative cardiac patients Page 74

Table 10. Study population characteristics of all patients Page 84

Table 11. Cardiac conditions in all patients admitted to the study Page 85

Table 12. Operative details and patient outcomes of all patients admitted to the study Page 86

Table 13. Intraoperative procedures and events Page 87

Table14. Postoperative procedures and events Page 88

Table 15. Intravascular central lines, urinary catheters, pacing wires and intercostal drains in all study patients Page 89

Table 16. Microbial isolates for all patients Page 90

Table 17. All patients with multiple HAI infection sites Page 93

Table 18. Microbial isolates from patients with HAI of all sites diagnosed in PICU Page 95

Table 19. Univariate analysis of patient characteristics, course and outcome data for those who developed or did not develop infection of any site Page 98

Table 20. Operative details for those who developed and did not develop HAI in PICU Page 100

Table 21. Details of invasive catheters and lines related to HAI in PICU Page 101

Table 22. Final multiple regression model of associations with HAI Page 101

LIST OF FIGURES

Fig. 1. Sites of PICU acquired infection (60 infections in 43 patients) Page 92

Fig. 2. Infections within 48 hours post surgery Page 92

Fig. 3. Postoperative day of first isolate detected in all study patients Page 96

Fig. 4. Pathogens associated with infection sites in patients diagnosed with infection in PICU Page 97

Fig. 5. Pulmonary infections including VAP and nosocomial pneumonia Page 94

GLOSSARY

A-line	Arterial line
ASD	Atrial septal defect
AV	Atrioventricular
AVSD	Atrioventricular septal defect
BAL	Bronchoalveolar lavage
BSI	Bloodstream infection
CHG	Chlorhexidine gluconate
CLABSI	Central line-associated bloodstream infection
CF	Cardiac failure
CHD	Congenital heart disease
CPB	Cardiopulmonary bypass
CRP	C-reactive protein
CVP	Central venous pressure line
del22q11	Chromosome 22 deletion syndrome
DSC	Delayed sternal closure
EHA	Estimated height for age
ETTi	Endotracheal tube intubation
EWA	Estimated weight for age
FFP	Fresh frozen plasma
GORD	Gastro-oesophageal reflux disease
HAI	Hospital acquired infection
HLHS	Hypoplastic left heart syndrome
HIV	Human immunodeficiency virus
ICD	Intercostal drain
ICU	Intensive care unit
LAD	Left anterior descending
LAP	left atrial pressure lines
LBCV	Left brachio-cephalic vein

LFA	Left femoral artery
LFV	Left femoral vein
LICD	Left intercostal drain
LIJV	Left internal jugular vein
LOS	Length of stay
LRA	Left radial artery
LSV	Left subclavian vein
MV	Mechanical ventilation
NI	Nosocomial infection
NPA	Nasopharyngeal aspirate
PA	Pulmonary atresia
PCT	Procalcitonin
PDA	Patent ductus arteriosus
PHT	Pulmonary hypertension
PCICU	Paediatric cardiac intensive care unit
PICU	Paediatric intensive care unit
PLT	Platelets
RBC	Red blood cells
RCWMCH	Red cross war memorial children's hospital
RRA	Right radial artery
RFA	Right femoral artery
RICD	Right intercostal drain
RIJV	Right internal jugular vein
RFV	Right femoral vein
RVOTO	Right ventricular outflow tract obstruction
SD	Standard deviation
SIRS	Systemic inflammatory response syndrome
SSI	Surgical site infection

TA	Tracheal aspirate
TA	Tricuspid atresia
TGA	Transposition of the great arteries
TI	Tricuspid incompetence
TOF	Tetralogy of fallot
UTI	Urinary tract infection
VSD	Ventricular septal defect
VAP	Ventilator associated pneumonia
WCC	White cell count
WHO	World health organisation

TITLE: Acquired infections in paediatric patients after cardiac surgery

CHAPTER 1

INTRODUCTION

BACKGROUND OF PAEDIATRIC CARDIAC SERVICES IN SOUTH AFRICA, A DEVELOPING COUNTRY'S PERSPECTIVE

There is a significant burden of paediatric cardiac disease in South Africa (Hoosen, Cilliers et al. 2011). The population of South Africa is approximately 51 million (Statistics South africa 2011) and the prevalence of congenital cardiac disease is approximately 4-6 per 1000 live births. Thus approximately 11 000 children with congenital heart disease (CHD) are born every year (Hoosen, Cilliers et al. 2010). With appropriate care, the prognosis for most of these children is excellent, with at least 85% expected to survive to adulthood (Hoosen, Cilliers et al. 2011).

In 2006, approximately 1 300 patients were operated on for CHD in South Africa, 800 of them in the public service hospitals, which serve close to 85% of the population. This means that less than 25% of the children in South Africa with CHD who rely on the public health services received the care they needed (Hoosen, Cilliers et al. 2011).

Thus the burden of paediatric cardiac disease is not being addressed. There are eight South African units (five major public sector centres and three private sector centres) available for paediatric cardiac surgery (Hewitson, Brink et al. 2002) and there are long waiting lists for most elective surgeries at these units (Saxena 2009). In addition, the rest of Africa cannot really access this system.

According to an editorial published in the South African Medical Journal, the reasons contributing to this resource limited situation are threefold (Hoosen, Cilliers et al. 2011). Firstly, paediatric cardiac services are unable to meet the demand due to a paucity of trained paediatric cardiologists (Hoosen, Cilliers et al. 2011). Secondly, the capacity to successfully manage the full patient load in public sector hospitals is limited by the scarcity of adequately trained and experienced paediatric cardiothoracic surgeons, limited theatre availability and postoperative intensive care, which requires highly specialised nursing and medical management (Hoosen, Cilliers et al. 2011). Thirdly, CHD is commonly missed, misdiagnosed or identified too late. This is most important, because as many as 20% of CHD cases present with life-threatening illness in the neonatal period, where survival depends on timely diagnosis, management and referral (Hoosen 2011).

Survivors of CHD without surgical intervention require frequent hospital visits and repeated admissions for the complications of unoperated CHD. This continued need for highly specialized medical treatments places a significant financial and emotional burden on already impoverished caregivers and families (Hoosen 2011). Timely diagnosis and surgical management of CHD is thus an obvious financial benefit for both the families and health systems in resource poor settings.

IMPACT OF HOSPITAL ACQUIRED INFECTION (HAI) ON PAEDIATRIC CARDIAC PATIENT AFTER SURGERY

A HAI is a localised or systemic condition resulting from an adverse reaction to the presence of an infectious agent(s) or its toxin(s) that was not present on admission to the hospital. An infection is considered to be hospital acquired if all elements of Centres for Disease Control (CDC) site-specific infection criteria were not present during the first 48 hours of hospital admission but were all present on or after the 3rd calendar day of admission to the hospital (the day of hospital admission is calendar day 1) (Centers for Disease Control and Prevention 2014).

HAIs represent a major complication in paediatric intensive care unit (PICU) patients undergoing cardiac surgery and are associated with significant morbidity and mortality (Levy, Ovadia et al. 2003, Grisaru-Soen, Paret et al. 2009, Pasquali, He et al. 2013). HAIs contribute to prolonged duration of hospital and ICU stays (Levy, Ovadia et al. 2003, Grisaru-Soen, Paret et al. 2009, Pasquali, He et al. 2013). As noted previously, cost-containment is highly relevant to performing congenital heart surgeries in developing countries. Prolonged durations of stay in the intensive care unit (ICU) due to HAIs could inflate costs after cardiac surgery (Pasquali, He et al. 2013). Every effort needs to be made to prevent the causes of increased duration of ICU and hospital stay in order to contain costs (Rao 2007).

HAIs therefore represent a major complication and a considerable clinical, emotional and financial burden in patients undergoing cardiac surgery (Siddiqui, Mir et al. 2011, Levy, Ovadia et al. 2003, Abou Elella, Najm et al. 2010). Identifying and instituting measures to prevent and manage these HAIs in a resource-limited setting are clinically and financially beneficial.

CHAPTER 2

LITERATURE REVIEW

OBJECTIVES OF THE LITERATURE REVIEW

The objectives of the literature review were to determine the epidemiology, aetiology and described incidence of HAIs in postoperative cardiac patients in paediatric intensive care units (PICU); to define the patients at risk for developing HAIs and to describe the morbidity and mortality associated with HAIs.

METHODS

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Study design: Any study design was considered for inclusion.

Participants: neonates, infants and children (0 -18 years) admitted to PICU following cardiac surgery.

Outcome measures: Epidemiology, incidence, cause and outcome of HAI in terms of duration of hospital and PICU stay and mortality. Measures of risk associated with HAIs included delayed sternal closure, surgical complexity scoring systems, use of corticosteroids, cardiopulmonary bypass factors, staffing in an ICU, inflammatory markers of infection and genetic factors.

Exclusion criteria: articles published in a language other than English, studies including animal models.

LITERATURE SEARCH STRATEGY

The following databases were searched for English articles published up until 25 May 2014: PubMed, University of Cape Town Libraries search engine and Journal publication sites: *Pediatric Critical Care Medicine, Intensive care Medicine, The New England journal of medicine, The Journal of thoracic and cardiovascular surgery, The Annals of Thoracic Surgery, Annals of Pediatric Cardiology, Anesthesiology, Critical Care Medicine* and *Pediatric cardiology*. The search terms used were: postoperative infections OR cardiac surgery OR postoperative cardiac surgery infections OR PICU infections OR hospital acquired infections post cardiac surgery OR cardiac surgery infections OR nosocomial infections post cardiac surgery OR bloodstream infections post cardiac surgery OR infections in postoperative cardiac patients with the modifying term “paediatric” OR “pediatric”.

Reference lists of identified articles were scanned for papers relevant to the objectives of the literature review.

Abstracts of identified articles were reviewed and relevant articles identified which focussed on the terms: hospital acquired infections, nosocomial infections, blood stream infections, urinary tract infections, surgical site infections, ventilator associated pneumonia and devise associated infections in paediatric patients in an intensive care unit following cardiac surgery. Results were synthesised narratively.

RESULTS OF THE LITERATURE SEARCH

4125 articles were initially identified, of which 1636 articles were identified as relevant (see above); and 113 articles were included in the review (Appendix 1).

SCOPE OF THE PROBLEM

Hospital acquired infection is defined as a localised or systemic condition that 1) results from adverse reaction to the presence of an infectious agent(s) or its toxin(s) and 2) was not present or incubating at the time of admission to the hospital. The presence and classification of the HAI is based on clinical findings, laboratory evidence and clinical judgment of the attending physician (Garner, Jarvis et al. 1996).

HAIs are thought to be an important cause of morbidity and mortality in paediatric patients following cardiac surgery, although epidemiological information regarding acquired infections following paediatric cardiac surgery is limited (Wheeler, Jeffries et al. 2011, Tantawy, Seliem et al. 2012, Barker, O'Brien et al. 2010, Algra, Driessen et al. 2012, Grisaru-Soen, Paret et al. 2009, Levy, Ovadia et al. 2003). Specifically, no published data is available for the South African population. It is important to obtain data in this population in order to accurately identify patients at risk for postoperative HAI, and to suggest strategies for preventing infections and optimising patient management and outcome.

The **morbidity** associated with HAIs includes prolonged antibiotic usage, increased resistance of microorganisms to antimicrobials, reoperation, prolonged hospital and ICU stays, and longer periods of mechanical ventilation and inotropic support (Barker, O'Brien et al. 2010, Tantawy, Seliem et al. 2012). The development of these infections has overwhelming emotional and financial impacts (Abou Elella, Najm et al. 2010) for patients and their family (Tantawy, Seliem et al. 2012).

The most common HAIs previously reported in postoperative cardiac PICU patients are: bloodstream infections (BSIs), including catheter-related BSIs (CRBSIs) (2.6% -68.2%) (Grisaru-Soen, Paret et al. 2009, Levy, Ovadia et al. 2003, Abou Elella, Najm et al. 2010, Bezzio, Scolfaro et al. 2009, Barker, O'Brien et al. 2010, Mastropietro, Barrett et al. 2013, Bakshi, Vaidyanathan et al. 2007, Alvarez, Fuentes et al. 2012); lower respiratory tract infections (LRTIs) including ventilator associated pneumonia (VAP) (1% – 51.2%) (Grisaru-Soen, Paret et al. 2009, Siddiqui, Mir et al. 2011, Tan, Sun et al. 2004, Shi, Zhao et al. 2008, Algra, Driessen et al. 2012, Rosanova, Allaria et al. 2009, Alvarez, Fuentes et al. 2012); urinary tract infections (UTIs) (<1% - 17.2%) (Grisaru-Soen, Paret et al. 2009, Levy, Ovadia et al. 2003, Siddiqui, Mir et al. 2011, Algra, Driessen et al. 2012, Mastropietro, Barrett et al. 2013) and surgical site infections (SSIs) (1.53% -25%)(Barker, O'Brien et al. 2010, Grisaru-Soen, Paret et al. 2009, Levy, Ovadia et al. 2003, Allpress, Rosenthal et al. 2004, Hafez, Saied et al. 2012, Nateghian, Taylor et al. 2004, Chaudhuri, Shekar et al. 2012, Woodward, Son et al. 2011, Tantawy, Seliem et al. 2012, Harder, Gaies et al. 2013).

Identification of risk factors for HAI is important because if patients at risk can be identified prior to surgery, procedures may be adjusted to reduce further risk and necessary interventions may be implemented postoperatively to reduce the overall risk of acquiring HAIs.

Bloodstream infection (BSI) and other Hospital acquired infection (HAI): incidence and risk factors in postoperative cardiac patients.

The incidence of BSI and other HAI rates with associated factors are presented in Table 1. The reported incidence of hospital acquired infections (HAIs) in a paediatric ICU (PICU), in paediatric cardiovascular surgery patients specifically, ranges from 2.6% - 68% (Tantawy, Seliem et al. 2012, Siddiqui, Mir et al. 2011, Barker, O'Brien et al. 2010, Algra, Driessen et al. 2012, Grisaru-Soen, Paret et al. 2009, Levy, Ovadia et al. 2003, Bakshi, Vaidyanathan et al. 2007, Rosanova, Allaria et al. 2009, Mastropietro, Barrett et al. 2013, Alvarez, Fuentes et al. 2012, Sarvikivi, Lyytikainen et al. 2008, Pasquali, He et al. 2013). The incidence of HAI in the general PICU population ranges from 6% - 15% (Richards, Edwards et al. 1999, Urrea, Pons et al. 2003, Singh-Naz, Sprague et al. 1996), which is markedly lower than may be expected in postoperative cardiac PICU patients, and is presumed to be due to immune and inflammatory responses to cardiac surgery (Allen, Hoschtitzky et al. 2006).

Table 1. Bloodstream and other hospital acquired infection rates in postoperative cardiac patients

Citation	Population	Sample size	Study type	BSI	Other HAI	Conclusions
(Levy, Ovadia et al. 2003)	Israel, 0 - 18 years, PCICU	335 post cardiac surgery patients	Prospective observational study	10 (33/335)	16.4 (55/335)	High complexity score, neonatal age, prolonged ICU stay, and open chest postoperatively were risk factors of HAI.
(Bakshi, Vaidyanathan et al. 2007)	India, neonates (< 1month), PICU	330 post cardiac surgery patients	Retrospective review	21.2% (70/330)		Predictors of postoperative BSI on multivariate analysis were use of cardiopulmonary bypass (OR, 2.0 [95% CI, 1.1–4]; P = 0.004), reintubation (OR, 7.7 [95% CI 3.6-16.6]; P = 0.002), and surgical site infection (OR, 4.1 [95% CI, 1.7-111.1]; P = 0.015).
(Sarvikivi, Lyytikainen et al. 2008)	Finland, 0 - 18 years, PICU	511 post cardiac surgery patients	Retrospective review including a prospective post discharge survey	4% (19/511)	6.3/1000 patient days	All severe nosocomial infections (NIs) were detected during the postoperative hospital stay. Respiratory and gastrointestinal infections were common and often led to rehospitalisation, thus increasing costs.
(Bezzio, Scolfaro et al. 2009)	Italy, 0 - 18 years, following cardiac surgery with	205 CVCs inserted in 153 patients	Prospective observational study	11.8% (18 episodes of BSIs per 135)		The mean rate of CRBSI was 11.7 episodes per 1,000 CVC-days. The risk of infection increased 6 times if CVCs stayed in situ for 7 – 10days (OR, 6.2 [95% CI, 1.4–27.4]; P =

Citation	Population	Sample size	Study type	BSI	Other HAI	Conclusions
	central venous catheters					.017) and 14 times if CVCs stayed in situ more than 10 days (OR, 14.3 [95% CI, 3.1–65.4]; P = .001). The subclavian vein route was a risk factor for developing sepsis. The placement of CVCs during a febrile episode was associated with an increased risk of CRBSI. The authors concluded that staff specifically trained to handle the central venous catheters with proper aseptic techniques and an appropriate patient to medical staff ratio remained the most effective measures to prevent CRBSIs.
(Grisaru-Soen, Paret et al. 2009)	Israel, PICU, 0 - 18 years	356 post cardiac surgery patients, 381 admissions to the PICU	Prospective observational Case control study	65.8% (96/146)	38.3% (146/381)	Risk factors for nosocomial infection (NI): age < 2 months, congenital malformations, postoperative complications, and open-chest procedure. Infection prevention and control measures were reported as important in preventing nosocomial infections Authors noted: the study patients were significantly younger than the controls (52.7% vs. 18.7%, respectively, were < 2 months of age). The study

Citation	Population	Sample size	Study type	BSI	Other HAI	Conclusions
						patients also had a relatively prolonged length of stay in the PICU and a higher number of multiple surgeries (14.0% vs. 1.1%). The authors reported a high percentage of utilisation of central venous catheters, the median days of central venous catheter in the HAI group and the control group were 8.5 (4-14) and 1 (1-2), respectively (P < 0.001).
(Rosanova, Allaria et al. 2009)	Argentina, PICU, 0 - 18 years	350 patients post cardiac surgery	Prospective study	5% (17/350)	11% (38/350)	Underlying diseases **(**genetic disorders, undernutrition**)**, (OR, 4.22 [95% CI, 1.38-1.28]; P < 0.012), inotropic support (with epinephrine) (OR, 4.04 [95% CI, 1.17-13.9]; P < 0.027), and postoperative stay longer than 12 days (OR, 1.08 [95% CI, 1.03-1.14]; P < 0.003), were found to be risk factors for infections.
(Abou Elella, Najm et al. 2010)	Saudi Arabia, PCICU, 0 – 140 months	311patients post cardiac surgery	Prospective cohort study	8.6% (27/311)		Risk factors for the development of BSI after paediatric cardiac surgery were lower patient weight, high surgical complexity score open sternum postoperatively, longer duration of central lines, and prolonged paediatric cardiac ICU and hospital stay. Catheter line related BSI rate 25.8 per 100 central line days

Citation	Population	Sample size	Study type	BSI	Other HAI	Conclusions
						The authors postulated that the relatively high BSI rate in their population may have been attributable to multiple factors: including a different patient population, extensive use of invasive devices, a high percentage of neonates undergoing complex cardiac surgery, and the relative malnourished status of many of their patients.
(Barker, O'Brien et al. 2010)	USA, 0 – 18 years	30078 surgery from 48 centres in North America	Retrospective review of The Society of Thoracic Surgeons Congenital Heart Surgery Database	2.6% (no data)	2.8% (857/30078)	Major infection: 2.6% septicaemia, 0.3% mediastinitis, and 0.09% endocarditis. Postoperative length of stay was greater in those with major infection (length of stay >21 days, 69.9% versus 10.7%). Young age, high complexity, previous cardiothoracic operation, preoperative length of stay more than 1 day, preoperative ventilator support, and presence of a genetic abnormality were associated with major infection after backward selection.
(Wheeler, Jeffries et al. 2011)	USA, 0 – 18 years	PCICU, patients post cardiac surgery	Review article: predisposition, infection / insult, response,			Postoperative sepsis occurs in nearly 3% of children undergoing cardiac surgery and significantly increases length of stay in the paediatric cardiac intensive care unit as well as the risk for mortality.

Citation	Population	Sample size	Study type	BSI	Other HAI	Conclusions
			organ dysfunction / failure (PIRO) concept			Predisposition: gender (increased severity of illness and mortality in males compared to females), nutritional status (increased morbidity and mortality with malnutrition or obesity), genetic factors (gene polymorphisms) and chromosomal / malformation syndromes (trisomy 21 / 22q deletion sequence) may increase the risk and severity of sepsis. The authors concluded that several questions for the management of critically ill neonates and children with sepsis and underlying CHD remain: impact of chronic hypoxaemia on the outcome from sepsis, the need for better biomarkers for risk stratification and therapeutic monitoring and the effect of CPB on subsequent risk for HAIs.
(Siddiqui, Mir et al. 2011)	Pakistan, CICU, under 1month – 19 years	329 post cardiac surgery patients	Prospective observational cohort study	34.6% (9/26)	7.9% (26/329)	Authors concluded that the low incidence of HAIs in the study may reflect strict implementation and adherence to the institutional Infection Control policy including strict visit regulations (one parent at a time), hand hygiene and a 1:1 nurse-to-patient ratio in high dependency/intensive care areas.

Citation	Population	Sample size	Study type	BSI	Other HAI	Conclusions
(Dudeck, Horan et al. 2011)	USA, National Healthcare Safety Network (NHSN) Report, Data Summary for 2010, Device -associated Module	30 hospitals, Pediatric cardiothoracic	Multicentre, retrospective	2.1 per 1000 central line days		The authors recommended that hospital facilities should use the data in the report and their own data to guide local prevention strategies and other quality improvement efforts to reduce the occurrence of HAIs.
(Algra, Driessen et al. 2012)	Netherlands, 0 - 18 years following cardiac surgeries performed with CPB	364 patients, 412 procedures	Retrospective study	25% (32/102)	25% (102/412)	Variables most predictive of an infection: age less than 6 months, postoperative PICU stay longer than 48 hours, and open sternum for longer than 48 hours.
(Tantawy, Seliem et al. 2012)	Egypt, PCICU,	175patients after cardiac surgery	Prospective observational study	40% (48/119)	68% (119/175)	Nosocomial infections were associated with poor hand hygiene and younger age.

Citation	Population	Sample size	Study type	BSI	Other HAI	Conclusions
	infants under 1 – 14 years					
(Alvarez, Fuentes et al. 2012)	Spain, PICU, 1 day – 14 years	194 patients after cardiac surgery	Retrospective cohort study	68.2%	11.9%	Prolongation of antibiotic prophylaxis > 48 hours (OR, 1.01; P < 0.05), central venous access maintenance time (OR 1.004; P < 0.05), and duration of mechanical ventilation (OR 1.004: P < 0.005) increased the infection rate. The authors concluded that the suspension of antimicrobial prophylaxis in the first 48 hours after surgery did not increase the rate of nosocomial infection. Every additional hour for which prophylaxis was maintained multiplied the risk of nosocomial infection by 1.01.
(Mastropietro, Barrett et al. 2013)	USA, PICU, < 1month – under 5 years	76 patients post cardiac surgery	Retrospective study	12.1% (7/58)	36% (27/76)	Prolonged duration of endotracheal intubation (OR 1.27 [95% CI, 1.03-1.55]; P = 0.023) and days of corticosteroid exposure (OR 1.47 [95% CI, 1.08-1.99] P = 0.015) were significant risk factors for infection.
(Pasquali, He et al. 2013)	USA, 0 - 18 years	32856 patients post	Retrospective review		3.7% (1225/32856)	Hospitals with the highest infection rates had longer length of stay (LOS) (13.2 vs 11.7 days, P < 0.001) and increased hospital costs ($71,100 vs $65,100, P <

Citation	Population	Sample size	Study type	BSI	Other HAI	Conclusions
		cardiac surgery (28 centers)	The Society of Thoracic Surgeons Congenital Heart Surgery Database was linked to resource utilisation data from the Pediatric Health Information Systems Database for hospitals participating in both (2006 to 2010).			0.001). The proportion of variation in costs and LOS explained by infection was 15% and 6%, respectively. The authors concluded that infection after congenital heart surgery contributed to prolonged LOS and increased costs on a hospital level.

CVC Central venous catheter

CRBSI Catheter related bloodstream infection

LOS Length of stay

PCICU Paediatric cardiac intensive care unit

All studies reportedly used the CDC definitions for HAIs. Interpretation of CDC criteria is open to variation, and strict and consistent adherence to definitions has not been verified in these studies. Further limitations of these studies include variability in patient profiles, differing surgical complexities, differing study designs, retrospective nature of the studies and the variability in patient treatments and infection control protocols between the institutions. Some studies tried to overcome the limitations by conducting prospective studies with a cohort of comparable paediatric cardiac surgery patients (Grisaru-Soen, Paret et al. 2009, Bezzio, Scolfaro et al. 2009, Levy, Ovadia et al. 2003, Rosanova, Allaria et al. 2009, Abou Elella, Najm et al. 2010, Tantawy, Seliem et al. 2012). These studies have small sample sizes and the interventions and outcomes investigated differed between the studies. The incidence of bacteraemia and fungaemia associated with HAIs was the focus in a number of studies (Levy, Ovadia et al. 2003, Abou Elella, Najm et al. 2010, Rosanova, Allaria et al. 2009) with few reporting on viral aetiologies of HAIs (Grisaru-Soen, Paret et al. 2009).

It is clear that there is marked variation in the incidence of HAIs amongst various studies. This is evident in the difference in BSI rate in developing country studies such as Pakistan (34.6%) (Siddiqui, Mir et al. 2011) and Egypt (40%) (Tantawy, Seliem et al. 2012) reporting high HAI rates compared to an Argentinian study (5%) (Rosanova, Allaria et al. 2009). The Argentinian study (Rosanova, Allaria et al. 2009) was conducted at a tertiary referral institution with patients cared for in a general paediatric ICU setting similar to this study population. It is interesting to note that Siddiqui et al (Siddiqui, Mir et al. 2011) commented on a strict institutional infection control policy with 1:1 nurse-to-patient ratio in their dedicated paediatric cardiac intensive care unit (PCICU) resulting in a low overall HAI rate (7.7%) compared to a high HAI rate reported by Tantawy et al (68%) in their PCICU with nurse-to-bed ratio 1:3 or 1:4. This institution has a similar 1:1 nurse-to-patient ratio to the study conducted in Pakistan.

Developed countries reported marked variation in BSI rates ranging from low rates in the PCICUs of Saudi Arabia (8.6%) (Abou Elella, Najm et al. 2010) and Israel (10%) (Levy, Ovadia et al. 2003) compared to Grisaru-Soen et al (Grisaru-Soen, Paret et al. 2009) reporting a high BSI rate (65.8%) in their study population. The study setting and workload was similar in the two previous studies conducted in Saudi Arabia and Israel as each had nine and 12 bed units respectively and admitted about 350 patients annually. The distribution of HAIs is not only affected by the affluence of the country but also institutional policies and protocols such as nurse-to-patient ratio and institutional infection control policies.

Various patient, environmental and interventional procedures contribute to the **risk of developing HAIs**. Identified factors contributing to risk include high surgical complexity score, neonatal age, prolonged ICU stay, and open chest postoperatively (Abou Elella, Najm et al. 2010, Algra, Driessen et al. 2012). Prolonged duration of ventilation and PICU stay have repeatedly been identified as risk factors, but further studies are needed to determine whether these are cause or consequence of HAI (Barker, O'Brien et al. 2010, Rosanova, Allaria et al. 2009, Alvarez, Fuentes et al. 2012, Mastropietro, Barrett et al. 2013, Pasquali, He et al. 2013).

The implementation of and adherence to institutional infection prevention and control policies, including strict hand hygiene, and adequate nurse-patient ratio have been shown to reduce the incidence of HAIs in paediatric ICU patients post cardiac surgery (Siddiqui, Mir et al. 2011, Grisaru-Soen, Paret et al. 2009). The absence of specific policies has been reported as a risk factor for the development of HAIs (Siddiqui, Mir et al. 2011, Grisaru-Soen, Paret et al. 2009). To understand the reasons for this variation in incidence of HAIs amongst various studies one has to look at the risk factors for developing HAIs within specific patient groups.

Risk factors for bloodstream infections such as high surgical complexity score, prolonged ICU stay, open chest postoperatively, younger age (< 2 months) and undernutrition overlap with risk factors for other HAIs (Abou Elella, Najm et al. 2010, Rosanova, Allaria et al. 2009). Longer duration of central lines (> 7 days) is a risk factor specific to BSI (Abou Elella, Najm et al. 2010, Bezzio, Scolfaro et al. 2009)

An Italian study conducted by Bezzio et al. (Bezzio, Scolfaro et al. 2009) reported that infants and children with central venous catheter (CVC) insertion in the subclavian vein after cardiac surgery were almost five times more likely to develop a catheter related bloodstream infection (CRBSI) than patients who had an insertion in another vein. The authors were unable to provide reasons for this result. Abou Elella et al. (Abou Elella, Najm et al. 2010) identified high surgical complexity score and prolonged PICU and hospital stay as risk factors for the development of BSIs. Genetic factors may play an important role as well, and there are several gene polymorphisms that have been linked with an increased susceptibility to sepsis (Wheeler, Jeffries et al. 2011).

It is known that the risk of BSI is reduced by adequate antiseptic skin preparation immediately before central venous catheter insertion and by keeping microbial density at the insertion site low while the catheter is in place (O'Grady, Alexander et al. 2011, Safdar, Maki 2004). Most catheter-associated

BSIs result from contamination of the catheter by bacteria residing on patients' skin at the time of device insertion, later from microorganisms migrating from the skin to catheter tip, or after catheter hub contamination, and often also by patients' own skin flora (Safdar, Maki 2004, Levy, Katz et al. 2005). There is a strong correlation between the number of organisms colonising the insertion site of the CVC and the risk of BSI (Levy, Katz et al. 2005). Chlorhexidine gluconate (CHG), which has broad antimicrobial activity, prolonged residual effect, and superiority over iodophor skin preparations, is the recommended agent for disinfecting skin before catheter insertion in surgical patients (Bleasdale, Trick et al. 2007, Safdar, Maki 2004, O'Grady, Alexander et al. 2011).

Risk factors for surgical site infections (SSIs) after paediatric cardiovascular surgery

The reported incidence of SSIs in postoperative cardiac patients ranges from 26% - 27% in studies conducted in the Netherlands (Algra, Driessen et al. 2012) and Egypt (Hafez, Saied et al. 2012) to 1% - 7.5% in studies conducted in USA (Woodward, Son et al. 2011) and Israel (Grisaru-Soen, Paret et al. 2009) respectively. Similar to this study, Algra et al (Algra, Driessen et al. 2012) had an institutional prophylactic antibiotic policy perioperatively, compared to the Egyptian authors (Hafez, Saied et al. 2012) who reported no uniform guidelines were in place guiding antibiotic prophylaxis to prevent SSIs. The patient setting for the study conducted by Grisaru et al (Grisaru-Soen, Paret et al. 2009) was similar to our institution, admitting about 380 postoperative cardiac patients annually to the general PICU, however the study patient population was significantly younger (52% < 2 months of age). **Various risk factors for SSIs** after paediatric cardiovascular surgery have been reported and are outlined in Table 2.

Preoperative risk factors include: Younger age, previous sternotomy and prolonged preoperative hospital / ICU stay. Patients with a higher preoperative leukocyte count had an increased risk for SSIs (Levy, Ovadia et al. 2003, Ben-Ami, Levy et al. 2008, Costello, Graham et al. 2010, Sohn, Schwartz et al. 2010). Intraoperative factors include: longer duration of surgery, use and duration of CPB, use of deep hypothermia and intraoperative blood transfusions (Nateghian, Taylor et al. 2004, Costello, Graham et al. 2010). Postoperative factors include: delayed sternal closure, prolonged ventilation, low cardiac output, prolonged use of central vascular catheters (CVC), prolonged ICU stay and elevated leukocyte count (Allpress, Rosenthal et al. 2004, Nateghian, Taylor et al. 2004, Ben-Ami, Levy et al. 2008, Alvarez, Fuentes et al. 2012).

A recurring factor identified as contributing to increased risk was younger age (< 2 months) (Allpress, Rosenthal et al. 2004, Levy, Ovadia et al. 2003, Grisaru-Soen, Paret et al. 2009). Various authors postulated that this population group inherently has an increased risk for HAIs post cardiac surgery since the surgeries are expected to be complex and high risk with patients having prolonged hospital and ICU stays (Pollock, Ford-Jones et al. 1990, Mrowczynski, Wojtalik et al. 2002).

Sohn et postulated that the complexity of congenital cardiac defects and the aggressive medical management required to support patients through their recovery placed children at high risk for SSI (Sohn, Schwartz et al. 2010). The authors concluded that the use of perioperative medical interventions increased the risk of SSI in young children after cardiac surgery. However, the study also concluded that multiple severity of illness scores [Pediatric risk of Mortality III (PRISM III), Neonatal Therapeutic intensity scoring system (NTISS), Therapeutic intensity scoring (TISS-76)], the Risk Adjustment for Congenital Heart Surgery (RACHS-1) category, and longer duration of postoperative antimicrobials were not associated with SSI.

A study conducted by Woodward et al, (Woodward, Son et al. 2011) aimed to determine the incidence of, and preventative practice regarding paediatric surgical site infections. A 31-question on-line survey regarding paediatric SSIs was sent to 89 congenital heart programs. The study concluded that neither program size nor delayed sternal closure were associated with increased incidence of SSIs and that variations in preoperative measures, antibiotic regimens, and wound care did not statistically impact the incidence of SSI. Programs with protocols to monitor and control blood glucose levels postoperatively had statistically lower infection rates (1.04 vs. 2.35, $P = 0.03$). A limitation to the study is the level of non-responders to the online and mailed surveys. Thirty-eight (43%) of the 89 programs responded which the authors acknowledged was a concerning source of bias. They argued that despite this limitation the data reflected valuable new information about the institutional protocols and policies of a large number of paediatric cardiac surgery programs. One has to challenge the data obtained from this study due to the low response rate and the inherent biased nature of questionnaire-based studies that rely on the individual responder’s perception of their clinical practice.

As with other HAIs in postoperative paediatric cardiac patients, various prevention strategies such as antibiotic prophylactic regimes and infection control policy implementation have been used to reduce the incidence of SSIs. Skin decontamination as part of an infection control policy with 4% Chlorhexidine gluconate pre-operative bathing has been shown to reduce microbial counts on the skin, including gram negative and gram positive organisms, and reducing incidence of SSIs (Bleasdale, Trick et al. 2007). Antimicrobial prophylaxis using Cefazolin has been shown to be clinically and cost effective in reducing the incidence of SSIs (Mauermann, Sampathkumar et al. 2008).

Higher risk severity scores are associated with developing HAI, and specific risk factors such as prolonged ventilation, prolonged use of central vascular access may in turn contribute to prolonged ICU stay. However, it is unclear what the primary risk factor would be e.g. prolonged CVC use occurs in a patient with BSI to administer antibiotics versus the child developed a BSI due to prolonged use of CVC due to prolonged ICU stay? Teasing out specific risk factors and the overlapping effect of each is why more studies are needed into HAIs in this population group.

In review, unfortunately, the majority of these studies have small sample sizes. The protocols for preoperative care, prophylactic antibiotics, wound care and follow up after surgery differ between the studies. This makes it difficult to compare findings and relate these findings to the wider population of paediatric cardiac surgery patients. It becomes evident that multiple factors contribute to increasing risk of SSIs in postoperative cardiac patients with younger age (< 2 months) being a consistent risk factor. This suggests that infection prevention strategies should be directed particularly at ways to reduce risk of acquiring HAIs in this vulnerable group of younger patients.

Table 2. Surgical site infection rates

Citation	Population	Sample size	Study type	SSI (%)	Conclusions
(Levy, Ovadia et al. 2003)	Israel, 0 - 18 years, PCICU	335 post cardiac surgery patients	Prospective study	8% (26/335)	High complexity score, neonatal age, prolonged ICU stay, and open chest postoperatively were risk factors of HAI. Authors postulated that the relatively high rate of surgical wound infection was due to the unit being exclusive to patients after cardiac surgery.
(Allpress, Rosenthal et al. 2004)	USA, < 1 month – 18 years following cardiovascular surgery in a regional medical center.	826 patients	Prospective observational study	2.3 % (19/826)	Age < 1 month, longer duration of bypass time, longer duration of ventilator use, longer duration of hospitalisation prior to surgery (> 1 day) and longer duration of surgery were independently associated with hospitalised SSI after cardiovascular surgery in children.
(Nateghian, Taylor et al. 2004)	Canada, < 18 years, underwent open-heart surgery	1117 cardiac surgeries	Prospective case-control study	3.4% (38/1117)	Longer duration of surgery was a significant risk factor for SSI. There was a trend toward an increased incidence of SSI (P < 0 .25) for children with failure to thrive, or for those who required inotropes or had an elevated serum lactate in the first 24 hours postoperation.

(Ben-Ami, Levy et al. 2008)	Israel, CICU, 0 – 18 years	1821 post cardiac surgery patients	Retrospective review	2.69% (49/1821)	Three variables emerged as significant independent risk factors for SSI: young age (< 1 year) (OR, 0.63 [95% CI, 0.47-0.85]; P < 0.001 for each additional year), cyanotic heart disease (OR, 4.93 [95% CI, 1.98 - 2.3]; P < 0.001), and central venous catheter (CVC) dwell time (OR, 1.15 [95% CI, 1.06 - 1.24]; P < 0.001 for each additional day). Gram negative infections were significantly associated with preoperative oxygen treatment. The main bacterial pathogens were *Staphylococcus aureus* and *Pseudomonas aeruginosa*.
(Grisaru-Soen, Paret et al. 2009)	Israel, PICU, 0 - 18 years	356 post cardiac surgery patients, 381 admissions to the PICU	Prospective Case control study	7.5% (11/146 episodes of HAI)	Risk factors for HAI: age < 2 months, congenital malformations, postoperative complications, and open-chest procedure.
(Costello, Graham et al. 2010)	USA, CICU, 0 – 18 years	2645 post cardiac surgery cases	Prospective study	73 SSIs occurred in 67 patients	Independent risk factors for any type of SSI were age younger than 1 year (OR, 2.28 [95% CI, 1.18-4.39]; P = 0.01) and duration of cardiopulmonary bypass greater than 105 minutes (OR, 1.92 [95% CI, 1.02-3.62]; P = 0.04). Independent risk factors for organ space SSI were aortic cross-clamp time greater than 85 minutes (OR, 5.61 [95% CI, 1.06-

					29.67]; P = 0.04) and postoperative exposure to at least three separate red blood cell transfusions (OR, 7.87 [95%CI, 1.63-37.92]; P = 0.01). When only those potential risk factors known preoperatively were considered, age younger than 1 year (OR, 2.56 [95%CI, 1.35-4.87]; P = 0.004) independently predicted the subsequent development of any type of SSI, and preoperative hospitalisation (OR, 3.30 [95%CI, 1.26-8.59]; P = 0.01) independently predicted the subsequent development of organ space SSI.
(Sohn, Schwartz et al. 2010)	USA, Neonatal ICU (NICU) and PICU, 0 – 18 years	726 surgical procedures performed in 626 post cardiac surgery patients	Retrospective cohort study	6.3% (46/726)	Children with SSIs were more likely to have been < 30 days old (OR, 2.9 [95% CI, 1.2-70]; P = 0.21), to have a perioperative medical device (Preoperative gastrostomy tube (OR, 5.1 [95%CI, 1.6-16.3]; P = 0.006) , Intraoperative femoral central vascular catheter (OR, 3.1 [95%CI, 1.3-7.5]; P = 0.01), Intraoperative epicardial wire placement (OR, 25.5 [95% CI 3.8-169.5]; P = 0.001) and to use parenteral nutrition (OR, 3.3 [95%CI, 1.4-7.9]; P = 0.007).
(Siddiqui, Mir et al. 2011)	Pakistan, CICU, under 1 month – 19 years	329 post cardiac surgery patients	Prospective cohort study	7.7% (2/26)	Authors concluded that the low incidence of HAIs in the study may reflect strict implementation and adherence to the institutional Infection Control policy including strict visit

					regulations (one parent at a time), hand hygiene and a 1:1 nurse-to-patient ratio in high dependency / intensive care areas.
(Woodward, Son et al. 2011)	USA, Eighty-nine congenital heart programs were sent a 31 question on-line survey regarding pediatric sternal wound infections, < 18 years	8774 cardiac surgeries	Multicenter review (retrospective)	1.53% (1.53 per 100 cardiac surgeries)	Programs with protocols to monitor and control blood glucose levels postoperatively had statistically lower infection rates, and those that sent mediastinal cultures at time of delayed sternal closure reported lower infection rates (1.34 vs. 1.74, P = 0.051). Variations in preoperative measures, antibiotic regimens, and wound care did not statistically impact incidence of sternal wound infection.
(Tantawy, Seliem et al. 2012)	Egypt, PCICU, infants under 1 – 14 years,	175 patients after cardiac surgeries	Prospective study	17.5% (21/119)	Nosocomial infections were associated with poor hand hygiene and younger age.
(Hafez, Saied et al. 2012)	Egypt, < 15 years to > 65 years, undergoing cardiothoracic	1394 patients (cardiothoracic = 855, urologic 539).	Prospective study	17% = SSI total (187/1062)	Increased risk of SSI for those who underwent cardiothoracic surgeries, increased duration of hospital stay before and after surgery, antibiotics < 24 hours before surgery, and dirty wounds. Overuse of antibiotics was found to be an important risk factor.

	and urologic surgeries	1062 patients followed up completely (30 days postoperative)		27.1% = SSI cardiothoracic 43% SSIs occurred after discharge (81/187)	The authors identified various potential factors contributing to the high rate of SSIs including the limited resources allocated to ICU, lack of hospital accreditation, low nurse-to-patient ratio, limited intensive care expertise, and status as a teaching hospital that includes several trainees and young surgeons. Moreover, the hospital had no uniform guidelines on antibiotic prophylaxis to prevent SSIs.
(Chaudhuri, Shekar et al. 2012)	Australia, Adults post cardiac surgery	6876 patients underwent cardiac surgery	Retrospective review	1% (70/6876) Deep sternal wound infections	Superficial swabs predicted the pathogen 75% of the time. Specific to Staphylococcus aureus, the positive predictive value of a superficial sternal swab was found to approach 100%. Colonisation with multi-resistant organisms is 100% predictive of the pathogen in DSWI. The absence of gram negative organisms from superficial swabs or blood cultures (n = 48) has a negative predictive value of 98%. The inclusion of blood cultures predicted the pathogen 82% of the time across all types of bacterial infections.
(Algra, Driessen et al. 2012)	Netherlands, 0 - 18 years following cardiac surgeries	364 patients, 412 procedures, 127 infections	Retrospective study	26% (33/127)	Variables most predictive of an infection: age less than 6 months, postoperative paediatric intensive care unit stay longer than 48 hours, and open sternum for longer than 48 hours. SSIs were mostly incisional SSI (n = 24,consisting of both superficial and

	performed with CPB				deep incisional SSI), and nine organ/space SSI (mediastinitis in five cases, and pleurisies in four cases).
(Alvarez, Fuentes et al. 2012)	Spain, PICU, 1 day – 14 years	194 patients after cardiac surgery	Retrospective cohort study	9.1%	Prolongation of antibiotic prophylaxis > 48 hours (OR, 1.01; $P < 0.05$), central venous access maintenance time (OR 1.004; $P < 0.05$), and duration of mechanical ventilation (OR 1.004: $P < 0.005$) increased the infection rate. The authors concluded that the suspension of antimicrobial prophylaxis in the first 48 hours after surgery did not increase the rate of nosocomial infection.

Impact of delayed sternal closure on HAIs after paediatric cardiovascular surgery

Delayed sternal closure (DSC) may be required in the care of paediatric patients who have undergone cardiac surgery to minimise postoperative respiratory and hemodynamic instability (Jogi, Werner 1985, Gangahar, McGough et al. 1981, McElhinney, Reddy et al. 2000, Ozker, Saritas et al. 2012).

Although necessary for the treatment of certain unstable patients, DSC may expose patients to an increased risk of HAIs, including bloodstream (Das, Rubio et al. 2011) and surgical site infections (SSIs) (Shin, Jhang et al. 2011) (Table 3). Ozker et al (Ozker, Saritas et al. 2012) significantly associated an increased mortality rate with increased cross clamp time (CCT) and DSC in postoperative paediatric cardiac patients. The limitations of these studies include their retrospective nature, small sample size, variability in antibiotic treatment and prophylaxis protocols, and variability in patient profiles. DSC is frequently used in more complex surgical cases as indicated by the high mean comprehensive Aristotle score (13.2 ± 3.1) in the study conducted by Shin et al. Johnson et al (Johnson, Jaggers et al. 2010) and Das et al (Das, Rubio et al. 2011) tried to overcome the limitations by choosing a specific comparable cohort of neonatal patients with hypoplastic left heart syndrome (HLHS) after cardiac surgery. Johnson et al (Johnson, Jaggers et al. 2010) suggested that more frequent use of delayed sternal closure is associated with longer length of stay and higher postoperative infection rates. Das et al (Das, Rubio et al. 2011) reported that their neonatal study population, undergoing stage 1 Norwood procedure, with DSC had a fourfold increased risk of developing bloodstream infection in-hospital.

In contrast to this study's patient population, the study populations' of Johnson et al (Johnson, Jaggers et al. 2010), Das et al (Das, Rubio et al. 2011) and Shin et al (Shin, Jhang et al. 2011) were limited to DSC following palliative cardiac procedures in neonatal patients. Similar to this study's patient profile DSC was performed following various cardiac conditions in the studies conducted in Turkey (Ozker, Saritas et al. 2012), USA (Harder, Gaies et al. 2013) and Canada (Bowman, Rebeyka et al. 2013).

Maintenance of sternal opening care also varied between the studies e.g. Shin et al (Shin, Jhang et al. 2011) applied sternal traction sutures to increase the volume of the thoracic cavity and irrigated the mediastinal space with a crystalloid solution every two days from the day of sternal opening (Shin, Jhang et al. 2011). Ozker et al (Ozker, Saritas et al. 2012) used a rigid plastic material to keep the chest widely open and an airtight synthetic transparent patch was used to cover the sternal gap, which was sutured to the skin with running polypropylene sutures. The dressing was changed in ICU daily in an aseptic manner. In some cases sterna were left open but skins were closed primarily. Their study patients were evaluated for sternal closure on a daily basis and taken to theater for closure trial when ready.

Shin et al (Shin, Jhang et al. 2011) reported that prolonged ventilator support and complexity of the cardiac anomaly increase the risk of adverse outcomes after procedures to repair congenital cardiac anomalies. After adjusting for these variables, duration before DSC did not appear to be a risk factor for surgical mortality, postoperative infection, or wound dehiscence. Strategies to prevent BSIs in paediatric postoperative cardiac patients therefore could be directed at reducing duration of ventilator support rather than focussing on factors associated with delayed sternal closure. Harder et al and Bowman et al also concluded that the duration of DSC was not a significant risk factor for SSI (Harder, Gaies et al. 2013, Bowman, Rebeyka et al. 2013).

These studies do not provide a clear consensus of whether delayed sternal closure is a risk factor for SSIs and rather indicate that multiple strategies may be needed to reduce the risk for HAIs in postoperative cardiac patients. Recurring at risk groups identified within postoperative cardiac patients are younger age (neonatal age) and increased severity of cardiac condition. The risk factor may well be neonatal age more than actual DSC, thereby, suggesting this group of cardiac patients be the focus of infection control strategies perioperatively.

Table 3. Delayed sternal closure (DSC)

Citation	Population	Sample size	Study type	Outcome (%)	Conclusions
(Johnson, Jaggers et al. 2010)	USA, neonates with hypoplastic left heart syndrome (HLHS) undergoing stage 1 palliation (Norwood procedure with modified Blalock – Taussig shunt or right ventricle to pulmonary artery conduit)	1283 patients (45 centers) DSC was used in 74% of cases	Multicentre review of Society of Thoracic Surgeons Congenital Database 2000 to 2007. Centers were characterized on the basis of the proportion of cases at each center for which DSC was used: low (≤ 25% of cases), middle (26% – 74% of	BSI Low DSC use 4.5% (5/111) Middle DSC use 13.6% (55/406) High DSC use 12.4% (95/766)	Centers with high and middle delayed sternal closure use had prolonged length of stay (OR, 2.83 [95% CI, 1.46–5.47] P= 0.002 and OR, 2.23 [95% CI, 1.17–4.26] P = 0.02, respectively) and more infection (OR, 2.34 [95% CI, 1.20–4.57] P = 0.01 and OR, 2.37 [95% CI, 1.36–4.16] P = 0.003, respectively). Authors suggest that more frequent use of delayed sternal closure is associated with longer length of stay and higher postoperative infection rates.

			cases), and high (≥ 75% of cases).		
(Das, Rubio et al. 2011)	USA, neonates with hypoplastic left heart syndrome (HLHS) undergoing stage 1 Norwood procedure, PCICU	110 patients, Delayed sternal closure 61% (67/110)	Retrospective review, single institution	BSI overall 22% (24/110) BSI in delayed sternal closure group 83% (20/24)	Patients with DSC had a fourfold increased risk (odds ratio 3.9, P = 0.03) of developing bloodstream infection in-hospital. Predominant organisms were coagulase negative *Staphylococcus* Species.
(Shin, Jhang et al. 2011)	Republic of Korea, 2 days – 20 years, after cardiac surgery	154 patients underwent delayed sternal closure, 37.7% (58/154) patients	Retrospective review	3.3% (5/150) Sternal wound infection (deep and superficial) Mean comprehensive Aristotle score 13.2 ± 3.1	Long ventilatory support and complexity of the cardiac anomaly increased the risk of adverse outcomes after procedures to repair congenital cardiac anomalies. Longer duration before DSC was not a risk factor for surgical mortality, postoperative infection, or wound dehiscence.

		underwent palliative procedures.		After excluding 4 patients who died before sternal closure 150 patients were used for analysis.	
(Ozker, Saritas et al. 2012)	Turkey, 0 – 2 years, after cardiac surgery	38 patients underwent DSC	Retrospective review	The mean sternal closure time was 2.9 days Mortality rate 34.2% (13/38)	Postoperative infection rate statistically increased with cardiopulmonary bypass time (CPBT), sternal closure time (SCT) and intensive care unit (ICU) stay time (P = 0.039; P = 0.01; P = 0.012). Mortality rate significantly increased with increased cross clamp time (CCT), SCT, and extracorporeal membrane oxygenation (ECMO) use (P = 0.017; P = 0.026; P = 0.03). Single ventricular physiology was found to be risk factor for mortality in delayed sternal closure (P< 0.007). The most common microorganism detected from cultures was gram negative: *Enterobacter aerogenes* (20%) and *Klebsiella Pneumonia* (20%).
(Harder, Gaies et al. 2013)	USA, 0 – 18 years, post cardiac surgery	375 patients underwent DSC	Retrospective review	SSI 11% (43/375)	Multiple periods (> 1) of DSC (OR, 5.9[95% CI, 1.7-20.1] P = 0.05) and ECMO (OR, 2.9 [95% CI, 1.1-7.6] P = 0.03) were independent risk factors for SSI.

					The duration of initial DSC was not statistically significant (OR, 1.7 [95% CI, 0.7-3.8] P = 0.23).
(Bowman, Rebeyka et al. 2013)	Canada, post cardiac surgery	130 patients underwent DSC	Retrospective review	SSI 13.7% (18/130)	There was a trend toward increased SSIs in patients undergoing delayed sternal closure in beds in the open bay of the PICU. There was no statistically significant effect of the duration of open sternum on the rate of SSI or organ space infection (No OR, CI or P values noted).

CPBT Cardiopulmonary bypass time

SCT Sternal closure time

<u>Risk factors for nosocomial pneumonia including ventilator associated pneumonia (VAP) after paediatric cardiovascular surgery</u>

Nosocomial pneumonia has been defined according to criteria of the Centers for Disease Control and Prevention (CDC) (Centers for Disease Control and Prevention 2014). VAP is defined as nosocomial pneumonia developing 48 hours or more after initiation of mechanical ventilation (Roeleveld, Guijt et al. 2011). Nosocomial pneumonia (NP) represents an important cause of morbidity and mortality in postoperative paediatric cardiac patients and increases hospital costs (Tan, Sun et al. 2004).

General risk factors for NP in ICU patients include the prior administration of broad spectrum antibiotics (e.g. third generation cephalosporins) (Tan, Sun et al. 2004), duration of mechanical ventilation, severity of illness, reintubation, transport out of the ICU and the use of histamine-2 blockers (Chastre, Fagon 2002, Alvarez, Fuentes et al. 2012). **Nosocomial pneumonia,** including VAP, in postoperative paediatric cardiac patients has frequently been associated with complex CHD compared to simple CHD (see Table 4) (Tan, Sun et al. 2004). Roeleveld et al (Roeleveld, Guijt et al. 2011) associated VAP development with transfusion of fresh frozen plasma (FFP) and high patient mortality risk scores (Roeleveld, Guijt et al. 2011). Patients with VAP in this population group have been shown to have longer duration of ventilation and longer ICU stay (Roeleveld, Guijt et al. 2011, Rosanova, Allaria et al. 2009).

Duration of mechanical ventilation (MV) has become a critically important issue for resource allocation and is correlated with postoperative morbidity and mortality. Prolonged mechanical ventilation (PMV) after cardiac surgery in children has been associated with postoperative morbidity and mortality, as well as increased ICU and hospital resource utilisation. Shi et al (Shi, Zhao et al. 2008) also reported that independent risk factors for prolonged mechanical ventilation in infants and neonates were higher RACHS-1 (risk adjustment for surgery for congenital heart disease ($P = 0.041$), nosocomial pneumonia ($P = 0.001$), low cardiac output syndrome ($P = 0.001$), postoperative cumulative positive fluid balance ($P = 0.032$), and extubation failure (Shi, Zhao et al. 2008). Extubation failure was defined as the reinstitution of mechanical ventilator support (including non-invasive mechanical support) within 24 hours after extubation (Shi, Zhao et al. 2008). Their study population was much younger (≤ 3 months) yet mechanically ventilated shorter durations (median 48 hours) compared to Fischer et al (median age 1.3 years; median MV duration 3 days) who reported a lower VAP rate (9.6%) and did not associate rate of VAP with increased complexity of surgery. Fisher et al reported a 3.7 days median delay of extubation in children following surgery for CHD attributable to VAP (Fischer, Allen et al. 2000). This study's population age was similar to Fischer et al (Fischer, Allen et al. 2000) who also reported a smaller caseload of approximately 150 cardiac surgeries admitted annually to their PICU compared to approximately 300 admitted annually postoperatively to this institution.

Siddiqui et al (Siddiqui, Mir et al. 2011) and Tantawy et al (Tantawy, Seliem et al. 2012) are two studies with similar study populations and settings, both reporting a high VAP rate (38.5% and 35% respectively) with significant differences in nurse-to-patient ratios (1:1 and 1:3-4 respectively). This may once again reflect the importance of strict implementation and adherence to the institutional Infection Control policy. This study's staffing setting was similar to Siddiqui et al (Siddiqui, Mir et al. 2011) with a nurse-to-patient ratio of 1:1 and their study population similarly included patients ventilated preoperatively.

Nosocomial pneumonia and prolonged duration of ventilation are inherently linked and each is a risk factor for the other. The risk factors contributing to NP and PMV thus have to be identified and effective preventive measures adhered to such as infection control policies and early extubation from mechanical ventilation.

These study findings are limited by small sample size, retrospective nature of the studies and differences in patient and cardiac surgery profiles. However, it is important to note that recurring risk factors are younger age, longer duration of ICU stay and non-adherence to infection prevention and treatment policies.

Table 4. Hospital acquired pneumonia infection rates and risk factors

Citation	Population	Sample size	Study type	Outcome (%)	Conclusions
(Fischer, Allen et al. 2000)	Switzerland, 0 – 18 years, NICU and PICU, post cardiac surgery	272 patients	Retrospective review	VAP 9.6% (26/272)	The rate of VAP was not associated with complexity of surgery ($P = 0.22$), or CPB ($P = 0.23$). Risk factors associated with delayed extubation were: other respiratory complications (chylothorax, airway stenosis, diaphragm paresis), prolonged inotrope support and the need for secondary surgery.
(Tan, Sun et al. 2004)	China, infants following open-heart surgery, single institution, Paediatric Cardiovascular Surgical ICU	311 patients	Retrospective study	VAP 21.5% (67/311)	The incidence of NP was more frequently associated with complex congenital heart defect compared to simple congenital heart defects. Gram negative bacilli remained the most common pathogens. There was a trend of increasing antibiotic resistance in these isolates.
(Shi, Zhao et al. 2008)	China, infants ≤ 3 months after cardiac	172 patients	Retrospective study	Nosocomial pneumonia (NP) including VAP 51.2%	Higher RACHS-1 score, nosocomial pneumonia, low cardiac output syndrome, fluid retention postoperatively, and extubation failure were risk factors for prolonged mechanical

Citation	Population	Sample size	Study type	Outcome (%)	Conclusions
	surgery, Surgical ICU			(88/172) Incidence of prolonged mechanical ventilation (PMV) 35.4% (61/172) Mortality in PMV patients was 6.6% (5/61)	ventilation (≥ 72hours) in neonates and young infants undergoing reparative surgery for congenital heart disease.
(Grisaru-Soen, Paret et al. 2009)	Israel, PICU, 0 - 18 years	356 post cardiac surgery patients, 381 admissions to the PICU	Prospective Case control study	NP including VAP16.4% (24/146 episodes of HAI)	Risk factors for nosocomial infection: age < 2 months, congenital malformations, postoperative complications, and open-chest procedure.

Citation	Population	Sample size	Study type	Outcome (%)	Conclusions
(Rosanova, Allaria et al. 2009)	Argentina, PICU, 0 - 18 years	350 patients post cardiac surgery	Prospective study	VAP 1% (5/350)	Underlying diseases (genetic disorders, undernutrition) (OR, 4.22 [95% CI, 1.38-1.28]; P < 0.012), inotropic support (with epinephrine) (OR, 4.04 [95% CI, 1.17- 13.9]; P < 0.027), and postoperative stay longer than 12 days (OR, 1.08 [95% CI, 1.03-1.14]; P < 0.003), were found to be risk factors for infections. Organisms detected as a cause for VAP were *Haemophilus influenzae non type b* and *Acinetobacter species*.
(Siddiqui, Mir et al. 2011)	Pakistan, CICU, under 1month – 19 years	329 post cardiac surgery patients	Prospective cohort study	VAP 38.5% (10/26)	Authors concluded that the low incidence of HAIs in the study may reflect strict implementation and adherence to the institutional Infection Control policy including strict visit regulations (one parent at a time), hand hygiene and a 1:1 nurse-to-patient ratio in high dependency/intensive care areas.
(Roeleveld, Guijt et al. 2011)	Netherlands, paediatric patients following cardiac surgery and mechanically ventilated for	125 patients	Retrospective cohort study	Rate of VAP 17.1/1000 mechanical ventilation days. 8.8%	Patients with VAP had longer duration of ventilation and longer ICU stay. Risk factors associated with the development of VAP were a PRISM III score of ≥10 and transfusion of fresh frozen plasma. Oral hygiene with oral swabs using water was used.

Citation	Population	Sample size	Study type	Outcome (%)	Conclusions
	≥24 hours, PICU			(11/125)	
(Dudeck, Horan et al. 2011)	USA, National Healthcare Safety Network (NHSN) Report, Data Summary for 2010, Device - associated Module	13 hospitals, Pediatric cardiothoracic	Multicentre, retrospective	0.7/1000 of mechanical ventilation days	The authors recommended that hospital facilities should use the data in the report and their own data to guide local prevention strategies and other quality improvement efforts to reduce the occurrence of HAIs.
(Tantawy, Seliem et al. 2012)	Egypt, PCICU, infants under 1 – 14 years,	175 patients after cardiac surgery	Prospective study	VAP 35% (42/119)	Nosocomial infections, including VAP, were associated with poor hand hygiene and younger age.
(Alvarez, Fuentes et al. 2012)	Spain, PICU, 1 day – 14 years	194 patients after cardiac surgery	Retrospective cohort study	13.6%	Prolongation of antibiotic prophylaxis > 48 hours (OR, 1.01; $P < 0.05$), central venous access maintenance time (OR 1.004; $P < 0.05$), and duration of mechanical ventilation (OR 1.004: $P < 0.005$) increased the infection rate.

Citation	**Population**	**Sample size**	**Study type**	**Outcome (%)**	**Conclusions**
					The authors concluded that the suspension of antimicrobial prophylaxis in the first 48 hours after surgery did not increase the rate of nosocomial infection.

<u>Incidence and risk factors of urinary tract infections (UTIs) in postoperative paediatric cardiac patients</u>

Incidence and risk factors of **urinary tract infections (UTIs)** in postoperative cardiac patients are presented in Table 5. Incidence varies from 1% to 17.2% with identified risk factors being younger age, poor hand hygiene, prolonged duration of hospital stay and prolonged use of urinary catheter device (Tantawy, Seliem et al. 2012, Siddiqui, Mir et al. 2011, Algra, Driessen et al. 2012, Grisaru-Soen, Paret et al. 2009, Dudeck, Horan et al. 2011, Rosanova, Allaria et al. 2009, Mastropietro, Barrett et al. 2013). Mastropietro et al (Mastropietro, Barrett et al. 2013) reported the highest rate (17.2%) in their cohort of patients limited to younger age (≤ 5yrs), higher duration of ICU stay (≥ 7 days) and higher basic Aristotle score (≥ 7). Despite the increased cardiac disease severity score (ASA score ≥ 3) reported in the Argentinian study (Rosanova, Allaria et al. 2009) the reported incidence of UTI in this population group was the lowest.

This study's setting was similar to Rosanova et al (Rosanova, Allaria et al. 2009) with approximately 350 postoperative cardiac patients admitted annually to the PICU, however our population group was younger and had a lower cardiac disease severity scoring. Strategies adopted by Tantawy et al (Tantawy, Seliem et al. 2012) in their PCICU to reduce UTI and overall HAI rates included specific urinary catheter care supervision modules and random unplanned observations of hand washing between patients of attending nurses. Adherence to infection control policies has emerged as an important intervention in reducing the incidence of UTIs in this population group (Siddiqui, Mir et al. 2011).

Table 5. Rates of UTIs in postoperative cardiac patients

Citation	Population	Sample size	Study type	Outcome	Conclusions
(Rosanova, Allaria et al. 2009)	Argentina, PICU, 0 – 18 years	350 patients post cardiac surgery	Prospective study	1% (3/350)	Underlying diseases (genetic disorders, undernutrition) (OR, 4.22 [95% CI, 1.38-1.28]; P < 0.012), inotropic support (with epinephrine) (OR, 4.04 [95% CI, 1.17- 13.9]; P < 0.027), and postoperative stay longer than 12 days (OR, 1.08 [95% CI, 1.03-1.14]; P < 0.003), were found to be risk factors for infections.
(Grisaru-Soen, Paret et al. 2009)	Israel, PICU, 0 - 18 years	356 post cardiac surgery patients, 381 admissions to the PICU	Prospective Case control study	9.6% (14/146 episodes of HAI)	Risk factors for NI: age < 2 months, congenital malformations, postoperative complications, and open-chest procedure. The authors reported a high percentage of utilisation of urinary catheters (median days of urinary catheter in the HAI group and the control group were 7 and 1, respectively).
(Dudeck, Horan et al. 2011)	USA, National Healthcare Safety Network (NHSN) Report, Data Summary for	10 hospitals, Pediatric cardiothoracic	Multicentre, retrospective	2.3 per 1000 urinary catheter days	The authors recommended that hospital facilities should use the data in the report and their own data to guide local prevention strategies and other quality improvement efforts to reduce the occurrence of HAIs.

	2010, Device-associated Module				
(Siddiqui, Mir et al. 2011)	Pakistan, CICU, under 1month – 19 years	329 post cardiac surgery patients	Prospective cohort study	3.8% (1/26)	Authors concluded that the low incidence of HAIs in the study may reflect strict implementation and adherence to the institutional Infection Control policy including strict visit regulations (one parent at a time), hand hygiene and a 1:1 nurse-to-patient ratio in high dependency/intensive care areas.
(Tantawy, Seliem et al. 2012)	Egypt, PCICU, infants under 1 – 14 years	175 patients after cardiac surgeries	Prospective study	7.5% (9/119)	Nosocomial infections were associated with poor hand hygiene and younger age.
(Algra, Driessen et al. 2012)	Netherlands, 0 - 18 years following cardiac surgeries performed with CPB	364 patients, 412 procedures, 127 infections	Retrospective study	11.8% (15/127)	Variables most predictive of an infection: age less than 6 months, postoperative paediatric intensive care unit stay longer than 48 hours, and open sternum for longer than 48 hours.
(Mastropietro, Barrett et al. 2013)	USA, PICU, < 1month – under 5 years	76 patients post cardiac surgery	Retrospective study	17.2% (10/58) (27 patients had 58 HAIs)	Prolonged duration of endotracheal intubation (OR 1.27 [95% CI, 1.03-1.55]; P = 0.023) and days of corticosteroid exposure (OR 1.47 [95% CI, 1.08-1.99] P = 0.015) were significant risk factors for infection.

Immune and inflammatory responses after cardiopulmonary bypass (CPB)

Some patients require cardiac surgery with CPB. In addition to the other factors associated with HAI, **CPB induces immune responses** that contribute to relative immunosuppression and may predispose to HAI (Wheeler, Jeffries et al. 2011, Fuhrman, Zimmerman et al. 2011). CPB in combination with ischemia-reperfusion injury, hypothermia, and surgical trauma, elicits a complex, systemic inflammatory response syndrome (SIRS) that is characterized by activation of the complement, coagulation and fibrinolytic pathways, release of endotoxin, activation of leukocytes and the vascular endothelium, and release of pro-inflammatory cytokines (Wheeler, Jeffries et al. 2011, Fuhrman, Zimmerman et al. 2011). Collectively, these pathways result in endothelial damage, capillary leak and organ dysfunction (Fuhrman, Zimmerman et al. 2011). The magnitude of this response varies (Gravlee 2008, Raja, Dreyfus 2005). SIRS in its most severe form may include one or more of the following clinical manifestations: pulmonary, renal, gut, central nervous system, and myocardial dysfunction; coagulopathy; vasoconstriction; capillary permeability; vasodilatation; accumulation of increased interstitial fluid; haemolysis; pyrexia; and increased susceptibility to infections and leucocytosis (Gravlee 2008).

Efforts to limit inflammation include design of smaller circuits to reduce requirements for blood in the prime, the use of biocompatible circuits, the addition of steroids to the prime, and the use of modified ultrafiltration at the termination of bypass (Fuhrman, Zimmerman et al. 2011). Lowering the temperature of the patient has also been shown to reduce adherence of neutrophils to the endothelium (Gravlee 2008). These manoeuvres are intended to limit blood-circuit interactions, decrease the production of mediators, and filter inflammatory mediators out of the circulation (Fuhrman, Zimmerman et al. 2011). CPB temperature has been considered but not proven to have an effect on HAI (Stocker, Shekerdemian et al. 2011).

CPB affects both the innate and adaptive immunity systems. CPB generates an unphysiologic (detrimental) innate immune response manifested as a whole body SIRS. At the same time, CPB induces the cellular and humoral constituents of the adaptive immune system to undergo quantitative and qualitative changes, leading to a temporary immunodeficiency. The degree of immunosuppression is directly related to the magnitude and duration of the surgical procedure, to the volume of transfused blood and duration of CPB (Gravlee 2008).

Longer durations of surgery and CPB time have previously been identified as independent risk factors for SSIs acquired after cardiac surgery in paediatric patients (Allpress, Rosenthal et al. 2004, Nateghian, Taylor et al. 2004). The authors (Allpress, Rosenthal et al. 2004) postulated that the reasons for this risk association included: possible increased bacterial contamination of the operative site with increased duration of surgery, and cellular damage resulting from drying and handling of tissues. Longer procedures are also a marker for more complex procedures, which is another variable that may contribute to risk of infection (Allpress, Rosenthal et al. 2004). Nahum et al reported longer duration of CPB had been associated with bacterial infection in febrile postoperative paediatric cardiac patients (Nahum, Schiller et al. 2012). An Egyptian study (Tantawy, Seliem et al. 2012) reported a significant mortality risk amongst postoperative cardiac patients who had prolonged CPB and ischemic times, and developed HAIs.

Bayer et al (Bayer, Dogan et al. 2009) demonstrated that CPB produced an absolute decrease in the number of circulating cells in most lymphocyte subsets. The most profound decreases were seen in the absolute numbers of all lymphocyte subsets in the early postoperative period (Table 6). This state of immune suppression may result in an increased risk of sepsis in children undergoing cardiac surgery for palliation or repair of CHD.

In addition, there are likely several reasons that children with CHD are at a particularly increased risk of HAIs. CPB together with several **other predisposing factors** may increase the risk and severity of infection in postoperative cardiac paediatric patients. These include chronic hypoxia and other co-morbid conditions associated with cyanotic CHD likely affecting the host immune response, as well as the need for invasive supportive devices and technology may also increase the risk of HAI in this population (Wheeler, Jeffries et al. 2011). Importantly, sepsis is a significant and independent risk factor for increased duration of mechanical ventilation, cardiac intensive care unit (CICU) LOS, healthcare costs, and mortality in children with CHD (Wheeler, Jeffries et al. 2011). Further factors associated with risk are genetic factors (e.g. 22g11 deletion or DiGeorge sequence), age (increased mortality at younger age) (Wynn, Cornell et al. 2010) and nutritional state (increased morbidity with malnutrition)(Carcillo 2005, Nguyen, Nguyen et al. 2005).

<u>Genetic and malformation syndromes</u>

There are several well described **genetic and malformation syndromes** (e.g., 22q11 deletion or DiGeorge sequence and Trisomy 21) that are associated with congenital heart malformations and defects in immunity (Wheeler, Jeffries et al. 2011). McDonald (McDonald, Dodgen et al. 2012) reported on the impact of 22q11.2 deletion on the postoperative course of children after cardiac surgery. The authors reported an increased incidence of fungal infection and wound infection in the del22q11 group, and prolonged BSIs and UTIs. Genetic and malformation syndromes may influence the clinical and surgical outcomes of congenital heart defects, both because of peculiar anatomic cardiac features and because of associated extracardiac abnormalities (McDonald, Dodgen et al. 2012) (Table 6).

Table 6. Immune studies in postoperative surgery patients

Citation	Population	Sample size	Study type	Outcome	Conclusions
(Bayer, Dogan et al. 2009)	Ankara, 16 -96 months, underwent CPB surgery	28 patients	Prospective study Peripheral blood samples were obtained preoperatively, and at 48 hours and three months postoperatively to study total lymphocyte count, T - lymphocytes, and T-lymphocyte subsets.	Total lymphocyte count and absolute total T lymphocyte (CD3+) and absolute T helper cell (CD4+) counts decreased significantly within 48 hours after CPB ($P < 0.05$). T suppressor (CD8+) and natural killer cell levels also decreased in the early period ($P < 0.05$). These values increased to preoperative values three months after cardiac surgery ($P < 0.05$).	Significant decreases in absolute natural killer cell count, total lymphocyte count, total T cells and their subsets in the early period of CPB may be due to extravasation and / or T-cell activation during and after the operation. The authors suggest that this predisposes paediatric patients to a higher risk of infections.

(McDonald, Dodgen et al. 2012)	USA, 1 day - 18 years, after cardiac surgery	173 patients, 65 patients in the 22q11 group and 108 patients in the control group	Retrospective review	Increasing numbers of patients in del22q11 group compared to the control group needed dialysis during the immediate postoperative stay 28% (18) and 14% (15) respectively ($P < 0.02$). The incidence of fungal infection (14 vs. 0 $P < 0.001$) and wound infection 18 vs. 14 $P < 0.01$) was higher in the del22q11 group than in the control group, respectively.	Children with del22q11 have a higher risk of postoperative complications after cardiac surgery, with no difference in length of mechanical ventilation, ICU LOS, hospital LOS, or mortality.

del22q11 Chromosome 22 deletion syndrome

Use of corticosteroids in postoperative paediatric cardiac patients

Children undergoing congenital heart surgery often receive **corticosteroids** with the aim of reducing the inflammatory response after cardiopulmonary bypass (Graham, Atz et al. 2011). Glucocorticoids modulate the inflammatory response, stimulate release of anti-inflammatory cytokines, and play a role in limiting capillary leak (Suominen, Dickerson et al. 2005, Kilger, Weis et al. 2003).

Studies have reported that corticosteroids are effective at reducing levels of certain inflammatory markers in this setting). However, mounting evidence questions the benefit of corticosteroids in relation to clinical outcomes (Robertson-Malt, Afrane et al. 2007, Graham, Atz et al. 2011, Pasquali, Hall et al. 2010) (Table 7).

Some studies have failed to demonstrate a significant clinical benefit associated with corticosteroids and found that corticosteroids may be associated with increased morbidity and HAIs (Pasquali, Hall et al. 2010, Pasquali, Li et al. 2012). Pasquali et al. published a study in 2010 concluding that corticosteroids were associated with longer hospital and ICU length of stay and greater infection rates. The same authors published a neonatal study in 2012 and reported no significant mortality or length-of-stay benefit associated with any methylprednisolone regimen versus no steroids, and no difference in postoperative infection. Graham et.al (Graham, Atz et al. 2011) reported on the combined preoperative and intra-operative use of glucocorticoids in neonatal cardiac surgery. They concluded that steroid use did not favourably affect early clinical outcomes (inotrope support, mechanical ventilation, hospital stay).

A study conducted by Clarizia et al 2011 (Clarizia, Manlhiot et al. 2011) found that intra-operative steroid use in children (0 – 18 years) was associated with lower chest tube volume loss in the first 24 postoperative hours, shorter durations of stay in ICU and hospital. Use of an additional preoperative dose resulted in further improvements, especially in reducing duration of mechanical ventilation. Patients in the cohort who received steroids were younger, had longer CPB and aortic cross-clamp times, and had higher incidence of delayed sternal closure. Their findings suggested that targeted use of steroids for younger, more complex patients may provide the most benefit.

However Mastropietro et al concluded that for children undergoing complex cardiac surgery, greater cumulative duration of corticosteroid exposure was independently associated with postoperative infection (Mastropietro, Barrett et al. 2013).

Table 7. Use of corticosteroids in postoperative paediatric cardiac patients

Citation	Population / Sample size	Study type / Steroid regime	Outcome	Conclusions
(Pasquali, Hall et al. 2010)	The Pediatric Health Information Systems Database was used to evaluate outcomes associated with corticosteroids in children (0 - 18 years of age) undergoing congenital heart surgery at 38 US centers, 46730 patients	Retrospective cohort study	No difference in mortality among corticosteroid recipients and non-recipients (OR, 1.13 [95% CI, 0.98-1.30]; P = 0.07). Corticosteroids were associated with longer length of stay (least square mean difference, 2.18 days [95% CI, 1.62-2.74 days]; P = < 0.001), greater infection (OR, 1.27 [95% CI, 1.10-1.46]; P = 0.001), and greater use of insulin (OR, 2.45 [95% CI, [2.24-2.67]; P = < 0.001).	No significant benefit associated with corticosteroids and corticosteroids may be associated with increased morbidity, particularly in lower-risk patients (RACHS-1: 1 to 3).
(Graham, Atz et al. 2011)	USA, 76 neonates (age < 30 days) after cardiac surgery, PCICU	Prospective randomised double-blind controlled study Methylprednisone:	The incidence of low cardiac output syndrome was 46% (17/37) in the single dose methylprednisolone (MP) group and 38% (15/39) in the 2-dose methylprednisolone group.	Preoperative and intraoperative steroid use did not favourably affect clinical outcomes (inotrope support, mechanical ventilation,

		2 dose: 30mg/kg 8 hours preoperatively and intraoperatively in the CPB prime Or 1 dose: 30mg/kg intraoperatively in CPB prime	Plasma creatinine and lactate was higher in the immediate postoperative period in the 2-dose MP group compared with single dose MP.	hospital stay). Preoperative MP dosing may exacerbate peri-operative renal dysfunction.
(Wald, Preze et al. 2011)	USA, single centre, 52 paediatric patients	Prospective cohort study	17.6% (9/51) had low (< 3mcg/dL) baseline postoperative total cortisol, yet all these patients had normal (> 9 mcg/dL) stimulation tests. The corticosteroid-binding globulin levels declined postoperatively and showed marked variability between patients. Patients with free cortisol post-stimulation > 6mcg/dL (35%) had a longer length of stay, higher inotrope scores, greater fluid requirement, and longer ventilator times.	Although hypothalamic-pituitary-adrenal axis dysfunction may play a role in low-cardiac-output syndrome among children undergoing congenital heart surgery, using total cortisol to investigate such dysfunction may be inadequate. Decreased corticosteroid-binding globulin levels and marked free cortisol increase, after stimulation, were

				associated with worse clinical outcomes.
(Clarizia, Manlhiot et al. 2011)	Canada, single centre, neonate – 5 years, 221 patients after cardiac surgery with a comprehensive Aristotle score ≥ 10	Retrospective cohort study. Methylprednisolone: 10mg/kg evening prior to surgery + 10mg/kg morning of surgery + 30 mg/kg added to bypass circuit Or 30mg/kg at induction / added to bypass prime Or No steroids	134 (61%) patients received intraoperative steroids, of these 44 (33%) also received preoperative doses. Intraoperative steroid use was associated with lower chest tube volume loss in the first 24 postoperative hours and shorter durations of stay in intensive and hospital. Use of an additional preoperative dose resulted in further improvements, especially a reduction in duration of mechanical ventilation.	Intraoperative steroid use was associated with improved postoperative outcomes for children undergoing high-risk cardiac surgery, with further benefits associated with a preoperative dose.
(Pasquali, Li et al. 2012)	USA, 3180 neonates underwent	Retrospective cohort study	22% received methylprednisolone both the day before and day of surgery, 12% on the day before surgery only, and 28% on the day of	No mortality or length-of-stay benefit (total or ICU) associated with any methylprednisolone regimen

	cardiac surgery, multicentre	Various methylprednisolone regimes vs. No steroids	surgery only; 38% did not receive any perioperative steroids.	versus no steroids in neonates undergoing heart surgery. A higher risk of infection was suggested in the lower surgical risk group overall OR, 2.6 [95% CI 1.3–5.2].
(Mastropietro, Barrett et al. 2013)	USA, PICU, < 1 month – under 5 years, 76 patients post cardiac surgery	Retrospective study	All patients received intraoperative methylprednisolone 30mg/kg, 48% received postoperative hydrocortisone, and 86% received periextubation dexamethasone.	Prolonged duration of endotracheal intubation (OR 1.27 [95% CI, 1.03-1.55]; P = 0.023) and days of corticosteroid exposure (OR 1.47 [95% CI, 1.08-1.99] P = 0.015) were significant risk factors for infection.

It is important to note that these studies differ in patient and surgical characteristics (age, surgical complexity) and that the administration of steroids differs in terms of time of administration and type of steroid used. Retrospective data review is subject to the limitations of the available data in medical records or databases. There may be other unmeasured patient or center factors that affect the receipt of corticosteroids and / or outcome. These may include, among others, those relating to cardiopulmonary bypass protocols, which may vary from center to center, such as the use of modified ultrafiltration (Elliott 1993, Andreasson, Gothberg et al. 1993). It is possible that some of these factors may be confounding factors not accounted for in the analyses (Pasquali, Hall et al. 2010).

Clarizia et al admitted that the retrospective nature of their study meant that selection bias could not be entirely excluded regarding which patients received steroids despite the use of a propensity score to adjust for nonrandom assignment. Secondly, while reporting beneficial effects of combined preoperative and intraoperative dosing, they were unable to assess outcomes associated with preoperative administration alone, or infer an optimal timing for administration of both the intraoperative and preoperative dose (Clarizia, Manlhiot et al. 2011).

These studies do not provide a clear consensus of whether corticosteroid use reduces risk of acquiring HAIs in this population group. The studies rather suggest that emphasis should be on reducing cumulative corticosteroid exposure in postoperative cardiac surgery patients in order to reduce risk of developing HAIs.

<u>Red blood cell (RBC) transfusion in paediatric cardiac surgery patients</u>

Costello et al reported that younger patients undergoing longer surgical procedures and those requiring more postoperative blood transfusions were at greatest risk for SSI (Costello, Graham et al. 2010). These findings were supported by a study done by Salvin et al. (Salvin, Scheurer et al. 2011) who reported that patients requiring RBC transfusion were younger, more likely to have single ventricle physiology, required more complicated cardiac surgery, and were more acutely ill than those in the low transfusion (< 15ml/kg) or non-transfusion groups. RBC transfusion was associated with longer hospital length of stay, and the strongest association was found in the high transfusion group (> 15ml/kg).

These authors suggested that further investigation is required into whether additional preventive strategies, including restrictive blood transfusion policies may reduce the risk of HAI.

Perioperative antibiotic use in paediatric cardiac surgery patients

Prophylactic antibiotics (Table 8) are routinely given to patients undergoing cardiac surgery to prevent the occurrence of nosocomial infections. Prolonged maintenance of therapy seems to increase the incidence of multiresistant strains, whereas limitation thereof does not seem to lead to a greater incidence of nosocomial infection (Kato, Shime et al. 2007). Kato et al further recommended that the implementation of a protocol of perioperative antimicrobial prophylaxis in pediatric cardiac surgery, supervised by an infection control expert, might reduce rates of postoperative infection, development of resistant pathogens, and lower antibiotic-related costs.

Guidelines by the Society of Cardiothoracic Surgeons recommend that antibiotic use be limited to 48 or even 24 hours (Bratzler, Houck et al. 2005, Edwards, Engelman et al. 2006). A study conducted by Alvarez et al (Alvarez, Fuentes et al. 2012) reported that prolonged antibiotic prophylaxis increased the infection rate in postoperative cardiac patients. The study findings supported the statement that limiting antibiotic prophylaxis to ≤ 48 hours post surgery does not increase the HAI rate.

Postoperative administration of antibiotics is thus an effective prophylaxis strategy to reduce the risk of acquiring HAI in postoperative cardiac patients. It is recommended that duration of use be limited to ≤ 48 hours to reduce risk of developing resistant organisms.

Table 8. Perioperative antibiotic use in paediatric cardiac surgery patients

Citation	Population	Sample size	Study type	Outcome (%)	Conclusions
(Kato, Shime et al. 2007)	Japan, PICU, neonate – 18yrs, single centre, after cardiac surgery	390	Prospective interventional study In the intervention group: prophylaxis was recommended to be discontinued < 48 hours postoperative and, glycopeptides were strongly recommended for patients at high risk of methicillin - resistant *Staph.aureus*	SSI: (0% vs. 18%) and HAI: (11% vs. 39%) were significantly lower in the intervention group than in the control group. Antimicrobials were administered for a median of 4 days (range 2 – 14) in the intervention group, 7 days (3 – 35) in controls.	There was a trend toward a lower frequency of postoperative infections, significantly lower costs of antimicrobial therapy and a significantly lower rate of newly acquired nasal colonisation with antibiotic-resistant pathogens in the intervention group (8%) than in controls (17%). Limiting the duration of prophylactic antimicrobials was cost-effective and reduced the risk of acquiring resistant pathogens without increasing the frequency of postoperative infections. The use of glycopeptides in selected patients at high risk of methicillin-resistant *Staph. aureus* infection can lower the risk of postoperative infections.
(Alvarez, Fuentes et al. 2012)	Spain, neonate – 14 years, after	194 patients	Retrospective cohort study	HAI rate = 11.9% SSI rate = 9.1%	Prolongation of antibiotic prophylaxis > 48 hours, central venous access maintenance time, and intubation increased the infection rate.

	cardiac surgery, ICU			The median duration of antibiotic prophylaxis was 72 hours (range 24 to 176), with the most-used prophylaxis regimen being second - generation cephalosporins plus aminoglycosides.	The suspension of antibiotic prophylaxis in the 48 hours after surgery did not increase the incidence of nosocomial infection.

Diagnosis and treatment of HAIs

As mentioned above, cardiac surgery with extracorporeal circulation (CPB) often evokes a systemic inflammatory response syndrome (SIRS). Fever is the main symptom, and intervention is usually not necessary. However, sometimes fever following cardiac surgery is a sign of early bacterial infection warranting antibiotic therapy (Nahum, Schiller et al. 2012). Sensitive and specific markers of infection are, therefore, needed to distinguish patients with systemic infection from unwell patients who are not septic or those infected with viruses. A summary of studies identifying reliable **s**eptic markers in postoperative cardiac patients is presented in Table 9.

Among several inflammatory markers used are procalcitonin (PCT), C-reactive protein (CRP) and immature leukocytes (bands) (McMaster, Park et al. 2009). SIRS also causes increases in these inflammatory markers, which may make the accurate clinical and laboratory diagnosis of infection in the post-CPB patient difficult (McMaster, Park et al. 2009). **Appropriate treatment of sepsis** relies on early and accurate **diagnosis** and contributes to reduced morbidity and mortality (Hatherill, Tibby et al. 1999). Conversely, more accurate diagnosis of sepsis will reduce unnecessary antibiotic use and hence reduce the risk of selecting out resistant organisms.

Procalcitonin (PCT) has relatively recently been considered to be one of the best markers of bacterial infection with many advantages. It is an indicator that arises early, with a peak 6 -12 hours after bacterial stimulus, and a half-life of 24 - 30 hours (unlike CRP). It is considered to offer greater sensitivity and specificity for both invasive and non-invasive infection and allows better differentiation between viral and bloodstream infections than C-reactive protein (Nahum, Schiller et al. 2012, Garcia, Gargallo et al. 2012). The value of PCT may be uncertain after surgery since it may increase moderately in the case of SIRS, as a result of surgical stress due to CPB, without the presence of infection. There are limited and conflicting data on the value of PCT in the postoperative period in children and regarding its superior discriminatory power compared to other markers of infection after CPB (Garcia, Gargallo et al. 2012, Beghetti, Rimensberger et al. 2003, Rey, Los Arcos et al. 2007).

Nahum et al. 2012 (Nahum, Schiller et al. 2012) conducted a study of 665 patients following paediatric cardiac surgery and reported significantly higher PCT levels in febrile patients with proven bacterial infection (median 5.9 ng/ml vs. median 0.85 ng.ml ($P = 0.04$). Garcia 2012 (Garcia, Gargallo et al. 2012) also found PCT a useful biomarker to discriminate infection after CPB in children. This study found the optimal cut off for procalcitonin was > 2 ng/mL at day 1 and > 4 ng/mL at day 2. There was a greater sensitivity and specificity than with CRP as an infection predictor.

A combined UK / Australian study (McMaster, Park et al. 2009) compared PCT versus C-reactive protein and immature-to-total neutrophil ratio (ITR) as markers of infection after CPB in children. This study confirmed in children the findings from adults that PCT concentrations may increase after CPB even in the absence of infection. CRP was found to be a poor marker of sepsis in this study and children with a PCT < 2.2 ng/mL or ITR < 0.08 were unlikely to have definite or probable sepsis. The authors suggested that an increase in the marker is more likely to suggest infection than a single value, particularly in the first days post-bypass. This study supported findings by Celebi et al that daily PCT measurements in patients might help identify postoperative infections (Celebi S, Koner O, et al, 2006).

Seguela (Seguela, Joram et al. 2011) conducted a French study to evaluate the diagnostic value of PCT as a marker of infection after CPB in children The study reported that the best cut-off value to differentiate infected children from healthy children was 13 ng/mL with 100% sensitivity and 85% specificity, before the third postoperative day. The authors suggested that a PCT done earlier during the postoperative period avoided unnecessary treatment or non-initiation of treatment of infections. In addition, the authors commented that McMaster et al (McMaster, Park et al. 2009) were interested only in overall PCT values until the fifth postoperative day and that no distinction had been made according to the normal PCT rise in the immediate 2–3 days after cardiopulmonary bypass (Seguela, Joram et al. 2011). Seguela suggested therefore that high PCT values of the initial postoperative days, before the third postoperative day, might have been reduced enabling earlier detection of infection. The authors further recommended the PCT measurement be repeated during the postoperative period (Seguela, Joram et al. 2011) to guide the clinician regarding antibiotic treatment duration.

A study conducted by Nguyen-Vermillion et al (Nguyen-Vermillion, Juul et al. 2011) showed that the perioperative patterns of CRP differed by diagnosis and inflammatory state. The authors concluded that serial measurements might be more informative than CRP magnitude. This was supported by a study done by Nahum et al (Nahum, Livni et al. 2012) who reported on serial measurements of **C-reactive protein (CRP**) and whether **CRP velocity** (rate of the change in CRP from the morning after surgery to fever day) after cardiac surgery in children may assist clinicians in differentiating postoperative fever due to bacterial infection from fever due to non-infectious origin. The authors reported a highly significant change in CRP over time among febrile patients with proven bacterial infection compared with febrile patients without bacterial infection group. The further suggested that

CRP / CRP velocity should not serve as the sole tool for this purpose, and it should be combined with other clinical and laboratory data and good clinical judgment (Nahum, Livni et al. 2012).

These studies differ in sample size, population characteristics, institutional infection rates, postoperative management protocols and antibiotic protocols. These factors limit the extrapolation of their findings to other institutions and population groups. An important point to note from the studies is the trend of changes over time rather than an absolute value when using these markers to diagnose infection in postoperative cardiac patients. A second important point is that in children who develop proven or suspected bacterial sepsis, PCT has been found to be a more useful marker than CRP or ITR, where these values are more affected by CPB. PCT changes more quickly than ITR, and the test is more reproducible resulting in the earlier initiation of antibiotic therapy. PCT and ITR had good negative predictive power, meaning that a child with a normal test was unlikely to have sepsis so that antibiotics can be withheld or stopped sooner (McMaster, Park et al. 2009).

Table 9. Septic markers in postoperative cardiac patients

Citation	Population	Sample size	Study type	Outcome	Conclusions
(Celebi S, Koner O, et al, 2006)	Turkey, 0 - 7 years, post cardiac surgery, ICU	33 patients	Prospective observational study	Double-peak PCT curves were observed in the systemic inflammatory response syndrome and organ failure (SIRS+OF) patients with infection during the intensive care unit stay.	In the SIRS+OF group of patients, peak PCT levels were found to be highly predictive for mortality and organ failure development, whereas CRP levels were not.
(McMaster, Park et al. 2009)	UK and Australia, neonate – 20 years, PICU	283 patients	Prospective interventional cohort study	Serum PCT concentration > 2.2 ng/mL was the best cut-off value for the diagnosis of sepsis, 84% sensitivity and 72% specificity. Positive Predictive Value of 32% meaning, only a third of children with high values of PCT and ITR had definite or probable sepsis.	CRP was a poor marker of sepsis. Children with a PCT < 2.2 ng/mL or ITR < 0.08 were unlikely to have definite or probable sepsis.
(Nguyen-Vermillion, Juul et al. 2011)	USA, neonates ≤ 44 weeks corrected gestational age,	55 patients	Prospective interventional study.	Surgery alone did not cause an increase in CRP: CRP remained < 1.0 mg/dL at all time points in 24% of patients. CRP values can increase during the postoperative period but the CRP values	Serial measurements may be more informative than CRP magnitude.

	undergoing thoracic / abdominal surgery			decline on postoperative day 3 in the absence of infection.	
(Garcia, Gargallo et al. 2012)	Spain, PICU, ≥ 1 month – 16 years, after cardiac surgery with CPB	231	Prospective study	HAI rate = 9.5% (22/231) Significant differences were detected in the PCT values of the infected group vs. the noninfected group, especially at day 2 (P = 0.000). There were no differences in the CRP values. The optimal cutoff for PCT was > 2 ng/mL at day 1 and above 4 ng/mL at the day 2.	The evolution of PCT values after CPB was useful in the diagnosis of bacterial infection as a postoperative complication. There was a greater sensitivity and specificity than with CRP as an infection predictor.
(Nahum, Livni et al. 2012) Role of CRP velocity	Israel, neonate – 18 years, post cardiac surgery requiring CPB	121 patients	Prospective case - controlled study	Mean CRP velocity ([fCRP – 18hCRP]/ [fever time (days) – 0.75 day]) was significantly higher in the infectious group (4.0 + 4.2 mg/dL per d) than in the fever-only group (0.60 +1.6 mg/dL per d; P < .001). A CRP velocity of 4 mg/dL per day had a positive predictive value (PPV) of 85.7%	Serial measurements of CRP/CRP velocity after cardiac surgery in children may assist clinicians in differentiating postoperative fever due to bacterial infection from fever due to noninfectious origin.

				for bacterial infection with 95.2% specificity.	
(Nahum, Schiller et al. 2012) PCT level	Israel, after cardiac surgery with CPB	665 patients	Prospective case - controlled study	Higher PCT level in the group with fever and bacterial infection than in the group with fever only (median 5.9 ng/mL, 25th/75th percentiles 0.7and 12.4 ng/mL; median 0.85 ng/mL, 25th/75th percentiles0.5 and 1.6 ng/mL, respectively; P = 0.04) PCT value of 1.9ng/mL had a positive predictive value of 80.5% with 84.2% specificity for identifying bacterial infection.	PCT level may help to differentiate patients with bacterial infection from patients in whom the fever is secondary to nonbacterial infectious causes after cardiac surgery.
(Seguela, Joram et al. 2011)	France, PICU, ≥ 3days – 15 years after cardiac surgery with CPB	95 patients	Retrospective study	Before the third postoperative day, PCT median concentration was significantly higher in the infected group 20.24ng/mL (IQR 15.52–35.71) compared to 0.72 ng/mL (IQR 0.28 - 5.44) in the non-infected group (P = 0.008).	PCT was a discriminating marker of bacterial infection during the postoperative days following cardiopulmonary bypass in children. The authors suggested that after the 3rd postoperative day, a second assay at a 24

					hour interval could improve the sensitivity of the test.

SIRS+OF Systemic inflammatory response syndrome and organ failure

NEEDS FOR FUTURE RESEARCH

Studies detailing the epidemiology of HAIs in postoperative cardiac patients have identified various risk factors and suggested many management strategies for preventing and treating infections in this population group. Presently there are no South African paediatric studies of HAIs in cardiac surgery patients. The studies thus far have been limited by various factors that prevent the extrapolation of findings to this institution and the subgroups of postoperative cardiac patients.

Future studies need to be more homogenous in terms of:

- Study type: prospective randomised controlled studies or cohort studies are required
- Study population: age groups such as the high risk neonatal group, adequately powered study
- Associated co morbidities: genetic and malformation syndromes, nutrition state
- Surgical complexity category
- Infection control practices: preoperative, intraoperative and postoperative including: chlorhexidine body washing protocols, antimicrobial prophylaxis, antibiotic treatment, wound care, management of catheter device associated infection protocols, infection surveillance protocols
- Preoperative care: duration of hospital stay preoperatively, infection surveillance protocols
- Intraoperative care: CPB and surgical practices including sternal closure policies
- Postoperative care: duration of mechanical ventilation, use of blood and blood product protocols, staff to patient ratios, glucose control protocols

Recurring risk factors within the studies are younger age especially the neonatal age group and age < 2months, low birth weight, increased surgical complexity, increased duration of ICU and hospital stays, prolonged ventilation, prolonged use of catheter devices and adherence to infection control and prevention policies.

Factors not clearly associated as risk factors were: corticosteroid use perioperatively, open chest postoperatively, hyperglycaemia postoperatively, presence of genetic abnormality and previous cardiothoracic surgery. The questions still to be answered include:

- What are the specific risk factors for HAI for the individual postoperative cardiac paediatric patient and how are these to be addressed?
- Does reducing specific risk factors have a clinically relevant implication on outcome for HAIs, in reducing associated morbidity and mortality?

It is evident that the associated factors contributing to the risk for HAIs are multifactorial. Further studies are needed to identify modifiable factors such as presence of a viral or bacterial infection in the preoperative period, anemia, increased duration of hospitalisation prior to surgery, prolonged use of intravascular catheters, staffing resources. Currently, inconsistencies in information exist within these identifiable risk factors, methods to reduce infection rates and how these methods affect clinical outcomes in the post surgical cardiac paediatric patient. It is noticeable that studies investigating the role of viruses in perioperative HAIs in paediatric cardiac patients have been limited and this needs to be addressed.

The aim of identifying these risk factors in the cardiac surgery patient and rectifying inconsistencies in information would be to develop strategies for preventing and optimising management of HAIs in postoperative paediatric cardiac patients.

CHAPTER 3

AIM

The aim of the study was to determine the incidence of HAIs in postoperative cardiac patients admitted to the PICU at the Red Cross War Memorial Children's Hospital (RCWMCH).

OBJECTIVES

- To describe risk factors associated with HAIs in all children following cardiac surgery
- To describe morbidity associated with HAIs versus uninfected patients
- To describe the outcomes of patients (mortality, duration of PICU and hospital stay) with HAI compared to those who did not develop HAI
- To identify possible strategies for preventing infections and optimising clinical management

The information collected from this study could highlight the impact of acquired infections in post cardiac surgery patients. Measures can be identified to reduce and prevent resulting morbidity and mortality in this group of patients. This study will provide the baseline against which future practice improvement initiatives can be compared and benchmarked.

MATERIALS AND METHODS

RCWMCH is a tertiary academic hospital affiliated with the University of Cape Town, South Africa. It has a multidisciplinary twenty bed PICU that admits approximately 1200 patients per year, of which 250 – 300 are admitted postoperatively following cardiac surgeries.

This was a prospective observational study of all patients admitted to the PICU at RCWMCH following cardiac surgery during the period 19 September 2011 to 19 March 2012. There were no exclusion criteria.

Ethics approval was obtained from Faculty of Health Sciences Human Research Ethics Committee, University of Cape Town (Appendix 2).

Admitting wards were defined as the ward the patient was admitted from > 24 hours prior to going to theater. When a patient was admitted to a hospital ward on the morning of surgery, the patient was accepted as an admission from home. Some patients stayed with their mothers in the mother's accommodation (usually shared accommodation with parents of other children in the hospital) and were defined as being admitted from the Mother's room.

All children were weighed in their admitting wards prior to surgery by the nursing staff present on the patient's admission. Height (standing in toddler or older child) and length (neonate / infant) were documented in the admitting wards on the day of admission or checked by the principal investigator if not previously documented.

Daily data were collected, using a standardised data collection form, by the principal investigator (Appendix 3). Demographic, clinical, procedural and microbiological data were collected from the patients' medical records; and haematology, chemical pathology and microbiology laboratory records. Each patient was evaluated daily for evidence of a HAI. Data collected included:

a) Date / time of hospital and PICU admission and discharge.

b) Patient characteristics: age, growth parameters (height / length and weight data were collected and then expressed as a proportion of expected weight for age and expected height for age using World health organisation (WHO) standards), cardiac defect type, previous cardiac surgery details, preoperative medications.

c) Surgical information: type of surgical procedure and operation details.

d) Markers of inflammation: temperature, PCT, WCC, bands, haemoglobin, platelet count, glucose readings, pulmonary secretions, PaO_2 / FiO_2 ratio, chest radiography findings. The worst values over the preceding 24 hours were recorded. Data was recorded on a standardised form following the morning consultant ward round in ICU.

e) Identification of positive cultures including the identification of the pathogen and the infection source (wound, urine, chest, blood, CRBSI etc.).

f) Opinion of physician treating the patient whether the infection required treatment.

g) Antibiotics provided.

h) Details of events postoperatively: Bleeding, reintubation, cardiac arrest, chest-reopened, organ failure.

OPERATIVE MANAGEMENT OF PAEDIATRIC CARDIAC PATIENTS

In our institution different anaesthetists and five cardiothoracic surgeons shared the surgical work list. All patients undergoing cardiac surgery had percutaneously placed intravascular central lines before or at the time of surgery. Plain uncoated catheters were used as intravascular central lines in all patients. Anaesthetists generally placed the catheters at the time of surgery or the physician in the PICU before surgery placed the catheters. Atrial and ventricular pacing wires were placed by the cardiothoracic surgeons as well as transthoracic and transatrial lines if required.

The standard protocol in place during the study period was that all patients undergoing cardiac surgery received intravenous cefazolin 50 mg/kg/dose at the start of surgery and 6 hourly thereafter until the completion of surgery. A minimum of two doses were given, the second dose in PICU if operation duration was less than six hours. The patients with an open chest postoperatively were intended to receive 6 hourly doses of cefazolin until the chest was closed. “Adequate antibiotics given” was defined as complying with the above regimen. “Inadequate antibiotics” was defined as poor adherence to correct dosing, incorrect timing of antibiotic prophylaxis and doses not being prescribed.

Steroids were not administered according to a standard protocol during the study period. Intraoperatively, steroids were given at the discretion of the attending anaesthetist who decided on dosage, frequency and type of steroid if administered.

Patients who underwent cardiac surgery with CPB had CPB commenced using a Kids Infant oxygenator (Sorin® / KiDS®) together with a standard in-line filter. The priming solution consisted of packed red blood cells or stabilised human serum (SHS). Intermittent antegrade infusion of cold crystalloid St. Thomas solution No. 2 (Plegisol®, MMCTSLink 87) was administered as cardioplegia. The degree of hypothermia used (moderate – deep) and the use of ultrafiltration during rewarming was based on cardiothoracic surgeon / anaesthetic opinion.

The indication for delayed sternal closure was decided by the cardiothoracic surgical team and usually included the more complex surgical cases. Chest closure was done in the PICU within 48 hours post surgery unless further complications arose preventing chest closure (e.g. massive fluid overload, cardiovascular instability).

PROTOCOLS FOR THE CARE OF POSTOPERATIVE CARDIAC PATIENTS ADMITTED TO THE PICU

Four paediatric intensivists led PICU management with consultation from the cardiothoracic surgery team. Analgesia was sustained with continuous infusions of morphine and, if deemed necessary by the attending PICU physician, midazolam infusion and / or oral clonidine was added.

All catheters and skin sites were checked routinely as part of daily nursing care. The catheters were covered with sterile transparent adhesive cover after initial insertion. Routine change of central lines has not been adopted as a policy in our unit. Central lines are changed if there is a specific indication, including: local inflammation, leakage, suspected infection, or catheter malfunction. Routine infection control measures in the PICU stipulated that each time a central intravascular line was accessed, a sterile gauze pack with 0.5% chlorhexidine gluconate in 70% alcohol was used to clean the line port and to provide a sterile working surface.

On admission to the PICU postsurgery the patient had routine bloods taken, including arterial blood gas, full blood count, electrolytes, urea, creatinine and a coagulation profile. Thereafter the full blood count, arterial blood gas and renal markers were repeated four hourly for 24 hours. The coagulation profile was repeated if clinically indicated (signs of bleeding) or previously abnormal. All patients had routine chest radiography on admission to ICU following cardiac surgery. Radiography was repeated based on clinical assessment and physician decision.

Fever (>38°C) within the immediate 24 hour postoperative period was only investigated further if clinically indicated by increased inflammatory markers (increased WCC, immature leukocyte count or leucopaenia / neutropaenia) on routine bloods taken postsurgery, increasing organ dysfunction (hypotension, hypothermia, apnoea, vomiting, bradycardia, increased or altered pulmonary secretions) and criteria meeting the definitions of HAIs. The investigation guidelines used when an infection was suspected in the postoperative cardiovascular patients are shown in Appendix 4. The flow diagram was developed by consensus through a working group in the PICU. According to the guidelines for infection investigation all patients would have a blood culture done under sterile conditions when infection was suspected. One or more blood cultures were taken using a sterile technique via intravascular central lines or peripherally when clinically indicated for suspected BSI. Blood cultures were taken from the arterial catheter when available. If the arterial catheter could not be accessed to withdraw blood then the central venous catheter was used. If no central intravascular lines were accessible then a sterile peripheral blood culture was done. Urine dipstick via sterile urinary catheter collection was checked for nitrates / leukocytes and if positive was sent to the laboratory for microscopy, culture and sensitivities (MCS).

All wound sites were reviewed for pain, tenderness, localised swelling, redness, heat and pus. If any of these were present a pus swab was collected using an aseptic technique and sent for microscopy, culture and sensitivity investigation (MCS). Patients were not routinely screened for resistant organisms (MRSA) pre- or postoperatively.

Clinical signs and laboratory markers of infection appearing within 48 hours after cardiac surgery were considered to indicate infection acquired prior to surgery. The increasing trend of PCT, leukocyte count and immature leukocyte count or the presence of leucopoenia / neutropaenia were used as indicators of infection within the clinical context of signs of suspected infection. In accordance with the CDC definitions for diagnosing HAIs and CPIS criteria for diagnosing VAP during this study total leukocyte count and immature leukocyte count were used. In addition the physician treating the patient used these markers with trend of increasing PCT as indicators of infection. According to the the study protocol, specimens were to be collected on patients when an infection was suspected and required further investigation. Due to this study being observational I did not intervene in patient management by dictating to the attending physician when to collect or not collect the specimens. I recorded the results of all specimens collected from the study patients during their PICU admission.

For the purposes of this study, PICU hospital acquired infection (related to cardiac surgery) was defined as an infection not present or incubating at the time of PICU admission after cardiac surgery, with an onset of at least 48 hours postoperatively. Patients with an infection or on antimicrobials prior to surgery were not excluded from the study. Patients who developed infection within 48 hours after cardiac surgery and had not been in a hospital facility were defined as having a community-acquired infection. Patients who developed infection within 48 hours after cardiac surgery and had been in a hospital facility (ward other than PICU, mother's room area, other hospital) were defined as HAI outside PICU.

The definitions of Laboratory confirmed blood stream infections (BSI), urinary tract infections (UTI), and surgical site infections were based on the Centre of Disease control criteria (http://www.cdc.gov/ncidod/dhqp/pdf/nnis/NosInfDefinitions.pdf) (Appendix 5).

CDC definition of BSI:

- Patient has a recognised pathogen cultured from one or more blood cultures *and* organism cultured from blood is not related to an infection at another site
  or
- Patient has at least one of the following signs or symptoms: fever (>38ºC), chills, or hypotension *and* positive laboratory results are not related to an infection at another site
  or
- Patient ≤ 1 year of age has at least one of the following signs or symptoms: fever (> 38ºC core), hypothermia (< 36ºC core), apnea, or bradycardia *and* positive laboratory results are not related to an infection at another site

CDC definition of UTI:

- Patient had an indwelling urinary catheter in place for >2 calendar days, with day of device placement being Day 1, and catheter was in place on the date of event *and* at least 1 of the following signs or symptoms: fever (> 38°C); suprapubic tenderness*; costovertebral angle pain or tenderness* *and* a positive urine culture of ≥ 105 colony-forming units (CFU)/ml with no more than 2 species of microorganisms. Elements of the criterion must occur within a timeframe that does not exceed a gap of 1 calendar day between two adjacent elements

  or

- Patient had an indwelling urinary catheter in place for > 2 calendar days and had it removed the day of or the day before the date of event *and* at least 1 of the following signs or symptoms: fever (> 38°C); urgency*; frequency*; dysuria*; suprapubic tenderness*; costovertebral angle pain or tenderness* *and* a positive urine culture of ≥105 colony-forming units (CFU)/ml with no more than 2 species of microorganisms. Elements of the criterion must occur within a timeframe that does not exceed a gap of 1 calendar day between two adjacent elements

***With no other recognised cause**

CDC definition of SSI:

<u>Deep incisional SSI:</u>

- Infection occurs within 30 or 90 days after the operative procedure (where day 1 = the procedure date) *and*

involves deep soft tissues of the incision (e.g., fascial and muscle layers) *and* patient has at least one of the following:

a.) purulent drainage from the deep incision b.) a deep incision that spontaneously dehisces or is deliberately opened by a surgeon, attending physician** or other designee and is culture-positive or not cultured *and* patient has at least one of the following signs or symptoms: fever (>38°C); localised pain or tenderness. A culture-negative finding does not meet this criterion. c.) an abscess or other evidence of infection involving the deep incision that is detected on direct examination, during invasive procedure, or by histopathologic examination or imaging test.

<u>Organ/Space SSI:</u>

- Infection occurs within 30 or 90 days after the operative procedure (where day 1 = the procedure date) *and*

infection involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure *and* patient has at least 1 of the following:

a.) purulent drainage from a drain that is placed into the organ/space b.) organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space c.) an abscess or other evidence of infection involving the organ/space that is detected on direct examination, during invasive procedure, or by histopathologic examination or imaging test *and* meets at least one criterion for a specific organ/space infection site.

<u>Superficial incisional SSI:</u>

Infection occurs within 30 days after any operative procedure (where day 1 = the procedure date), *and* involves only skin and subcutaneous tissue of the incision *and* patient has at least 1 of the following:

a.) purulent drainage from the superficial incision b.) organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision c.) superficial incision that is deliberately opened by a surgeon, attending physician or other designee and is culture-positive or not cultured *and* patient has at least one of the following signs or symptoms of infection: pain or tenderness; localised swelling; redness; or heat. A culture negative finding does not meet this criterion d.) diagnosis of superficial incisional SSI by the surgeon or attending physician or other designee.

CDC Definition for pneumonia

Radiology

Two or more serial chest radiographs with at least **one** of the following: a.) New or progressive and persistent infiltrate b.) Consolidation c.) Cavitation d.) Pneumatoceles, in infants ≤1 year old

NOTE: In patients **without** underlying pulmonary or cardiac disease (e.g., respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary edema, or chronic obstructive pulmonary disease), one definitive chest radiograph is acceptable.

Signs / Symptoms

At least **one** of the following: a.) Fever (>38°C or >100.4°F) b.) Leukopenia (<4000 WBC/mm3) or leukocytosis (≥12,000 WBC/mm3)

For adults ≥70 years old, altered mental status with no other recognized cause *and* at least **one** of the following: c.) New onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements d.) New onset or worsening cough, or dyspnea or tachypnea e.) Rales or bronchial breath sounds f.) Worsening gas exchange (e.g., O2 desaturations [e.g., PaO2/FiO2 ≤240], increased oxygen requirements, or increased ventilator demand

Laboratory

At least **one** of the following: a.) Positive growth in blood culture not related to another source of infection b.) Positive growth in culture of pleural fluid c.) Positive quantitative culture from minimally contaminated LRT specimen (e.g., BAL or protected specimen brushing) d.) ≥5% BAL-obtained cells contain intracellular bacteria on direct microscopic exam (e.g., Gram's stain) f.) Histopathologic exam shows at least **one** of the following evidences of pneumonia:

- Abscess formation or foci of consolidation with intense PMN accumulation in bronchioles and alveoli
- Positive quantitative culture of lung parenchyma
- Evidence of lung parenchyma invasion by fungal hyphae or pseudohyphae

All patients suspected of UTI had a urinary dipstick done on urine obtained from a urinary catheter checking for leukocyte esterase and/or nitrate. If the dipstick was positive for nitrates / leukocytes then urine was sent to the microbiology laboratory for microscopy, culture and sensitivity testing. Due to limitations in follow up of the patients the investigation for surgical site infection was confined to acute infections presenting during the admission to the intensive care unit, infections reported during the postoperative stay in the cardiology ward and if a patient was readmitted to the PICU.

Considering that routine daily chest radiography is not practiced in this PICU, VAP was diagnosed using a modification of the Clinical Pulmonary Infection Score (CPIS), which has been found to be an effective and appropriate diagnostic system in this study site (Morrow, Argent et al. 2009, Morrow, Mowzer et al. 2012). The CPIS (Appendix 3) was calculated daily and assessed for development of VAP, as indicated by a score of ≥ 6 or an increase of > 2 from the previous score.

When ventilator associated pneumonia was suspected, a nonbronchoscopic bronchoalveolar lavage (BAL) or tracheal aspirate, white cell count, differential count and chest radiography was done. CPIS was included in the data collection form (Appendix 3). When the attending PICU consultant considered patients to be too unstable from a haemodynamic or ventilatory point for a BAL, a tracheal aspirate was done instead of a BAL. Towards the end of the study period, during February 2012, the PICU at RCWMCH introduced the VAP bundle of care and changes to the utilisation of ventilator circuits were made (Personal communication, A Argent).

Event definitions: Bleeding was defined as an event if additional treatments were needed, during and immediately postsurgery, to restore haemodynamic compromise including intravenous colloid / crystalloid solutions; blood or blood products or increased inotrope support was required. Any coffee ground aspirates noted was recorded as a complication indicating possible gastritis. Coagulopathy was defined as measurements that were beyond normal for the patient age range within the clinical context of a bleeding / at risk patient (National Health Laboratory Service (NHLS), South Africa). Systolic blood pressure limits were determined individually for each patient and the decision to treat hypertension / hypotension was determined by the attending PICU physician, cardiothoracic surgeon or anaesthetist.

Descriptors for organ dysfunction were based on the Pediatric Logistic Organ Dysfunction score (PELOD) definitions (Leteurtre, Martinot et al. 1999, Leteurtre, Duhamel et al. 2010). Organ failure focussed on renal, central nervous system and liver dysfunction.

Underweight for age was defined according to WHO growth chart standards: < -2 (standard deviation) SD of mean. Severely underweight was defined according to WHO growth charts: < -3rd SD of mean.

At RCWMCH PICU there was not a specific transfusion policy in place regarding blood transfusions in postoperative cardiac patients. The decision to transfuse was made by the attending physician (and cardiac surgeon) and generally depended on the blood loss and haemodynamic state of the patient and oxygenation requirements of the patient.

CONSENT

This study entailed observational research of a non-therapeutic and non-invasive nature and there was no increased risk and no interference with the mental or physical integrity of the patients involved in the study. The need for informed written consent was therefore waived by the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee.

DATA ANALYSIS

Data were collected prospectively in a standardized manner and stored in an MS Access (2007) database (Microsoft, Redmond, WA). After data collection was complete, descriptive statistical analysis was conducted as well as appropriate tests for comparing continuous and categorical data between groups with and without different categories of HAI.

Continuous variables were tested for normality using the Shapiro-Wilks *W* test. Univariate comparisons for continuous and categorical variables were performed using Mann-Whitney *U* and chi-square tests (or the Yates corrected chi-square test when cell values were < 10) respectively, with STATISTICA, version 8 (StatSoft, Tulsa, USA). Potential risk factors identified in the univariate analysis were then entered into stepwise logistic regression models using an online statistical program (Logistic Regression, http://statpages.org/logistic.html). A 95% significance level was set.

CHAPTER 4

RESULTS

PATIENTS

A total of 110 patients undergoing 126 cardiac surgical procedures were enrolled into the study. Patient characteristics, comorbid conditions and admission routes are presented in Table 10.

Table 10. Study population characteristics of all patients

Characteristics of study population	**n = 110 patients enrolled in study**
Male n (%)	47 (42.7%)
Age (months)	19 (6 – 72)
Weight (kilograms)	8 (5 – 16)
Normal	57 (51.8%)
Underweight (WHO growth charts: < -2 SD of mean)	40 (36.4%)
Severely underweight (< -3rd SD of mean)	13 (11.8%)
Height	
Normal (WHO growth charts: > -2 SD of mean)	99 (90%)
Stunted (< -2 SD of mean)	11 (10%)
Admitted	
From Mother's room	13 (11.8%)
Ward	82 (74.5%)
Neonatal ICU at referral hospital	1 (1%)
Home	5 (4.5%)
PICU	8 (7.2%)
Genetic syndromes and malformation syndromes	24 (22%)
Pre-existing medical illness	47 (42.7%)
Previous cardiac operation	28 (25.5%)
Ventilated prior to cardiac operation	9 (8.1%)
HIV status	
Exposed	13 (11.8%)
Infected	0
Unknown	1
History of prematurity	9 (8.2%)

Continuous data are median (interquartile range); categorical data are n (%)

HIV Human immunodeficiency virus WHO World health organisation

SD Standard deviation

COMORBID CONDITIONS

Genetic and congenital malformation syndromes in all patients admitted to the study

Of the 24 (22%) patients with genetic / malformation syndromes: 12 (10.9%) had Trisomy 21; three (2.7%) foetal alcohol syndrome; two (1.8%) 22Qdeletion; two (1.8%) William syndrome and one patient each had the following syndromes: retinoic acid embryopathy, Beckwith-Wiedeman syndrome, Goldenhar syndrome, Dandy-walker syndrome and Turner's syndrome.

Other comorbid conditions in all patients admitted to the study

Thirteen (11.8%) patients were HIV exposed, none were infected and HIV status was unknown in one patient.

Forty-seven (42.7%) patients had an additional pre-existing medical condition at the time of surgery. The most common pre-existing medical conditions were cardiac failure (n = 27, 24.5 %), pulmonary hypertension (n = 22, 2%), pneumonia (n = 7, 6.4%), gastro-oesophageal reflux disease (GORD) (n = 3, 2.7%) and thyroid dysfunction (n = 3, 2.7%). Some patients had more than one comorbid condition.

MEDICATIONS

Six (5.5%) patients were on omeprazole at the time of surgery. Diuretics were prescribed in forty-seven (42.7%) patients (furosemide, spironolactone and captopril).

Seventeen (15.5%) patients were receiving antibiotics prior to surgery: cefotaxime n = 3; ampicillin and gentamycin n = 2; piptazobactam and amikacin n = 2; rimacticid n = 2; vancomycin n = 1; ertapenem n=2; amoxyl n = 1; cephalexin n = 1; cloxacillin and ceftriaxone n = 1; prophylactic penicillin n = 2.

CARDIAC CONDITIONS

Cardiac conditions of patients are listed in (Table 11). The most common conditions were Tetralogy of Fallot (n = 19, 17.3%), ventricular septal defect (VSD) (n = 15, 13.6%) and atrioventricular septal defect (AVSD) (n = 15, 13.6%).

Table 11. Cardiac conditions in all patients admitted to the study

Cardiac conditions in all patients admitted to the study	**n = 110 patients admitted to the study (%)**
Tetralogy of Fallot	19 (17.3%)
VSD	15 (13.6%)
AVSD	15 (13.6%)
TGA	6 (5.5%)
TA	6 (5.5%)
Aortic coarctation	5 (4.5%)
PDA	4 (3.6%)
TAPVD	4 (3.6%)
Aortic valve abnormalities	4 (3.6%)
ASD	3 (2.7%)

Truncus Arteriosus	2 (1.8%)
Combinations of cardiac conditions: ASD, PDA, VSD	11 (10%)
Other cardiac conditions	15 (13.6%)

ASD Atrial septal defect

PDA Patent ductus arteriosus

TA Tricuspid atresia

TGA Transposition of the great arteries

TAPVD Total anomalous pulmonary vein drainage

Operation details and outcomes are itemised in Table 12. Five cardiothoracic surgeons and one cardiologist performed 126 procedures in different categories. Surgical incision sites included median sternotomy, thoracotomy and one combination of median sternotomy and thoracotomy. Forty-five (40.9%) patients received steroids intraoperatively: three received methyl prednisone and 42 received solumedrol.

The complexity categories used to describe the cardiothoracic surgical procedures are outlined in Appendix 6. This method categorised procedures by severity of illness and technical complexity (Levy, Ovadia et al. 2003).

Table 12. Operative details and patient outcomes of all patients admitted to the study

Operative details of all patients	**n = 126 cardiac surgical procedures (%)**
Received steroids	45 (40.9%)
Received adequate peri-operative antibiotics	81 (64.3%)
Category 1	45 (35.7%)
2	20 (15.9%)
3	34 (27.0%)
4	25 (19.8%)
Use of CPB	82 (65%)
Duration of CPB (min),	105 (76 – 140)
Aortic cross-clamp time (min)	63 (39 – 92)
Endotracheal tube intubation Nasal	110 (87.3%)
Oral	13 (10.3%)
Tracheostomy in place	2 (1.6%)
Delayed closure of sternum	6 (4.8%)
Procedures with intra-operative events	40 (31.7%)
Outcome of all patients	**n = 110 patients admitted to the study (%)**
Duration of ventilation (days),	2 (2 – 4)
Duration of PICU stay (days),	4 (2 – 7)

Postoperative events	77 (70%)
Mortality, n (%)	9 (8.2%)
Mortality, n (%) admitted from Mother's room	2 (15.4%)
Mortality, n (%) admitted from cardiac / surgical wards	7 (8.6%)

Continuous data are median (interquartile range, IQR), categorical data are n (%)

CPB Cardiopulmonary bypass

PICU Paediatric Intensive Care Unit

INTRAOPERATIVE PROCEDURES AND EVENTS

Fifty-nine (53.6%) patients received intraoperative blood products including patients who received blood used to prime the CPB machine and stabilise hemodynamic state. Fifty-seven intraoperative events occurred in 24 patients during 40 surgeries. The most common intraoperative events were bleeding (n = 19) and arrhythmias / conduction abnormalities (n = 16) (Table 13).

Table 13. Intraoperative procedures and events

Intraoperative blood products received in all operative procedures	**n = 59 patients received intraoperative blood products (%)**
Red blood cells	40 (67.8%)
Platelets	8 (13.6%)
Platelets, red blood cells	6 (10.2%)
FFP, platelets	2 (3.4%)
FFP, platelets, red blood cells	1 (1.7%)
FFP, red blood cells	1 (1.7%)
FFP	1 (1.7%
Intraoperative events during all operative procedures	**n = 57 intraoperative events (%)**
Bleeding	12 (21%)
Arrhythmia / Conduction abnormality	9 (15.8%)
Bleeding, arrhythmia	5 (8.8%)
Pulmonary Hypertension	3 (5.3%)
Hypokalaemia	2 (3.5%)
CPB restarted	2 (3.5%)
Endotracheal reintubation	2 (3.5%)
Detachment of tricuspid valve	2 (3.5%)
Other	20 (35%)

CPB Cardiopulmonary bypass

FFP Fresh frozen plasma

POSTOPERATIVE EVENTS **(Table 14)**

One hundred and sixty-six postoperative events occurred in 77 patients (70%). The most common events were reintubation, bleeding, pleural effusion, arrhythmia, cardiac arrest, and organ failure. The chest was re-opened in four patients. Three (14.3%) of the 21 reintubation events were following accidental extubation of three (1.8%) patients in PICU.

Table14. Postoperative procedures and events

Postoperative events following all operative procedures	**n = 166 postoperative events (%)**
Reintubation	21 (12.7%)
Bleeding	16 (9.6%)
Pleural effusion needing drainage (including chylothorax / haemothorax)	15 (9.0%)
Arrhythmia	14 (8.4%)
Cardiac arrest	11 (6.6%)
Organ failure	12 (7.2%)
Pulmonary Hypertension	10 (6.0%)
Hypertension	7 (4.2%)
Hypoglycaemia (< 3mmol/L)	7 (4.2%)
Hypotension	6 (3.6%)
Postextubation stridor	5 (3.0%)
Coffee ground aspirates	4 (2.4%)
Chest reopened	4 (2.4%)
In ICU	3 (75%)
In postoperative Cardiology ward E1	1 (25%)
Hemi-diaphragmatic paresis	3 (1.8%)
Seizure	3 (1.8%)
Hyperglycaemia (> 12mmol/L)	3 (1.8%)
Infective endocarditis	3 (1.8%)
Accidental extubation	2 (1.2)
Pericardial effusion	2 (1.2%)
Other	10 (6.0%)

INTRAVASCULAR CENTRAL LINES, URINARY CATHETERS, PACING WIRES, INTERCOSTAL DRAINS (ICDS)

(Table 15)

CVP lines were inserted in 109 (99%) patients. Arterial lines were inserted in 108 (98.2%) patients. Pacing wires were inserted in 53 (48%) patients. Mediastinal drains were inserted in 34 (30.9%) patients. One hundred and one ICDs were inserted in 68 (61.8%) patients. Some patients had more than one drain inserted.

One hundred and nine (99%) patients had a urinary catheter inserted: nine (8.1%) patients had PAP lines and two patients had LAP lines (1.8%) inserted.

Table 15. Intravascular central lines, urinary catheters, pacing wires and intercostal drains inserted in all study patients (n = 109)

CVP lines anatomic site of insertion	**n = 109 patients had CVP lines inserted (%)**
RIJV	85 (78.0%)
RFV	10 (9.2%)
LFV	9 (8.3)
LIJV	3 (2.8%)
LSV	1 (1%)
LBCV	1 (1%)
Site of arterial line insertion	**n = 108 patients had arterial lines inserted (%)**
LFA	42 (38.9%)
RFA	29 (26.9%)
RRA	18 (16.7%)
LRA	17 (15.7%)
Pacing wire site	**n = 53 patients had pacing wires inserted (%)**
Ventricular	33 (62.3%)
AV	18 (33.9%)
Atrial	2 (1.9%)
Pericardial and mediastinal drain site	**n = 54 patients had a pericardial and / or mediastinal drain inserted (%)**
Mediastinal	34 (65.4%)
Pericardial	21 (40.4%)
Intercostal drain site	**n = 101 intercostal drains were inserted (%)**
RICD	64 (63.4%)
LICD	37 (3.7%)

LBCV Left brachia-cephalic vein LFV Left femoral vein

LFA Left femoral artery

LICD Left intercostal drain

LIJV Left internal jugular vein

LRA Left radial artery

LSV Left subclavian vein

RFA Right femoral artery

RFV Right femoral vein

RICD Right intercostal drain

RIJV Right internal jugular vein

RRA Right radial artery

MICROBIAL ISOLATES (**Table 16)**

One hundred and ten patients were collectively followed over 612 patient days. Microbial isolates of all study patients are presented in Table 16.

Table 16. Microbial isolates for all patients (n = 75 microbial isolates for all 110 patients)

Microbial isolates on all specimens	**Blood (n = 10)**	**Respiratory (n = 53)**	**Wound (n = 10)**	**Urine (n = 2)**	**Total (n = 75)**
Gram negative	**7**	**31**	**3**	**2**	**43 (57.3%)**
Acinetobacter baumanii	3	9	1		13
Klebsiella pneumoniae	2	7		1	10
Haemophilus influenzae		5			5
Moraxella catarrhalis		4			4
Serratia marcescens	1	1	1		3
Citrobacter species			1		1
Pseudomonas		1			1
Enterobacteriaceae coli		1			1
Enterococcus faecium				1	1
Serratia liquefacies		1			1
Ralstonia mannitolyca		1			1
Sphingomonas paucimobilis	1				1
Stenotrophomonas		1			1
Gram positive	**3**	**4**	**6**		**13 (17.3%)**
Methicillin resistant Staph. aureus (MRSA)	2	1	3		6
Streptococcus pneumoniae		2			2
Staphylococcus aureus		1	1		2
Staphylococcus epidermidis			1		1

Staphylococcus haemolyticus	1				1
Diptheroids			1		1
Viral positive result on a multiplex PCR		**17**			**17 (22.3%)**
Adenovirus		6			6
RSV		6			6
Rhinovirus A		4			4
Parainfluenzae		1			1
Fungal		**1**	**1**		**2 (2.7%)**
Fungal spores		1			1
Candida albicans			1		1

INFECTIONS AND ANTIBIOTIC USE

Sixty HAIs occurred in 43 (39%) patients admitted to PICU following cardiac surgery. These HAI consisted of pulmonary infections (including VAP and nosocomial pneumonia) in forty-one (68.3%) patients; blood stream infection in eight (13.3%); surgical site infections in eight (13.3%), including superficial SSIs, and deep SSI in four (6.7%) patients (two with mediastinitis and two with infective endocarditis); and urinary tract infections in three (5%) patients (Figure 1). The central line-associated bloodstream infection (CLABSI) rate was 12.7 per 1000 central line days.

Ten (9%) patients had more than one infection site (Table 17). Four (3.6%) of these patients developed possible secondary BSIs, including two with SSI and two with VAP.

Twelve (27.9%) patients developed infections within 48 hours after cardiac surgery, all of which were respiratory infections: two (4.7%) patients acquired infections prior to admission to a hospital facility (community acquired), nine (20.3 %) acquired while admitted to a hospital facility outside PICU and one (2.3%) acquired in a patient admitted to PICU twenty days prior to surgery and remained admitted to PICU throughout (Figure 2). Of the two patients with community acquired infection one went on to develop a new VAP and one developed a new nosocomial pneumonia. Three of the patients with infection acquired in hospital facility outside of the PICU went on to develop a new VAP and four a new nosocomial pneumonia (Figure 2).

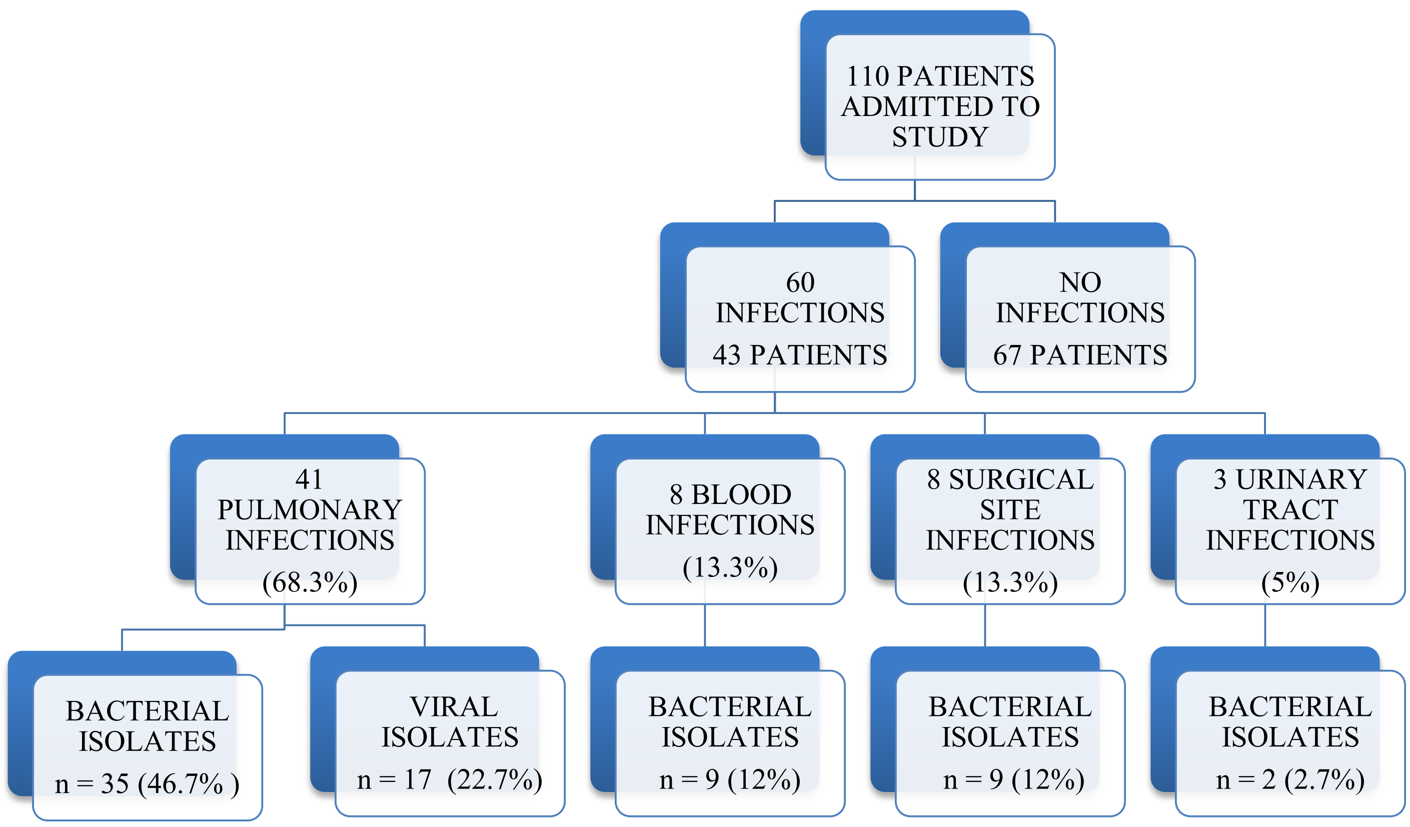

Fig. 1. Sites of PICU acquired infection (60 infections in 43 patients)

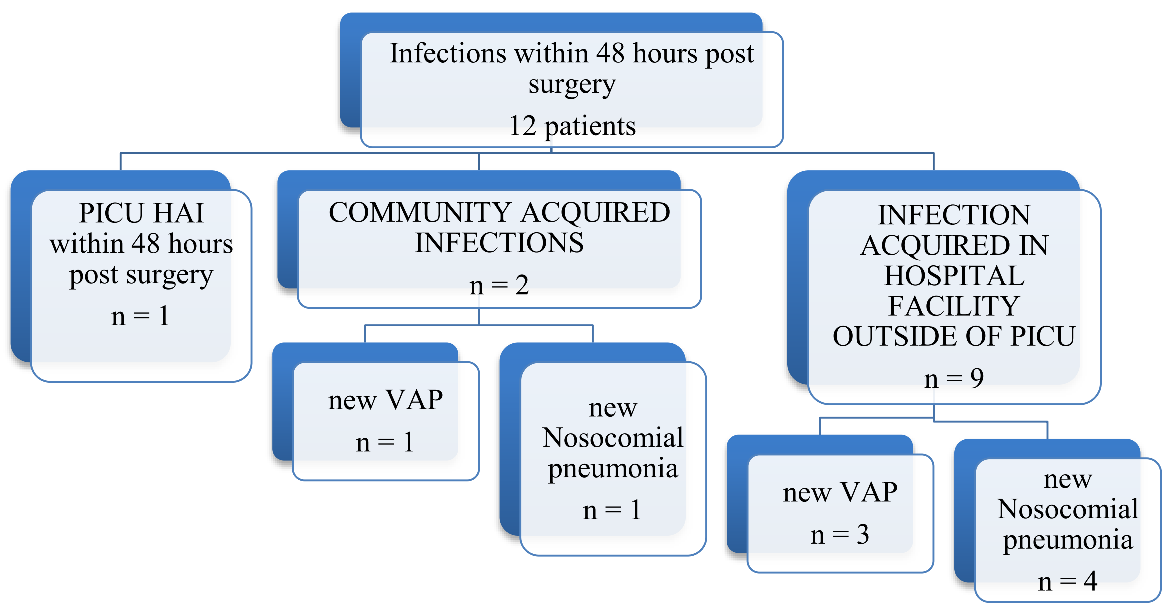

Fig. 2. Infections within 48 hours post surgery

Table 17. All patients with multiple HAI infection sites

Patient No.	Pulmonary (including VAP)	Wound (SSI-superficial)	Blood	Urine	Tissue (SSI-deep)	Aristotle score	Surgical category	Underlying cardiac lesion
1	1	1	1 *Staphylococcus haemolyticus*			13.8	4	Congenitally Corrected Transposition of the great arteries, PA, VSD
4	1 *Acinetobacter baumanii*	1 *Staphylococcus epidermidis*	1 *Acinetobacter baumanii* *(possible secondary BSI)*			11	4	Truncus arteriosus, VSD, ASD
6	1			1		3	4	PDA, ASD
28	1 *Klebsiella pneumoniae*		1 *Klebsiella pneumoniae* *(possible secondary BSI)*			9	3	TA, ASD, PDA
53	1		1 *Methicillin resistant Staph. Aureus (MRSA)*			9	3	AVSD

65	1	1				9	3	AVSD, Tricuspid incompetence
70	1	1 *Methicillin resistant Staph. aureus*	1 *MRSA* *(possible secondary BSI)*		1 *MRSA*	11	4	Truncus arteriosus
87		1 *Serratia*	1 *Serratia* *(possible secondary BSI)*			8	3	TOF
93	1	1	1 *Sphingomonas paucimobilis*			6	1	VSD, ASD
100	1	1			1	9	4	TA, ASD, VSD

The most common associated organisms with hospital acquired respiratory infections (n = 41, 68.3%) were gram negative (41%) and viral (23%) isolates. According to study criteria, 43 new VAP cases were diagnosed in 24 patients at median (IQR) of the eighth (4 – 14) postoperative day.

Seventeen (15.5%) patients were receiving antibiotics prior to cardiac surgery. Six patients (5.5%) receiving antibiotics prior to surgery were diagnosed with infection while in PICU.

ISOLATES IN PATIENTS WITH LIKELY HAI

Microbial isolates in all infections diagnosed in PICU following cardiac surgery

Microbial isolates from patients with presumed PICU HAIs are presented in Table 18. Thirty-six percent of isolates were detected in the first two postoperative days before signs of infection developed, and these results were used to guide antimicrobial therapy (Figure 3). In all other cases specimens were taken on the clinical suspicion of infection, and therefore the index specimen was considered likely to reflect the causative or associated pathogen. Data on isolates are only analysed for those patients who met the criteria for HAI.

Table 18. Microbial isolates from patients with HAI of all sites diagnosed in PICU

Microbial isolates	**Blood (n = 10)**	**Respiratory (n = 53)**	**Wound / Tissue (n = 10)**	**Urine (n = 2)**	**Total (n = 75)**
Postoperative day of first isolate (median, IQR)	**10 (6-12)**	**3 (2 -5)**	**Pus swab: 14 (5 – 19)** **Tissue: 24 (14 – 34)**	**3 (3 – 3)**	
Gram negative	**7 (8%)**	**31 (41.3%)**	**4 (5.3%)**	**2 (2.7%)**	**43 (57.3%)**
Acinetobacter baumanii	3	9	2		13 (29.5%)
Klebsiella pneumoniae	2	7		1	10 (22.7%)
Haemophilus influenzae		5			5 (11.4%)
Moraxella catarrhalis		4			4 (9.1%)
Serratia marcescens	1	1	1		3
Citrobacter species			1		1
Pseudomonas		1			1
Enterobacteriaceae coli		1			1
Enterococcus faecium				1	1
Serratia liquefacies		1			1
Ralstonia mannitolyca		1			1

Sphingomonas paucimobilis	1				1
stenotrophomonas		1			1
Gram positive	**3 (4%)**	**4 (5.3%)**	**5 (6.7%)**	**0**	**12 (16%)**
Methicillin resistant Staph. aureus (MRSA)	2	1	3		6 (50%)
Streptococcus pneumoniae		2			2 (17%)
Staphylococcus epidermidis			1		1 (8%)
Staphylococcus haemolyticus	1				1(8%)
Diptheroids			1		1
Viral positive result on a multiplex PCR	**0**	**17 (22.7%)**	**0**	**0**	**17 (22.7%)**
Adenovirus		6			6
RSV		6			6
Rhinovirus A		4			4
Parainfluenzae		1			1
Fungal		**1 (1.3%)**	**1 (1.3%)**		**2 (2.7%)**
Fungal spores		1			1
Candida albicans			1		1

PCR Polymerase chain reaction

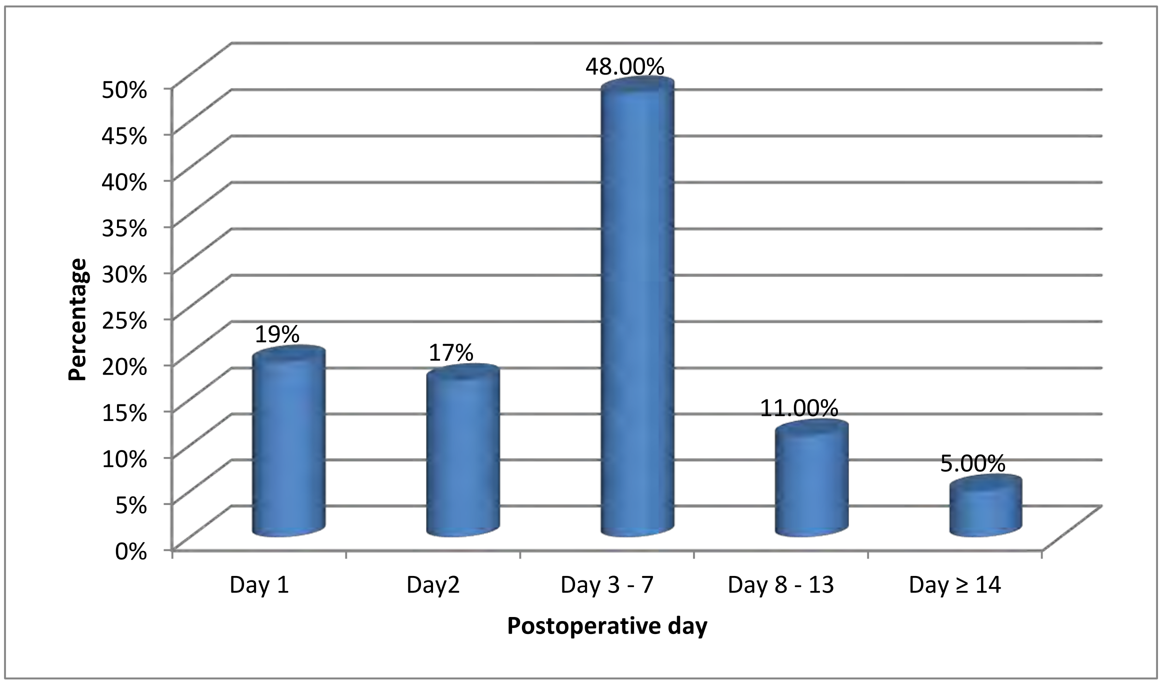

Fig. 3. Postoperative day of first isolate detected in all study patients

PULMONARY POSTOPERATIVE INFECTION

Fifty-three organisms were detected in respiratory specimens taken on 30 patients (27.3%); with ten organisms isolated on day one postoperatively (18.9% of organisms), nine organisms on day 2 (16.9%) and 26 organisms between day three and seven postoperatively (49%). Six organisms were cultured between day eight and 13 (11%) and three organisms were identified after 14 days (5.7%) (Figure 4).

Nineteen isolates were obtained from respiratory specimens in 17 patients taken in the first 48 hours after surgery, with subsequent signs of infection: A*cinetobacter baumanii* (n = 5, 26.3%), A*denovirus* (n = 4, 21.1%), *Haemophilus influenzae* (n = 2, 10.5%), *Klebsiella pn*. (n = 2, 10.5%), *RSV* (n = 2, 10.5%), *Moraxella catarrhalis* (n = 1, 5.3%), *Staphylococcus aureus* (n = 1, 5.3%) and *Streptococcus pn.* (n = 1, 5.3%) and *rhinovirus A* (n = 1, 5.3%).

Ten respiratory isolates were detected in nine patients within the first 48 hours after surgery, without any accompanying sign of clinical infection: A*cinetobacter baumanii* (n = 3), respiratory syncytial virus (n = 2), *methicillin resistant staphylococcus aureus* (MRSA) (n=1), *Haemophilus influenzae* (n = 1), *Moraxella catarrhalis* (n = 1), *Adenovirus* (n = 1) and *Rhinovirus* (n = 1). These subsequently were thought to indicate pre-existing infection or colonisation.

VAP was diagnosed with CPIS in twenty-four patients. Eight (33.3%) patients were not treated with antimicrobials and five (21%) had no detectable organism; one (4.2%) patient had a viral isolate detected ≤ 48 hours post surgery indicating possible previous infection or colonisation, one (4.2%) patient had a viral isolate detected on day four post surgery after being discharged from PICU and one (4.2%) patient had MRSA isolated on day one post surgery indicating possible colonisation (Figure 5). Seventeen patients were diagnosed with nosocomial pneumonia according to CDC criteria and did not meet VAP criteria according to CPIS (Figure 5). Five (29.4%) patients had detectable organisms and were not treated with antimicrobials; of these two (11.8%) patients had viral isolates ≤ 48 hours post surgery, one (5.9%) patient had an A*cinetobacter baumanii* isolated on day one post surgery and two (11.8%) patients had isolates detected on day 3 post surgery (A*cinetobacter baumanii* and *Adenovirus*). All these isolates were thought to indicate possible colonisation (figure 5).

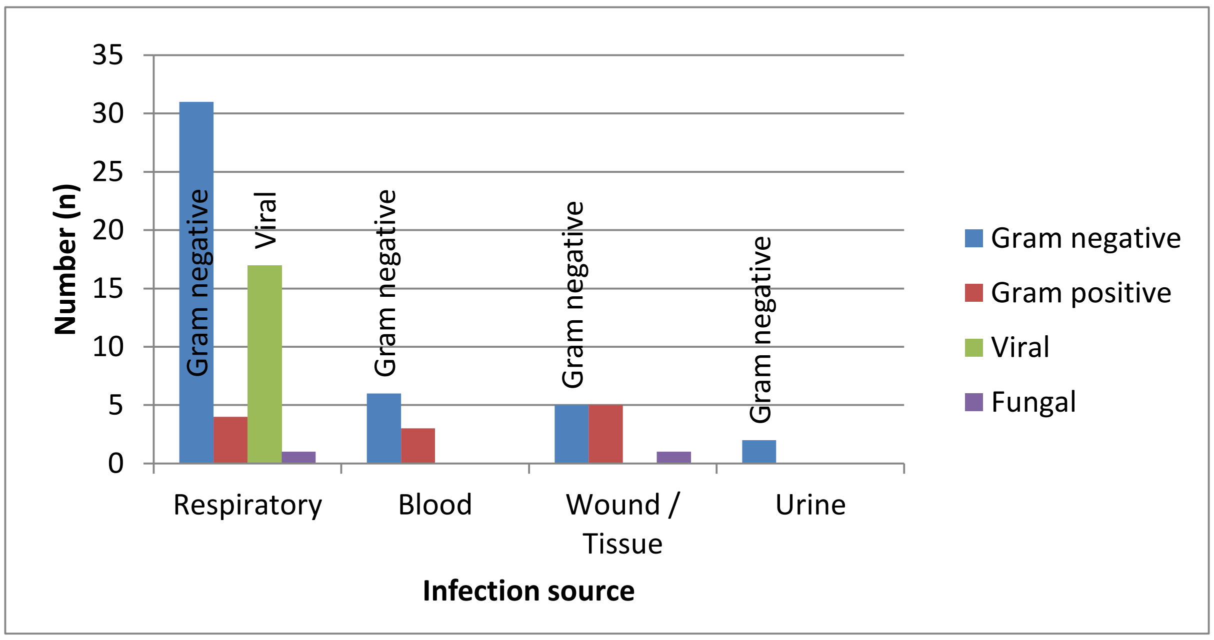

Fig. 4. Pathogens associated with infection sites in patients diagnosed with infection in PICU

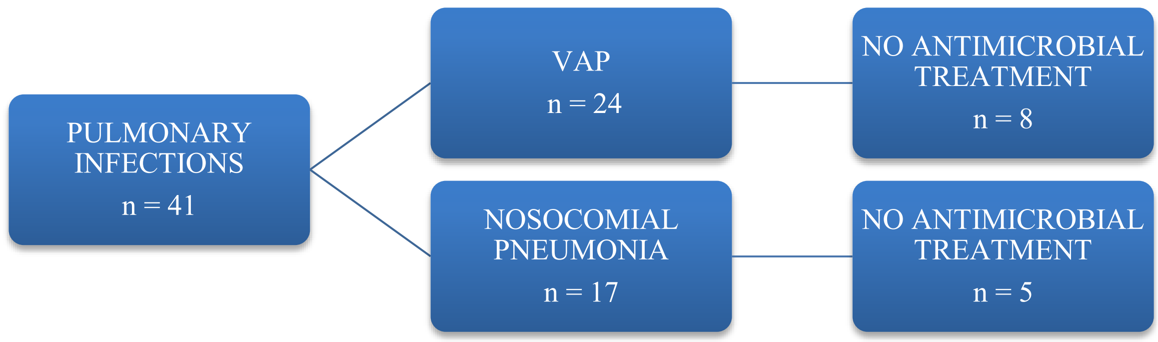

Fig. 5. Pulmonary infections including VAP and nosocomial pneumonia

ANALYSIS

UNIVARIATE DATA ANALYSIS (Table 19 – 21)

The differences in patient characteristics, course and outcome for those who developed HAI infection of any site in PICU and those who did not develop infection are presented in Table 19. Notably, a greater proportion of patients who developed HAI were underweight for age; experienced postoperative events; and had more reintubation episodes than those who did not develop infection. Patients with HAI had worse outcome in terms of prolonged PICU and hospital stay and duration of mechanical ventilation, but there was no difference in mortality between groups (Table 19).

Patients who developed HAI in PICU had higher Aristotle scores, lower CPB temperature (Table 20), and longer duration of arterial lines, CVP lines, pacing wires, urinary catheters and intercostal drains (Table 21) than uninfected patients.

Duration of hospital stay, in the wards or Mother's room, prior to PICU admission was significantly longer in those who developed HAI vs. those who did not develop infection (Table 19).

Table 19. Univariate analysis of patient characteristics, course and outcome data for those who developed or did not develop infection of any site

	HAI (n = 43)	**No HAI (n = 67)**	**P**
Male: Female	21:22	26:41	0.3
Age (months)	10 (6.5-45.5)	31 (6-84)	0.1
History of prematurity, n (%)	6 (14.0%)	3 (4.5%)	0.2
Weight (kg)	6 (4-11)	10 (5-17)	0.02
EWA (%)	73 (64-90)	78 (68-88)	0.41
UWA, n (%)	27 (62.8%)	26 (38.8%)	0.01
Height (cm)	67 (54-92)	85 (59-113)	0.03
EHA (%)	95 (90-99)	93(91-99)	0.99
Stunted, n (%)	5 (11.6%)	6 (9.0%)	0.9
Genetic and congenital malformation syndromes, n (%)	6 (14.0%)	6 (9.0%)	0.6
Previous operation, n (%)	11 (25.6%)	17 (25.4%)	0.98
HIV exposed, n (%)	2 (46.5%)	11 (16.4%)	0.1

Omeprazole, n (%)	2 (4.7%)	4 (6.0%)	0.9
Preoperative antibiotics (excluding antimycobacterial and oral antifungal nystatin)	6 (13.95%)	8 (11.9%)	0.99
Admitted from ward, n (%)	32 (74.4%)	50 (74.6%)	0.98
Admitted from Mother's room, n (%)	8 (61.5%)	5 (38.5%)	0.2
Steroids intraoperatively, n (%)	18 (41.9%)	27 (40.3%)	0.9
Number of dressing changes	1 (1-1)	1 (1-1)	0.37
Number of reintubations	0 (0-1)	0 (0-0)	0.037
RBC volume (ml)	12 (6-69)	12 (5-32)	0.64
PLT volume (ml)	14 (5-26)	4 (3-29)	0.29
FFP volume (ml)	8 (4-78)	15 (12-34)	0.49
Cryoprecipitate volume (ml)	15 (4-32)	15.5 (6.5-40)	0.52
Intraoperative events, n (%)	11 (25.6%)	32 (47.8%)	0.02
Postoperative events, n (%)	38 (88.4%)	39 (58.2%)	0.02
Duration of ventilation (days)	4 (3-7)	2 (2-2)	< 0.0001
Duration of PICU stay (days)	6 (4-13)	3 (2-5)	< 0.0001
Duration of stay prior to surgery (days)	8 (2-20)	2 (1-8)	0.0007
Duration of hospital stay (days)	21 (9-38)	9 (7-13)	< 0.0001
Mortality, n (%)	6 (20.1%)	3 (4.5%)	0.16

Unless otherwise stated, values expressed as median (interquartile range)

EHA Estimated height for age

EWA Estimated weight for age

FFP Fresh frozen plasma

HIV Human immunodeficiency virus

PLT Platelets

RBC Red blood cells

UWA Underweight for age

Table 20. Operative details for those who developed and did not develop HAI in PICU

	Operations leading to HAI (n = 56)	**Operations not leading to HAI (n = 69)**	**P**
Adequate perioperative antibiotics, n (%)	39 (69.6%)	42 (60.9%)	0.3
Surgeon, n (%)			
1	14 (25.0%)	28 (40.6%)	0.07
2	8 (14.3%)	12 (14.4%)	0.8
3	6 (10.7%)	6 (8.7%)	0.9
4	24 (41%)	22 (31.9%)	0.3
5	3 (5.4%)	1 (1.4%)	0.5
6	1 (1.8%)	0	
Category			
1	16 (28.6%)	29 (42%)	0.1
2	6 (10.7%)	14 (20.3%)	0.2
3	19 (34%)	15 (21.7%)	0.1
4	14 (7.1%)	11 (15.9%)	0.2
Aristotle score	9 (8-9)	8 (6-9)	0.007
Risk of Mortality [Paediatric index of mortality 2 score, (PIM2)]	0.05 (0.03 – 0.11)	0.04 (0.03 – 0.08)	0.37
CPB duration (min)	107 (79-143)	101 (70-140)	0.35
Aortic Cross Clamp Duration (min)	72.5 (40.5-93.0)	61 (39-91)	0.37
CPB Temperature	29.3 (24-31.95)	31.9 (27.7-33)	0.02
Delayed sternal closure, n (%)	5 (8.9%)	1 (1.4%)	0.1
Received RBC	20 (35.7%)	28 (40.6%)	0.6
RBC volume (ml)	80 (40-160)	100 (45-200)	0.89
Received PLT	5 (8.9%)	7 (10.1%)	0.8
PLT volume (ml)	105 (50-250)	200 (50-300)	0.25
Received FFP	2 (3.6%)	3 (4.3%)	0.80
FFP volume (ml)	122.5 (45-200)	140 (80-200)	0.80
Intubation site			

Nasal	52 (92.9%)	58 (84%)	0.4
Oral	4 (7.1%)	9 (13.0%)	0.4
Tracheostomy	0	1 (1.44%)	
Incision site			
Median sternotomy	48 (85.7%)	58 (84.0%)	0.4
Thoracotomy	5 (8.9%)	11 (15.9%)	0.4

Unless otherwise stated, values expressed as median (interquartile range)

Table 21. Details of invasive catheters and lines related to HAI in PICU

	HAI (n = 43)	No HAI (n = 67)	P
A-line duration (days)	5 (3-8)	2 (2-3)	<0.0001
CVP duration (days)	4 (3-6)	2 (2-3)	<0.0001
CVP 2 duration (days)	0 (0-1)	0	0.06
Pacing wire duration (days)	14 (7-20)	7 (5-9)	0.001
Urinary catheter duration (days)	3 (1-5)	2 (1-2)	0.003
Mediastinal drain duration (days)	2 (1.5-4.5)	2 (2-3)	0.61
PA line duration	5 (1-6)	1 (1-1)	0.39
ICD duration (days)	4 (1-6)	2 (1-3)	0.007
ICD 2 duration (days)	5 (3-6)	2 (1.5-3)	0.005
ICD 3 duration (days)	4.5 (1-9)	32 (32-32)	< 0.0001

Unless otherwise stated, values expressed as median (interquartile range)

MULTIVARIATE DATA ANALYSIS (Table 22)

The final stepwise multiple regression model is presented in Table 22. Being underweight for age, longer duration of A-line and longer duration of hospital stay prior to surgery were independently associated with development of HAI.

Table 22. Final multiple regression model of associations with HAI

Factors	Adjusted odds ratio	95% Confidence interval	P
Underweight for age	2.77	1.04-7.36	0.04
A-line duration	1.47	1.24-1.78	0.0001
Duration of stay prior to surgery	1.04	1.0-1.09	0.004

CHAPTER 5

DISCUSSION

This study demonstrated that infections are common among paediatric postoperative cardiac patients admitted to PICU in this setting. The **incidence of HAIs** was 39%, similar to the 38% rate reported by Grisaru-Soen et al (Grisaru-Soen, Paret et al. 2009) in a similar setting with a similar patient profile; but higher than the 11% reported in an Argentinian study (Rosanova, Allaria et al. 2009). Rosanova et al reported that the presence of underlying diseases, longer hospitalisation and inotropic support were risk factors for infections. A study conducted in USA (Mastropietro, Barrett et al. 2013) reported a similar HAI incidence of 36% in a cohort of patients undergoing more complex cardiac surgery (Basic Aristotle score ≥ 7) with longer duration of intensive care unit stays (≥ 7 days). A Dutch study also reported a high HAI incidence of 25% (Algra, Driessen et al. 2012). In this study (Algra, Driessen et al. 2012) variables most predictive of a HAI were: age less than 6 months, postoperative PICU stay longer than 48 hours, and open sternum for longer than 48 hours.

Lower HAI incidence rates can be achieved, as reported by a Pakistani study (Siddiqui, Mir et al. 2011), which reported a HAI rate of 7.9%. These authors postulated that the low incidence may reflect strict implementation and adherence to their institutional infection control policy including strict visit regulations (one parent at a time), hand hygiene and a 1:1 nurse-to-patient ratio in high dependency / intensive care areas. A study conducted in Israel (Levy, Ovadia et al. 2003) reported a HAI frequency of 16.4%. Similar to our institution they had up to 360 cardiac admissions per year, however, it was a dedicated paediatric cardiac ICU consisting of a smaller six-bed intensive care and a 12-bed intermediate care suite, in contrast to our unit, which is multidisciplinary. Their complexity of cardiac surgeries was similar to our study but 8% of their patients had open chests compared to 4% of patients in this study. Longer duration of open chest postoperatively was found to be a risk factor for HAI in the study by Levy et al. (Levy, Ovadia et al. 2003) but was not a factor contributing to HAI in our cohort – this may relate to the small number of children with delayed sternal closure in our study.

Several studies have examined the influence of a **dedicated paediatric cardiac intensive care unit (PCICU)** on patient outcomes. A study conducted in the USA (Eldadah, Leo et al. 2011) described a decrease in morbidity as evidenced by the decrease in wound infection and need for chest re-exploration when cardiac care was transitioned from the general PICU to care provided exclusively in the PCICU. The percentage of wound infection for their combined PICU dropped from 7.54% as compared with the dedicated CICU unit with only 0.82%. In addition, mortality declined from 3.5% to 0.8% and fewer children required resuscitation. An Indian study (Balachandran, Nair et al. 2011) similarly reported improved outcomes in terms of earlier extubation, and ICU discharge and reduced BSIs (9 % vs. 5 % p = 0.04) following establishment of a dedicated PCICU. The authors acknowledge that the cost-effectiveness of establishing a dedicated cardiac ICU was not analysed. The nurse-patient ratio was 1:1 and the nursing team worked in 8-hour shifts. This differs from Red Cross War Memorial Children's Hospital PICU, which is multidisciplinary including medical, neurosurgical, trauma and cardiothoracic patients. The nursing staff work 12-hour shifts and the nurse-patient ratio is similar at 1:1.

Causative organisms for HAIs in this study were mostly gram negative (58.7%), viral (22.7%), followed by gram positive (16%) and fungal (2.7%) isolates. The predominance of gram negative or gram positive organisms as causative organisms in HAIs differ between studies in this population group. Gram negative infections, most commonly *A.baumanii* and *K.pneumoniae* predominated in this study, contradicting other studies that reported a predominance of gram positive causative organisms (Siddiqui, Mir et al. 2011, Grisaru-Soen, Paret et al. 2009). Siddiqui et al reported a predominance of gram negative bacteria (62.5% of all isolates) with *Acinetobacter sp*. (12.5%), and *Pseudomonas aeruginosa* most prevalent (12.5%). Levy et al reported a similar gram negative predominance in their CICU, the main causative organisms were *Klebsiella spp*., *Enterobacter spp*. and *Pseudomonas spp*. followed by *Staphylococcus spp*. Possible reasons for the predominance in this study were less than optimal infection control protocols such as inadequate screening of patients for viral / bacterial organisms both presurgery and during hospitalisation and inadequate cohorting of patients when viral / bacterial isolates were detected.

Ten patients had **multiple infections** during their PICU stay. According to CDC definitions, each HAI has to be diagnosed in the absence of another infection site, but at present there is also no defined time period during which only one infection of the same event type may be reported for the same patient. The CDC definitions for BSI and UTI do take into consideration additional sites of infection: BSI that does not meet the criteria for a primary BSI can meet one of the criteria of a possible secondary BSI. UTI can de diagnosed in patients that match the clinical criteria and have cultured microorganisms from blood compatible with urinary tract site of infection (http://www.cdc.gov/ncidod/dhqp/pdf/nnis/NosInfDefinitions.pdf). It can, therefore, be difficult to identify multiple HAIs and the additional risk each contributes to developing further infections in different sites in this population group is unknown. This study has included the patients with possible secondary BSI in the total numbers for BSI and HAIs in order that all infections were identified and adequately treated.

A third of our study patients did not receive adequate perioperative **antibiotics**, however, this was not found to be a risk factor for developing HAI after multiple regression analysis. The poor adherence to antibiotic prophylaxis is concerning, and included incorrect doses, incorrect timing of antibiotic prophylaxis and doses not being prescribed. As mentioned above, this could be linked to the high number of varying anaesthetists, cardiothoracic surgeons and ICU medical staff. This could be the focus of a practice improvement initiative in the future.

Eight (11.9%) patients were started on antimicrobial treatment in PICU following cardiac surgery, but subsequently were not diagnosed with a HAI. The signs and symptoms of bacteraemia in the PICU setting are often subtle and nonspecific, and therefore a high index of suspicion is required. It is for this reason that sepsis work-up and empiric antibiotic therapy are often initiated in these patients. Knowledge of the main sites of HAI and the main pathogens that cause HAIs are important for the selection of the most appropriate antibiotic therapy in this setting.

Patients with HAI received more antibiotics than those who did not develop HAI, but there were cases that met the criteria for HAI, particularly VAP, who did not receive antibiotic therapy. It appears, therefore, that diagnosis based on clinical assessment or microbiological and lab indications of infections were treated appropriately**.** This has relevance in that if VAP is diagnosed exclusively on CPIS, overdiagnosis and inappropriate antibiotic use may occur. VAP scores remain an important tool for monitoring the trend of infection rates in an institution and may be an indicator of quality of care in the PICU. Our study identified 22.7% of infections in which viral isolates were associated. Viral associated infection would not need antibiotic treatment and could partly explain the reduced use of antibiotics in those with any HAI.

Pulmonary nosocomial infections were found to be the most common HAI in this study, accounting for 68% of all infection cases. This is much higher than previous studies done in the US (21%) (Richards, Edwards et al. 1999), Switzerland (6.9%) (Fischer, Allen et al. 2000) and Israel (16.4%) (Grisaru-Soen, Paret et al. 2009). During the period that this study was conducted implementation of a VAP bundle was initiated in our ICU. An audit of the VAP bundle of care revealed less than ideal rates of compliance, which could have contributed to the high rates of VAP. At the time of the study, the background PICU VAP rate was 22.4% (Morrow, Mowzer et al. 2012) with more recent data reporting VAP rate 3 – 6 per 1000 ventilator days (personal communication, A Argent).

This study has highlighted the challenges of diagnosing respiratory infections in this group of patients. VAP was diagnosed by a score of ≥ 6 on the CPIS more than 48 hours after initiation of ventilation or an increase of > 2 if the patient started with a high CPIS. When the patient met CDC criteria for nosocomial pneumonia more than 48 hours after initiation of ventilation and did not meet CPIS criteria for VAP that was diagnosed as nosocomial pneumonia. Diagnosing VAP on CPIS alone yielded a very high number, when we focussed down to those who actually received antibiotic therapy it came down to a much lower number. The dilemma is that we did not want to miss infection (high sensitivity), but at the same time we did not want to use inappropriate antibiotic therapy (specificity).

Twelve (27.9%) patients had respiratory infections that developed within 48 hours after cardiac surgery, reflecting both community acquired infection and nosocomial infections acquired outside PICU. This highlights the importance of considering strict implementation and adherence of infection control in areas outside of PICU, including the home environment and the various hospital facilities that act as admitting wards for paediatric cardiac surgery patients.

Although respiratory specimens were not taken in a standardised manner in all patients, the most commonly isolated organisms were gram negative bacilli (41.3%), viral isolates (22.7%), gram positive bacilli (5.3%) and fungi (1.3%). Gram negative predominance has been reported by Tan (86.1%) in China (Tan, Sun et al. 2004), Rosanova in Argentina (Rosanova, Allaria et al. 2009) and Roeleveld (Roeleveld, Guijt et al. 2011) in the Netherlands. The type of organisms isolated differed between studies yet all included *Acinetobacter* species. Roeleveld reported the most common organisms as *Haemophilus influenzae, Moraxella catarrhalis,* and *Pseudomonas aeruginosa*. Rosanova detected *Haemophilus influenzae non type b* and *Acinetobacter species.* Tan reported the main gram negative bacilli were *Acinetobacter baumanii* (13.9 %) and *Pseudomonas aeruginosa* (12.7%). The most commonly seen gram positive cocci in our study were *Staphylococcus aureus* (2.5%) and *Staphylococcus epidermidis* (2.5%) and the most common fungus was *Candida albicans* (6.3%). Subsequent to this study there has been a dramatic drop in the number of *Acinetobacter* isolates in the RCWMCH PICU following changes to utilisation of ventilator circuits (personal communication, A Argent). Changes to circuit utilisation were 1) utilisation of non-reusable ventilator circuits instead of multiple use circuits 2) reorganisation of the packing and cleaning of equipment used for intubation. At the same time circuit utilisation was changed, the VAP bundle of care was introduced in the PICU with initial compliance reported 40% in February 2012, increasing to 80% by November 2012 (Personal communication Heide Kunzmann).

Viral isolates were the second most common respiratory isolates and this has not been frequently reported in this population group. Roeleveld et al. (Roeleveld, Guijt et al. 2011) found *rhinovirus* by PCR in 18.2% of isolates, although the authors were unclear of the role this played in the aetiology of VAP. Viruses have been found to be responsible for up to 22% of paediatric nosocomial infections, and between eight and 14% of nosocomial lower respiratory tract infections in various settings (Raymond, Aujard et al. 2000, Valenti, Menegus et al. 1980, Ghani, Morrow et al. 2012). An Indian study of VAP reported that nine of 13 (69%) children who died following a diagnosis of VAP showed signs of viral infection on post-mortem (Bavdekar, Bhosale et al. 2011). This high rate of viral- associated nosocomial lower respiratory tract infections has been noted in previous studies in the same PICU, albeit not specific to cardiac surgery patients (Morrow, Argent et al. 2009, Ghani, Morrow et al. 2012). The fact that our study period was conducted during summer months could have underestimated the contribution of viruses to HAI, as viruses are more prevalent during the winter months.

The median day postoperatively of the first organism being detected from any respiratory specimen (NPA, TA, BAL) was three days. This finding could be an indication of **pre-existing infection or colonisation** in the patients undergoing cardiac surgery. Included in the number of patients with respiratory infections were nine patients with various microbial isolates detected ≤ 48 hours after cardiac surgery: Gram negative bacilli predominated including, A*cinetobacter baumanii, Haemophilus influenzae* and *Moraxella catarrhalis*. The second most frequent isolates were viral organisms consisting of *RSV, adenovirus* and *rhinovirus*. There are limited guidelines on the diagnosis of nosocomial viral infections. The challenges in diagnosing nosocomial viral infections using the CDC 48 hour rule are longer incubation periods of viral organisms and unknown duration of viral organism shedding after an original infection. Patients undergoing cardiac surgery in our institution were not routinely screened for viral infection prior to surgery. The role these organisms played in the aetiology of VAP is unknown and may highlight the need to screen for infection in asymptomatic paediatric patients prior to cardiac surgery. If patients are screened and found to be negative for viral organisms on admission and prior to surgery, then subsequently become positive > 48hours after hospital admission, the detected viral organism would more likely be considered the causative organism of a nosocomial infection.

Known associations with VAP in the PICU are extubation failure, duration of ventilation, and prolonged PICU and hospital length of stay (Shi, Zhao et al. 2008). Nine (8%) patients in this study were ventilated prior to undergoing a cardiac surgical procedure. Two (1.8%) of these were transferred from outside ICUs 24 hours prior to surgery. In this study we looked at overall duration of ventilation as a risk factor for acquiring HAI (hospital acquired infection). We did not investigate duration ventilated prior to cardiac surgery as a specific risk variable. Of the nine patients, one patient developed VAP and one patient a HAI acquired outside of this PICU. Duration of ventilation was not found to be associated with HAI (or VAP specifically) on univariate analysis, as previously reported (Shin, Jhang et al. 2011, Alvarez, Fuentes et al. 2012). In this study, reintubations were associated with developing HAI on univariate analysis, but not specifically associated with nosocomial respiratory infections. In this study, reintubations were not categorised into time periods indicating early or late reintubations. Time to reintubation was unfortunately not analysed and was beyond the scope of this study.

Blood infections were found in 13%, with associated organisms being predominantly gram negative (*Acinetobacter baumanii*, *Klebsiella pneumoniae*) and gram positive isolates (*MRSA*). There were no fungal blood isolates. The incidence is similar to that reported by Richards et al (15%) (Richards, Edwards et al. 1999) and Mastropietro et al (12%) (Mastropietro, Barrett et al. 2013) but lower than the 65.8% reported by Grisaru-Soen et al (Grisaru-Soen, Paret et al. 2009).

Previous studies (Odetola, Moler et al. 2003) have reported that BSI caused by gram negative organisms in the PICU were associated with many factors including transfer from another facility, the presence of congenital heart disease, failure to thrive, younger age (≤30 days), administration of prednisone and blood transfusion. Many of these factors that they reported are commonly seen in postoperative cardiac cases and could have played a role in this study. Other types of HAI also may increase the risk of BSI development, particularly with gram negative organisms (Abou Elella, Najm et al. 2010). In a study (Asembergiene, Gurskis et al. 2009) conducted in a general PICU population, secondary bacteremia occurred in 10.6% of children with a diagnosis of HAI with skin wound infection, pneumonia, and urinary tract infection the main primary sources of secondary bacteremia associated with HAI.

Consistent with findings from previous studies (Richards, Edwards et al. 1999, Grisaru-Soen, Paret et al. 2009, Bezzio, Scolfaro et al. 2009), the duration of central vascular catheters in situ was linked to the development of infection in both univariate and multivariate analyses. Bezzio et al. suggested that interventions to improve the adoption of sterile common barriers could reduce the rate of BSIs. This hypothesis was supported by the fact that the shortage of nurses in hospitals did not always allow for optimal medical assistance (because of high workloads and a patient-to-nurse ratio of 2:1), and the time required for assistance increased by the use of the various sterile barriers (Bezzio, Scolfaro et al. 2009). Their study reported no significant risk associated with BSI in lines inserted in the operating room or in the PICU. In our institution the majority of children have central lines placed in theater by the anaesthetists at the time of surgery. Compliance with the catheter related blood stream infection bundle of care was not assessed in our study.

Abou Elella et al. (Abou Elella, Najm et al. 2010) identified a lower rate of 8.6% BSI in all patients undergoing cardiac surgery with a similar report of gram negative organism predominance in their study. The predominant gram negative organisms were *Pseudomonas* and *Enterobacter*. The study differed in various aspects to our study in that it was conducted in a dedicated paediatric cardiac intensive care unit and perioperative antibiotics were administered at a higher dosage and for longer duration; all patients undergoing cardiac surgery were treated with intravenous cefazolin at a dose of 100 mg/kg/day in three divided doses, starting 30 min before surgery and continued until the chest tubes were removed after surgery. For the patients with an open chest postoperatively, intravenous ceftazidime and vancomycin were used as prophylaxis and continued until the chest was closed (48–72 hours postoperatively).

In our study gram positive organisms with most frequently isolated organisms *MRSA* and *Staphylococcus epidermidis* predominantly caused **SSIs**. Previous studies in this population group (Allpress, Rosenthal et al. 2004, Ben-Ami, Levy et al. 2008) have reported gram positive predominance with *Staphylococcus aureus* and *coagulase negative Staphylococcus* the most frequently detected isolates from wound sites. This differs from a study conducted by Hafez et al (Hafez, Saied et al. 2012) who reported gram negative predominance with *Klebsiella sp*. being the most frequently isolated organisms. The incidence of wound (12%) and tissue (3%) infections is lower than reported by the Egyptian study (Hafez, Saied et al. 2012), in which SSIs occurred in 187 (17%) of patients with complete follow-up, of which 106 (57%) occurred in-hospital and 81 (43%) occurred after discharge. Increased risk of SSI was found in those with increased duration of hospital stay before (OR 1.03; 95% CI 1.01-1.05) and after surgery (OR 1.07; 95% CI 1.04-1.09), and antibiotics

≤ 24 hours before surgery (OR 2.54; 95% CI 1.63-3.94). This study incorporated both adult and paediatric patients. Problems associated with stratifying an adult study to the paediatric population include the added comorbidities such as smoking and diabetes mellitus in the adult patients.

This study was conducted in a multidisciplinary twenty bed PICU with open bays with no physical walls separating patients. A Canadian study conducted by Bowman et al in an eighteen bed PICU (Bowman, Rebeyka et al. 2013) reported a trend toward increased SSIs in patients undergoing delayed sternal closure in beds in the open bay of their PICU.

We did not include assessment of pre-surgical skin decontamination measures. In our institution it is policy that all children receive chlorhexidine baths prior to surgery, however, implementation was not consistently monitored. Less than adequate skin decontamination could have contributed to the SSI rate. This requires prospective investigation. Hafez et al found a high risk of SSIs in patients who received an antiseptic preoperative shower one day before surgery. The use and the timing of preoperative showers to reduce SSIs continue to be controversial. A Cochrane Review of six randomized controlled trials found no clear benefit of using 4% chlorhexidine gluconate for preoperative showers for SSI prevention (Hafez, Saied et al. 2012). These authors concluded that developing a clear policy for preoperative showering is crucial given that this procedure has organizational and economic implications and involves both the nursing staff and hospital administrators.

Chaudhuri et al (adult study) (Chaudhuri, Shekar et al. 2012) reported that early microbiological diagnosis of deep sternal wound infections (DSWI) could improve outcomes by allowing targeted antibiotic treatment. Superficial sternal wound swabs predicted the pathogen 75% of the time. Specific to *Staphylococcus aureus*, the positive predictive value of a superficial sternal swab was found to approach 100%. Colonisation with multi-resistant organisms was 100% predictive of the pathogen in DSWI. The multiresistant organism screen, which included nasal and perineal swabs, predicted the pathogen of DSWI in all cases that had a positive screen. The inclusion of blood cultures predicted the pathogen 82% of the time across all types of bacterial infections. The authors concluded that routine testing and reporting of these samples could enable early and targeted antimicrobial therapy in DSWI to improve outcomes.

Delayed sternal closure was not found to have an impact on infections in this study in contradiction to previous studies by Das et al. (Das, Rubio et al. 2011) and Johnson et al. (Johnson, Jaggers et al. 2010)Das et al reported (Das, Rubio et al. 2011) a significantly higher rate of BSIs in patients with delayed sternal closure. Their population had a mean age of 4 days, mean weight 3 kg and was post stage 1 Norwood surgery which could indicate a more vulnerable population undergoing more complex surgery. Similarly Johnson et al also used a cohort of neonatal post Norwood procedure patients and reported a longer duration of stay and higher infection rates in patients undergoing delayed sternal closure (Johnson, Jaggers et al. 2010).

Urinary tract infections occurred in 5% of the study population with all causative organisms being gram negative bacilli (*Enterococcus faecium, Klebsiella pneumoniae*). All were associated with having catheters in situ. Siddiqui et al reported a similar incidence (3.8%) (Siddiqui, Mir et al. 2011) of urinary tract infections; whilst Doyle et al reported an incidence of 18% with E. *coli* and *Candida spp.* Richards et al reported UTI incidence of 15% (Richards, Edwards et al. 1999). All studies concluded associated risk of UTI with use of an invasive device.

The mortality rate in this study population was 8.2% and not significantly associated with acquiring HAIs. The high mortality rate in our institution during the study period could be due to the relatively small study population with the resultant bias. Other reasons could include delayed presentation for diagnosis with relatively high complexity scores and subsequently experiencing complications such as pulmonary hypertension. Factors mentioned in previous studies include long waiting lists that add to complications such as failure to thrive that may increase patient risk of acquiring HAIs and subsequent increased mortality (Grisaru-Soen, Paret et al. 2009, Rosanova, Allaria et al. 2009, Mrowczynski, Wojtalik et al. 2002, Barker, O'Brien et al. 2010).

Siddiqui et al (Siddiqui, Mir et al. 2011) reported a lower HAI rate; however, the case fatality rate was 19.2%. The authors did not associate increased mortality risk with higher complexity score (RACHS->3) and BSI. An Argentinian study (Rosanova, Allaria et al. 2009) with a setting similar to our institution reported an overall mortality rate of 11% not associated with nosocomial infections in postoperative paediatric cardiac patients. This differs from several previous studies such as Tantawy et al (Tantawy, Seliem et al. 2012) who observed a mortality rate during their study period of 30.8%. The authors reported patients with nosocomial infection had significant mortality of 25%. Factors associated with mortality risk were younger age, higher complexity score for congenital cardiac lesions, prolonged CPB and ischemic times, HAI, prolonged mechanical ventilation, prolonged central line insertion and the use of total parenteral nutrition (Tantawy, Seliem et al. 2012). Grisaru-Soen (Grisaru-Soen, Paret et al. 2009) reported a similar mortality rate of 9.7%, however, the crude mortality rate for patients with nosocomial infection was 23.7%, compared with 2.2% for patients without NI ($P < 0.001$). These mortality rates are higher than reported in developed countries such as Saudi Arabia (2.9%) (Abou Elella, Najm et al. 2010) and Netherlands (2.6%) (Roeleveld, Guijt et al. 2011). A USA review of heart surgery databases conducted by Barket et al (Barker, O'Brien et al. 2010) reported mortality risk was greater (22.2%) in those with HAIs than in those without HAIs (3%) with major infections (mediastinitis, septicemia and endocarditis) (p = < 0.001) being significantly associated with risk.

Univariate analysis identified being underweight for age, fewer intraoperative events, more postoperative events, and longer duration of PICU and hospital stay as being associated with infection. Further associations identified were higher Aristotle score and long duration of arterial lines, CVP lines, pacing wires, urinary catheters and intercostal drains. However, on multivariate analysis only **increased duration of A-line, being underweight for age, and increased duration of stay prior to surgery** were identified as being independently associated with HAI.

Previous studies have found that longer **duration of central lines** was associated with the development of HAIs (Abou Elella, Najm et al. 2010, Bezzio, Scolfaro et al. 2009). Similarly to the study conducted by Abou Elella et al (Abou Elella, Najm et al. 2010) this study reported a high use of intravascular catheter devices. The authors postulated that extensive use of invasive devices, and the relative malnourished status of many of their patients contributed to their findings. Also, the device utilisation ratio (the number of days of individual device use divided by the total days of stay) corresponds to the rate of PICU nosocomial infections (Slonim, Kurtines et al. 2001). Our study population had a high CLABSI rate of 12.7 per 1000 central line days. At the time of the study, the background central line associated BSI rate for the PICU was 9.6 per 1000 central line days (Personal communication Heide Kunzmann). Because of the design of this study, we could not determine if the patients required prolonged arterial catheter use monitoring because of their HAI (to enable continuous blood pressure monitoring or routine blood sampling), or if they were prone to HAI due to prolonged catheter use. In a study conducted by Ben-Ami et al (Ben-Ami, Levy et al. 2008) the authors postulated that the mean dwell time for CVCs in their study population was identical to the mean time of SWI onset (10 days), which supported the assumption that it was the duration of catheterisation that was a causative factor for the infection.

Being **underweight for age** has previously been associated with increased risk of acquiring HAI (Ades, Dominguez et al. 2010). Contributing factors in this population group may include poor socio-economic background, chronic illness, late presentation or malnutrition. During this study a full nutritional assessment was not conducted on each patient. Weight measured was a reflection at one point during the study period and UWA was defined according to WHO criteria of less than -2SD of mean. We are thus unable to report if being UWA was due to inadequate diet or a reflection of severity of the existing cardiac condition.

A few studies have previously reported **duration of stay prior to surgery** being associated with the development of HAIs (Hafez, Saied et al. 2012, Allpress, Rosenthal et al. 2004). Allpress et al and Hafez et al reported an increased incidence of SSIs in paediatric cardiac patients with longer presurgery hospital stays. Possible reasons for this could include an increased exposure to hospital acquired organisms and a worse clinical state prior to cardiac surgery. This study did not find a significant association with HAIs and increased severity of illness scores (PIM2), increased complexity of surgery scores (Aristotle score) or multiple previous surgeries.

Previous studies have found that HAIs did not correlate with **length of stay** (Bezzio, Scolfaro et al. 2009, Richards, Edwards et al. 1999). An Argentinian study (Rosanova, Allaria et al. 2009) with a setting similar to our institution associated postoperative stay longer than 12 days with increased risk of acquiring HAIs. These authors were unable to report if the prolonged stay was cause or consequence of developing HAIs. Prolonged length of stay in the PICU and prolonged hospital stay are reported more frequently in critically ill patients who may have more risk factors for infection (Grisaru-Soen, Paret et al. 2009, Levy, Ovadia et al. 2003). Grisaru et al reported a relatively prolonged length of stay in PICU and a higher number of multiple surgeries in the patients who developed HAIs (Grisaru-Soen, Paret et al. 2009). Consequently, the length of hospitalisation might be a consequence instead of a cause of HAI. Indeed, this variable was no longer a risk factor for HAI on multivariate analysis in our study.

Postoperative events have frequently been associated with HAI and have emerged as a predictor for mortality in patients with HAI after paediatric cardiovascular surgery (Grisaru-Soen, Paret et al. 2009). Intraoperative events occurred in 24 patients (22%) and postoperative events occurred in 77 patients (70%) during this study. Postoperative and intraoperative events reported included all events of bleeding and arrhythmia requiring intervention to restore hemodynamic stability in the intra- and postoperative cardiac patient. These are events that due to the nature of cardiac surgery and patient profile may be considered expected events and not necessarily adverse events due to surgical / anaesthetic / medical incidents. This may account for the high incidence reported. On univariate analysis our study found an association with increased postoperative events and the development of infection, however, this was not found to be a significant association on multivariate analysis.

Barker et al (Barker, O'Brien et al. 2010) reported that mortality and postoperative length of stay were greater in those with major infection (mortality, 22.2% versus 3.0%; length of stay > 21 days, 69.9% versus 10.7%). Young age, high complexity, previous cardiothoracic operation, preoperative length of stay more than 1 day, preoperative ventilator support, and presence of a genetic abnormality were associated with major infection after backward selection ($P < 0.001$) (Barker, O'Brien et al. 2010).

Genetic and congenital malformation syndromes were not found to be significantly associated with acquiring HAI; this may be due to the small sample of patients included. McDonald et al (McDonald, Dodgen et al. 2012) previously reported on the impact of 22q11.2 deletion on the postoperative course of children after cardiac surgery. The findings revealed an increased incidence of fungal infection and wound infection in the del22q11 group, more days of positive blood and urine cultures indicating prolonged infections.

The use of **blood and blood products** were not significantly associated with HAIs as previously reported by Salvin et al (Salvin, Scheurer et al. 2011). In this institution all RBC concentrates are leukocyte depleted. The administration of blood is at the discretion of the anaesthetist / surgeon / perfusionist intra-operatively and the paediatric intensivist postoperatively. RBC transfusions are generally given with the goal of improving oxygen delivery or blood volume. Our study population differed from the Salvin (Salvin, Scheurer et al. 2011) study in that their patients requiring RBC transfusion were younger (age < 28 days), more likely to have single ventricle physiology, required more complicated cardiac surgery, and were more acutely ill.

Corticosteroids have been used in cardiac surgery with the aim of reducing inflammatory response after CPB. Various studies have produced mixed results. Similar to Pasquali et al. (Pasquali, Li et al. 2012), no association was found between the use of **corticosteroids** and HAIs. In this study two types of steroids were used and dosing differed between patients and surgeries. Solumedrol was used in the majority of patients who received steroids intraoperatively (93.3%, 42 of 45 patients). This is consistent with previous reports, that patient selection, dosing, and timing for steroid administration are highly variable among institutions (Clarizia, Manlhiot et al. 2011).

An observational analysis including multiple US centres was unable to demonstrate a significant benefit and actually demonstrated an increased morbidity associated with steroid use, longer duration of hospital stay, and greater infection risk (Pasquali, Hall et al. 2010). A further analysis by Pasquali (Pasquali, Li et al. 2012) showed no significant mortality or length-of-stay benefit associated with any methylprednisolone regimen versus no steroids, and no difference in postoperative infection. In subgroup analysis by surgical risk group, there was a significant association of methylprednisolone with infection consistent across all regimens in the lower-surgical-risk group. Mastropietro et al reported that increased cumulative corticosteroid exposure was a significant risk factor for infection in complex paediatric cardiac surgery patients (Mastropietro, Barrett et al. 2013). All patients in the study received intraoperative methylprednisolone 30mg/kg, 48% received postoperative hydrocortisone, and 86% received periextubation dexamethasone. This study did not evaluate cumulative steroid exposure in the post cardiac surgery patients.

Clarizia et al (Clarizia, Manlhiot et al. 2011) demonstrated that intraoperative steroid use was associated with shorter durations of stay in intensive care and hospital. Their use of an additional preoperative dose resulted in further improvements, especially reduction in duration of mechanical ventilation. Patients in the cohort who received steroids were younger, had longer CPB and aortic cross-clamp times, and had higher incidence of delayed sternal closure. The finding that they also experienced better outcomes suggests that targeted use of steroids for younger, more complex patients may provide the most benefit.

This study found no association with CPB duration, CPB temperature and aortic cross clamp duration with HAIs. It has been well documented that open heart surgery with CPB can result in systemic inflammatory response, impaired immune reaction, and organ dysfunction in children. Clinical consequences of bypass-induced injury are more significant in high-risk operations such as those on neonatal patients and those requiring prolonged use of **CPB**, especially with the use of deep hypothermic circulatory arrest (Clarizia, Manlhiot et al. 2011). Moderate hypothermia at 28^0 C has been shown to offer better protection from systemic inflammatory response syndrome (SIRS) postoperative than normothermia (37^0 C) during CPB in the experimental setting (Stocker, Shekerdemian et al. 2011). Stocker et al in a double blind randomized controlled trial found no evidence that SIRS is influenced by CPB temperature. In this study temperatures achieved during CPB varied significantly ranging from deep hypothermia to normothermia in various severities of cardiac condition. I can therefore not say with certainty that lower CPB temperature was a reflection of a sicker patient or associated with more severe underlying cardiac lesion. Lower CPB temperature may merely relate to a different surgical challenge.

The **Aristotle Basic Complexity (ABC) score system** was developed by consensus to compare outcomes of congenital cardiac surgery. In this study, the ABC score was not associated with increased HAI. A study done by Al-Radi (Al-Radi, Harrell et al. 2007) adjusted ABC by including age at operation in predictive models with ABC. The predictive value of such models improved and a strong association with in-hospital mortality and length of stay was demonstrated.

<u>INTERVENTIONS INFLUENCING ICU INFECTION EPIDEMIOLOGY</u>

Hand hygiene is the single most important measure to reduce transmission of microorganisms between patients (Doyle, Buising et al. 2011). The use of alcohol-based hand rubs has led to markedly improved hand hygiene compliance, and particularly reduces transmission of MRSA. Sustained improvement in hand hygiene has been shown to be associated with a fall in ICU-acquired infection rates (Doyle, Buising et al. 2011).

Chlorhexidine body washes have been increasingly used in ICUs and other settings to prevent bacterial acquisition, colonisation, and infection. In ICUs, chlorhexidine bathing has been shown to substantially decrease MRSA acquisition, colonisation, and infection (at times with intranasal Mupirocin), bacteraemia, and MRSA ventilator pneumonia, and to reduce *A. baumannii* skin colonisation and bloodstream infections (with whole body washes with 4% chlorhexidine gluconate) (Doyle, Buising et al. 2011). Daily bathing with 2% chlorhexidine gluconate washcloths reduced primary bloodstream infections with the protection benefit evident after 5 or more days in the ICU (Bleasdale, Trick et al. 2007). As mentioned above, in our institution chlorhexidine bathing is done prior to surgery, however, the compliance with this protocol was not assessed.

BUNDLES OF CARE

A bundle is a set of a small number of evidence-based prevention practices that improve patient outcomes when performed collectively and consistently (Institute for Healthcare Improvement (IHI) Updated 2014). The CVC bundle includes the use of aseptic techniques, including maximal barrier precautions, hand washing, chlorhexidine insertion site antisepsis, and daily review and removal of unnecessary catheters (Berenholtz, Pronovost et al. 2004, McKee, Berkowitz et al. 2008). This bundle has achieved significant decreased bacteraemia, and is associated with cultural change in the ICU, and nearly eliminates CLABSIs (O'Grady, Alexander et al. 2002). Similar bundles are used to prevent VAP and catheter associated UTI (Muscedere, Dodek et al. 2008, Fuhrman, Zimmerman et al. 2011).

ANTIMICROBIAL USE IN THE ICU

Antimicrobial use in the ICU is an important factor influencing the epidemiology of infections in the ICU. It is known that frequent antibiotic use promotes selection of resistant microorganisms. A balance has to be met in the ICU with policies that promote early use of broad spectrum empirical antibiotics, followed by de-escalation to narrower spectrum antibiotics, or shortening the duration of treatment in response to investigation results or clinical improvement – in keeping with the Surviving Sepsis Guidelines (Dellinger, Levy et al. 2008).

LIMITATIONS

There are several limitations to this study. This study was conducted in a single tertiary centre with a relatively small sample size and short period of study (6 months), which may limit its generalisability. The follow-up was limited to the duration of hospital stay due to resource limitations. SSIs according to CDC criteria require 30 day follow up postoperatively, therefore SSIs that developed post hospital discharge would have been missed. However, a study done by Sarvikivi et al (Sarvikivi, Lyytikainen et al. 2008) designed to detect SSIs within 30 days after surgery, concluded that postdischarge SSI surveillance might not have clinical relevance in pediatric cardiac surgery patients.

Due to this study being observational I did not intervene in patient management. I can therefore not be sure that all specimens were taken for appropriate reasons according to the study protocols. I recorded the results of all specimens collected from the study patients during their PICU admission. The implication hereof was that specimens may have been collected in patients who did not strictly meet criteria for infection which inturn has implications for unnecessary investigation expenses, additional utilisation of antibiotics and challenges in the clinical interpretation of postive microbial detection.

The definition of pulmonary infections, including VAP, was based on clinical and microbiological criteria not included in the Infectious Diseases Society of America definition. Pulmonary infections included those diagnosed by CPIS VAP score ≥ 6 that were not treated with antimicrobials and no organism isolated. The diagnosis of respiratory infections could, therefore, have been over-estimated by using the CPIS scoring system. Diagnosing VAP using a modification of the CPIS was previously validated in this institution in a general PICU population and not in a cardiac surgery population (Morrow, Argent et al. 2009, Morrow, Mowzer et al. 2012).

The incidence of intraoperative events may have been under reported, as this relied on documentation in the patient records by the attending anaesthetist and cardiothoracic surgeon.

Patients being treated for infection with antimicrobials prior to cardiac surgery were not excluded from the study and the effect of pre-existing infection was not investigated in this study. The effects of co-existing HAIs in the same post cardiac surgery paediatric patient were not investigated. As an example raised inflammatory markers in a patient with BSI could influence using CPIS to diagnose VAP. It remains unclear whether one HAI predisposes to developing a secondary / additional HAI. This is the dilemma created by including patients with different types of HAIs in the same study instead of focussing on a specific HAI in a cohort of patients.

It is reasonable to suggest that longer duration of A-line and hospital stay may reflect increased disease severity in a cardiac patient.

In this study, indices of disease severity and cardiac surgery comlexity were not found to be significantly different between the group of patients that developed HAIs versus those who did not. The study population may have been too small to demonstrate this. The HAI group had younger infants, longer duration of CPB and more patients requiring delayed sternal closure which could indicate increased disease severity, however, this was not found to be significant on univariate analysis. The categories of surgery, PIM 2 scoring and Aristotle scores were not significantly different on final analysis. However, it is important to note that this study was not designed to investigate the relationship between specific causal-consequence factors increasing risk of acquiring HAIs in this population group.

Despite these limitations this study has revealed definite points of reference for HAIs in postoperative cardiac surgery patients and provided valuable information for the design of future prospective studies.

CHAPTER 6

CONCLUSION AND RECOMMENDATIONS

Gram negative and viral isolates were the most common organisms associated with HAIs developing in PICU after paediatric cardiac surgery. The incidence of HAI in this population was high with identified factors associated with risk being underweight for age, prolonged duration of A-lines and prolonged duration of stay prior to surgery. This study has shown that various issues may be related to the development of HAI in this group of patients.

Previous studies have found that longer duration of central lines was associated with the development of HAIs (Abou Elella, Najm et al. 2010, Bezzio, Scolfaro et al. 2009). Similarly to the study conducted by Abou Elella et al (Abou Elella, Najm et al. 2010) this study reported a high use of intravascular catheter devices. The authors postulated that extensive use of invasive devices, and the relative malnourished status of many of their patients contributed to their findings. Because of the design of this study, we could not determine if the patients required prolonged arterial catheter use monitoring because of their HAI (to enable continuous blood pressure monitoring or routine blood sampling), or if they were prone to HAI due to prolonged catheter use. Further delineation of the causal relationship between prolonged use of invasive devices (CVP lines, A-lines, pacing wires, ICDs and urinary catheters), severity of cardiac disease and risk of developing HAIs in this population group is needed.

Being underweight for age has previously been associated with increased risk of acquiring HAI (Ades, Dominguez et al. 2010). Contributing factors in this population group may include poor socio-economic background, chronic illness, late presentation or malnutrition. During this study a full nutritional assessment was not conducted on each patient. Weight measured was a reflection at one point during the study period and UWA was defined according to WHO criteria of less than -2SD of mean. We are thus unable to report if being UWA was due to inadequate diet or a reflection of severity of the existing cardiac condition.

A few studies have previously reported duration of stay prior to surgery being associated with the development of HAIs (Hafez, Saied et al. 2012, Allpress, Rosenthal et al. 2004). Possible reasons for this could include an increased exposure to hospital acquired organisms and a worse clinical state prior to cardiac surgery. This study did not find a significant association with HAIs and increased severity of illness scores (PIM2), increased complexity of surgery scores (Aristotle score) or multiple previous surgeries.

Perioperative factors such as intra- and postoperative complications and duration of stay prior to surgery, together with postoperative outcomes such as durations of ventilation, PICU and hospital stay are both indicators of severity of disease and proven risk factors for developing HAIs in this population group. Distinguishing cause from consequence would require further prospective, randomised and controlled clinical trials. This study’s findings may be used to inform suggestions for further studies into the management of paediatric cardiac patients with the aim to reduce durations of ventilation and durations of stay in PICU in an attempt to reduce risk of acquiring HAIs.

There is an urgent need for better biomarkers for risk stratification, therapeutic monitoring and to differentiate systemic inflammatory response syndrome (SIRS) from infection in this population. Improved understanding is needed of the impact of different CHD, and in particular, the effects of CPB, on the subsequent risk for HAIs. Understanding of the epidemiology, pathogen distribution, and antibiotic resistance profile may promote the rational use of antibiotics. This is crucial to reduce drug resistance, mortality, and hospital costs. Antimicrobial agents selected for treatment of HAIs should be effective against any likely pathogen but should not promote the development of further resistance.

Possible exposure to infectious organisms prior to surgery whether viral or bacterial organisms provide challenges in diagnosing nosocomial infection if pre-existing infection or colonisation is not detected prior to surgery. Further studies are needed to develop strategies for preventing and optimising the management of HAIs in postoperative paediatric cardiac patients (Wheeler, Jeffries et al. 2011). The strategies this institution would need to consider are:

- Pre-operative measures, such as optimising nutrition, active screening for colonisation and pre-existing infections
- Intra-operative measures, such as consistent steroid use and appropriate individually specific prophylactic antibiotic use (considering vancomycin use if MRSA colonised)
- Postoperative measures, such as policy implementation of HAI bundles of Care, for VAP, CRBSIs, CAUTIs, and SSIs, early extubation of mechanically ventilated patients, and early removal of arterial and venous central catheters, cohorting of patients with similar infective organisms
- Particular attention is required to address the complexities of diagnosing multiple HAIs in the same postoperative cardiac surgery patient.

APPENDICES

APPENDIX 1. REFERENCES

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APPENDIX 2. ETHICS APPROVAL

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za

09 September 2011

HREC REF: 424/2011

Dr I Appel
Intensive Care Unit
Red Cross War Memorial Children's Hospital

Dear Dr Appel

PROJECT TITLE: ACQUIRED INFECTIONS IN PAEDIATRIC PATIENTS AFTER CARDIAC SURGERY.

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 28 September 2012.

Please submit a progress form, using the standardised Annual Report Form (FHS016), if the study continues beyond the approval period. Please submit a Standard Closure form (FHS010) if the study is completed within the approval period.

Please advise Dr Tommy Blake, the Medical Superintendent, that the study is taking place at Red Cross Children's Hospital. The form is available on the Human Research Ethics Committee's Website.

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, HSF HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.

s.thomas

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) **This serves as notification of annual approval, including any documentation described below.**						
☑ Approved	Annual progress report		Approved until/next renewal date	28	09	2014
☐ Not approved	See attached comments					
Signature Chairperson of the HREC		pp T.Burgess	Date Signed	07	10	2014

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date form submitted	Protocol submitted September 2011		
HREC REF Number	424/2011	Current Ethics Approval was granted until	28 Sept 2013
Protocol title	Acquired infections in paediatric patients after cardiac surgery		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?		☐ Yes ☑ No	
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	ILSE APPEL		
Department / Office Internal Mail Address	pp. Dr. Brenda Morrow PICU, Red Cross Children's Hospital		

HUMAN RESEARCH ETHICS COMMITTEE
06 JAN 2014
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

1.1 Does this protocol receive US Federal funding?	☐ Yes	☑ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	☐ Yes	☐ No

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

APPENDIX 3. DATA COLLECTION FORMS

PATIENT	000 FOLDER #		
Date of hospital admission			
Date of PICU admission 1 Time	Date of PICU1 discharge Time		
Date of PICU admission 1 Time	Date of PICU1 discharge Time		
Age / Gestational age			
sex	Male	Female	
height		Estimated Height for age:	Nutritional state:
weight		Estimated Weight for age:	Nutritional state:
Cardiac lesion			
Previous surgical history			
Admitted from home / ward / mother's room			
Genetic Syndromes (e.g. Trisomy21, 22 Q deletion)			
Other medical illness:			
Medications preoperative (omeprazole)			

OPERATION	DATE			
Type – complexity score				
Surgeon				
CPB duration				
Cross clamp time				
Chest left open	Y N			
Antibiotics: time				
Blood products: volume, type				
Endotracheal tube intubation: nasal/oral intubation				
Date extubated				

INTRAOPERATIVE COMPLICATIONS				
Bleeding: blood transfusion, blood product transfusion volume, same donor, leukocyte depleted				
Cardiac arrest				
Reintubation				
Chest re-opened				

SURGICAL WOUNDS		DATE		
Mediastinotomy	Dressing change			
Y N				
Thoracotomy	Dressing change			
Y N				

CATHETERS/ LINES				
CVP	Site			
	Date inserted			
	Date removed			
	Dressing change			
Arterial line	Site			
	Date inserted			
	Date removed			
	Dressing change			
Pacing wires	Site			
	Date inserted			
	Date removed			
	Dressing change			
Urinary catheter	Date inserted			
	Date removed			
Mediastinal drain	Site			
	Date inserted			
	Date removed			
	Dressing change			
Intercostal chest drain	Site			
	Date inserted			
	Date removed			
	Dressing change			

VAP identification: Clinical Pulmonary Infection Score (CPIS).

Please tick appropriate box (worst value over previous 24 hours)

PARAMETER	**CPIS RANGE**	**CPIS SCORE**
Temperature (°C)	36.5-38.4	0
	38.5-39.0	1
	<36.0 or >39.0	2
Leukocyte count ($X\ 10^9/l$)	4.0-11	0
	≤3.9 ≥11.1 and no bands or ≥ 11.1 ≤17.0 and no differentiation done	1
	≥11.1 with bands or no differentiation done and leukocytes ≥17.1	2
Chest radiography	No CXR taken or no infiltrate	0
	Diffuse or patchy infiltrate	1
	Localised infiltrate	2
Pulmonary secretions	Absent or minimal	0
	Present and non purulent	1
	Present and purulent	2
PaO_2 (mmHg)/FiO_2	>240	0
	≤ 240	2
Organism isolated on BAL	No or Not Done	0
	Yes	2
	TOTAL SCORE	

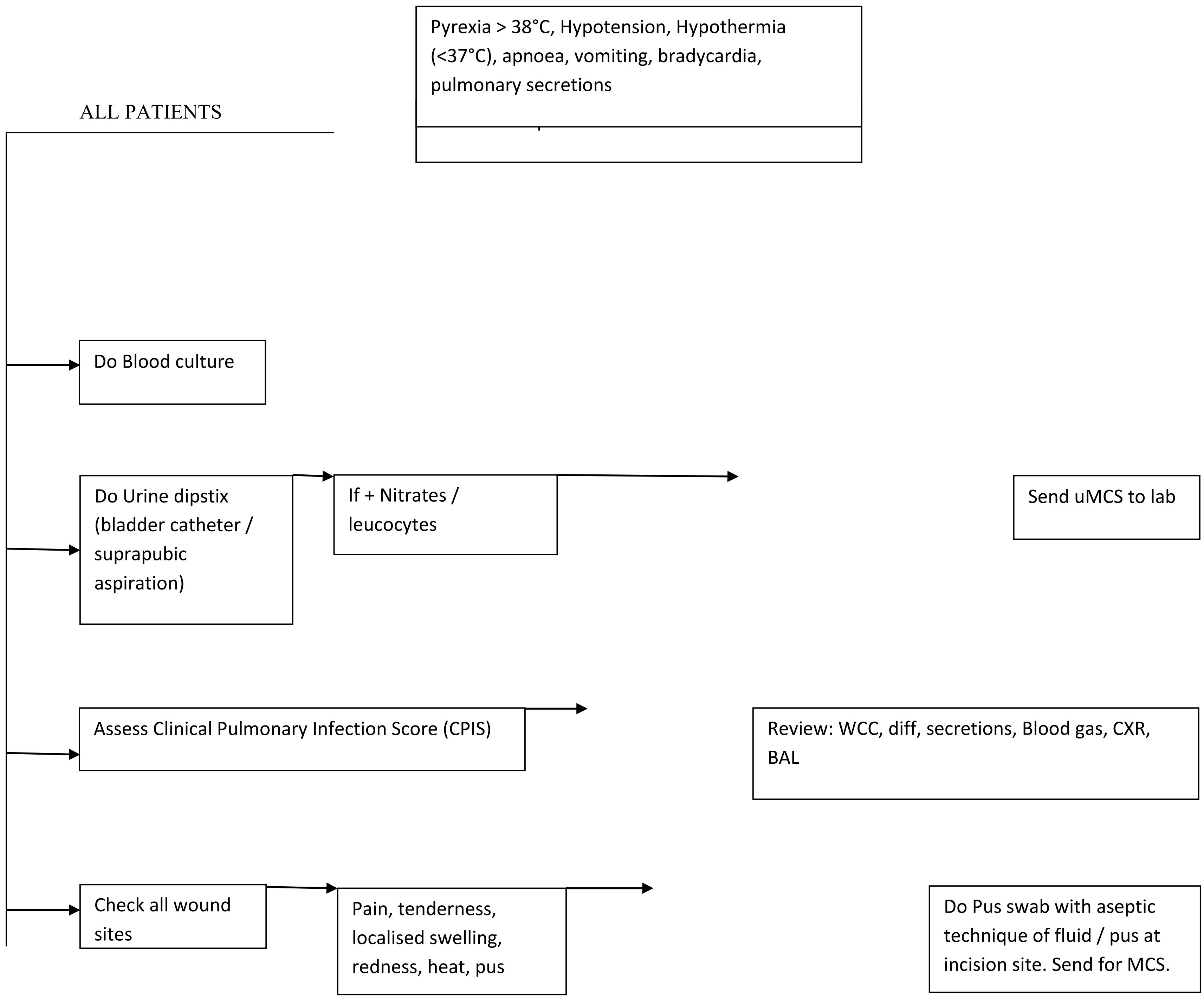
Circle if total score ≥ 6: VAP identified

worst value over previous 24 hours		DATE			
White cell count					
Bands					
Hb					
Platelets					
PCT					
Blood glucose					
T°	LOW				
	HIGH				
CXR findings					
Pulmonary secretions					
PaO_2 (mmHg)/FiO_2 **e.g. PaO_2 8, FiO_2 30% (8 x 7.5 / 0.3)**					
Cultured specimens:	BAL				
	Urine				
	Blood				
	Pus Swab				
Clinician opinion to treat infection		Y N N/A	Y N N/A	Y N N/A	Y N N/A
Suspected infection site					
CPIS					

ANTIMICROBIALS				
Type				
Date initiated				
ended				
Dosage				

COMPLICATIONS POSTOPERATIVELY	DATE			
Blood transfusion, blood product transfusion volume, same donor, leukocyte depleted				
Cardiac arrest				
Reintubation				
Chest re-opened				
Organ failure liver: AST, ALT, TSB, INR Renal: urea, creatinine				
Other:				

APPENDIX 4. GUIDELINES FOR INFECTION INVESTIGATION IN THE PICU



APPENDIX 5. CDC DEFINITIONS OF INFECTIONS (Centers for Disease Control and Prevention 2014)

Laboratory confirmed blood stream infections (BSI), urinary tract infections (UTI), and surgical site infections

Present on Admission (POA) Infections

If all of the elements used to meet a CDC site specific infection criterion are present during the two calendar days before the day of admission, the first day of admission (day 1) and/or the day after admission (day 2) and are documented in the medical record, the infection is considered POA. Infections that are POA should not be reported as HAIs.

Healthcare-associated infections (HAI)

A healthcare-associated infection (HAI) is a localised or systemic condition resulting from an adverse reaction to the presence of an infectious agent(s) or its toxin(s) that was not present on admission to the acute care facility. An infection is considered an HAI if all elements of a CDC/NHSN site-specific infection criterion were not present during the POA time period but were all present on or after the 3rd calendar day of admission to the facility (the day of hospital admission is calendar day 1).

Bloodstream infection (BSI)

Table 1. Laboratory-Confirmed Bloodstream Infection Criteria

Criterion	**Laboratory-Confirmed Bloodstream Infection (LCBI)** *Comments and reporting instructions that follow the site-specific criteria provide further explanation and are integral to the correct application of the criteria.* Must meet one of the following criteria:
LCBI 1	Patient has a recognized pathogen cultured from one or more blood cultures *and* organism cultured from blood is not related to an infection at another site. (See Appendix 1 Secondary BSI Guide)
LCBI 2	Patient has at least one of the following signs or symptoms: fever (>38^{o}C), chills, or hypotension *and* positive laboratory results are not related to an infection at another site (See Appendix 1 Secondary BSI Guide) *and* the same common commensal (i.e., diphtheroids [*Corynebacterium* spp. not *C. diphtheriae*], *Bacillus* spp. [not *B. anthracis*], *Propionibacterium* spp., coagulase-negative staphylococci [including *S. epidermidis*], viridans group streptococci, *Aerococcus* spp., and *Micrococcus* spp.) is cultured from two or more blood cultures drawn on separate occasions (see comment 3a below). Criterion elements must occur within a timeframe that does not exceed a gap of 1 calendar day between two adjacent elements.

	(See complete list of common commensals at http://www.cdc.gov/nhsn/XLS/master-organism-Com-Commensals- Lists.xlsx) **NOTE:** The matching common commensals represent a single element; therefore, the collection date of the first common commensal is the date of the element used to determine the Date of Event.
LCBI 3	Patient ≤ 1 year of age has at least one of the following signs or symptoms: fever (>38oC core), hypothermia (<36oC core), apnea, or bradycardia *and* positive laboratory results are not related to an infection at another site (See Appendix 1 Secondary BSI Guide) *and* the same common commensal (i.e., diphtheroids [*Corynebacterium* spp. not *C. diphtheriae*], *Bacillus* spp. [not *B. anthracis*], *Propionibacterium* spp., coagulase-negative staphylococci [including *S. epidermidis*], viridans group streptococci, *Aerococcus* spp., *Micrococcus* spp.) is cultured from two or more blood cultures drawn on the same or consecutive days and separate occasions (see Comment 3a below). Criterion elements must occur within a timeframe that does not exceed a gap of 1 calendar day between two adjacent elements. (See complete list of common commensals at http://www.cdc.gov/nhsn/XLS/master- organism-Com-Commensals-Lists.xlsx#common) **NOTE:** The matching common commensals represent a single element; therefore, the collection date of the first common commensal is the date of the element.
REPORTING INSTRUCTIONS	1. Report organisms cultured from blood as BSI–LCBI when no other site of infection is evident (see Appendix 1. Secondary Bloodstream Infection [BSI] Guide). 2. Catheter tip cultures are not used to determine whether a patient has a primary BSI. 3. When there is a positive blood culture and clinical signs or symptoms of localised infection at a vascular access site, but no other infection can be found, the infection is considered a primary BSI. 4. Purulent phlebitis confirmed with a positive semiquantitative culture of a catheter tip, but with either negative or no blood culture is considered a CVS-VASC, not a BSI, SST-SKIN, or a ST infection.

	5. Occasionally a patient with both peripheral and central IV lines develops a primary bloodstream infection (LCBI) that can clearly be attributed to the peripheral line (e.g., pus at the insertion site and/or matching pathogen from pus and blood). In this situation, enter “Central Line = No” in the NHSN application. You should, however, include the patient’s central line days in the summary denominator count. 6. If your state or facility requires that you report healthcare-associated BSIs that are not central line-associated, enter “Central Line = No” in the NHSN application when reporting these BSIs. You should, however, include all of the patient’s central line days in the summary denominator count.

Lower respiratory tract infection (LRTI), other than pneumonia

BRON-Bronchitis, tracheobronchitis, bronchiolitis, tracheitis, without evidence of pneumonia

Tracheobronchial infections must meet at least *1* of the following criteria:

1. Patient has no clinical or imaging test evidence of pneumonia

and patient has at least *2* of the following signs or symptoms: fever (>38°C), cough*, new or increased sputum production*, rhonchi*, wheezing* *and* at least *1* of the following:

a. positive culture obtained by deep tracheal aspirate or bronchoscopy

b. positive laboratory test on respiratory secretions. * With no other recognized cause

2. Patient ≤1 year of age has no clinical or imaging test evidence of pneumonia

and patient has at least *2* of the following signs or symptoms: fever (>38°C core), cough*, new or increased sputum production*, rhonchi*, wheezing*, respiratory distress*, apnea*, or bradycardia* *and* at least *1* of the following:

a. organisms cultured from material obtained by deep tracheal aspirate or bronchoscopy b. positive laboratory test on respiratory secretions c. diagnostic single antibody titer (IgM) or 4-fold increase in paired sera (IgG) for pathogen.

* With no other recognized cause

Pneumonia

There are 3 specific types of pneumonia: clinically-defined pneumonia (PNU1), pneumonia with specific laboratory findings (PNU2), and pneumonia in immunocompromised patients (PNU3). Listed below are general comments applicable to all specific types of pneumonia, along with abbreviations used in the algorithms and reporting instructions.

Table 11 shows threshold values for cultured specimens used in the surveillance diagnosis of pneumonia.

General comments

5. Physician diagnosis of pneumonia alone is not an acceptable criterion for healthcare-associated pneumonia.
6. Although specific criteria are included for infants and children, pediatric patients may meet any of the other pneumonia specific site criteria.

7. When assessing a patient for presence of pneumonia, it is important to distinguish between changes in clinical status due to other conditions such as myocardial infarction, pulmonary embolism, respiratory distress syndrome, atelectasis, malignancy, chronic obstructive pulmonary disease, hyaline membrane disease, bronchopulmonary dysplasia, etc. Also, care must be taken when assessing intubated patients to distinguish between tracheal colonization, upper respiratory tract infections (e.g., tracheobronchitis), and early onset pneumonia. Finally, it should be recognized that it may be difficult to determine healthcare-associated pneumonia in the elderly, infants, and immunocompromised patients since such conditions may mask typical signs or symptoms associated with pneumonia. Alternate specific criteria for the elderly, infants, and immunocompromised patients have been included in this definition of healthcare-associated pneumonia.
8. Healthcare–associated pneumonia can be characterized by its onset: early or late. Early-onset pneumonia occurs during the first 4 days of hospitalization and is often caused by *Moraxella catarrhalis*, *H influenzae*, and *S pneumoniae*. Causative agents of late-onset pneumonia are frequently Gram-negative bacilli or *S aureus*, including methicillin-resistant *S aureus*. Viruses (e.g., influenza A and B or respiratory syncytial virus) can cause early- and late-onset nosocomial pneumonia, whereas yeasts, fungi, legionellae, and *Pneumocystis carinii* are usually pathogens of late-onset pneumonia.
9. Pneumonia due to gross aspiration (for example, in the setting of intubation in the emergency room or operating room) is considered healthcare associated if it meets any specific criteria and the infection itself was not clearly present at the time of admission to the hospital.
10. Multiple episodes of healthcare-associated pneumonia may occur in critically ill patients with lengthy hospital stays. When determining whether to report multiple episodes of healthcare–associated pneumonia in a single patient, look for evidence of resolution of the initial infection. See Note following HAI definition in Chapter 2. The addition of or change in pathogen alone is not indicative of a new episode of pneumonia.
11. Positive Gram's stain for bacteria and positive KOH (potassium hydroxide) mount for elastin fibers and/or fungal hyphae from appropriately collected sputum specimens are important clues that point toward the etiology of the infection. However, sputum samples are frequently contaminated with airway colonizers and therefore must be interpreted cautiously. In particular, *Candida* is commonly seen on strain, but infrequently causes healthcare-associated pneumonia, especially in immunocompetent patients.

Abbreviations

BAL–bronchoalveolar lavage EIA–enzyme immunoassay FAMA–fluorescent-antibody staining of membrane antigen IFA–immunofluorescent antibody LRT–lower respiratory tract PCR–polymerase chain reaction PMN–polymorphonuclear leukocyte RIA–radioimmunoassay

Reporting instructions

• There is a hierarchy of specific categories within the major type pneumonia (PNEU). Even if a patient meets criteria for more than 1 specific site, report only 1:

o If a patient meets criteria for both PNU1 and PNU2, report PNU2. o If a patient meets criteria for both PNU2 and PNU3, report PNU3. o If a patient meets criteria for both PNU1 and PNU3, report PNU3.

12. Report concurrent lower respiratory tract infection (e.g., abscess or empyema) and pneumonia with the same organism(s) as PNEU.
13. Lung abscess or empyema without pneumonia is classified as LUNG.
14. Bronchitis, tracheitis, tracheobronchitis, or bronchiolitis without pneumonia are classified as BRON.

Table 2. Specific Site Algorithms for Clinically-Defined Pneumonia (PNU1)

<table>
<tr><th>Radiology</th><th>Signs/Symptoms/Laboratory</th></tr>
<tr><td rowspan="3">Two or more serial chest radiographs with at least one of the following:
• New or progressive and persistent infiltrate
• Consolidation
• Cavitation
• Pneumatoceles, in infants ≤1 year old NOTE: In patients without underlying pulmonary or cardiac disease (e.g., respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary edema, or chronic obstructive pulmonary disease), one definitive chest radiograph is acceptable.</td><td>FOR ANY PATIENT, at least one of the following:
• Fever (>38°C or >100.4°F)
• Leukopenia (<4000 WBC/mm) or leukocytosis (≥12,000 WBC/mm) • For adults ≥70 years old, altered mental status with no other recognized cause and at least two of the following:
• New onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements
• New onset or worsening cough, or dyspnea, or tachypnea
• Rales or bronchial breath sounds
• Worsening gas exchange (e.g., O_2 desaturations (e.g., $PaO_2/FiO_2 \le 240$), increased oxygen requirements, or increased ventilator demand)</td></tr>
<tr><td>ALTERNATE CRITERIA, for infants <1 year old:
Worsening gas exchange (e.g., O_2 desaturations [e.g., pulse oximetry <94%], increased oxygen requirements, or increased ventilator demand) and at least three of the following:
• Temperature instability
• Leukopenia (<4000 WBC/mm^3) or leukocytosis (≥15,000 WBC/mm^3) and left shift (≥10% band forms)
• New onset of purulent sputum or change in character of sputum, or increased respiratory secretions or increased suctioning requirements
• Apnea, tachypnea , nasal flaring with retraction of chest wall or grunting
• Wheezing, rales, or rhonchi
• Cough
• Bradycardia (<100 beats/min) or tachycardia (>170 beats/min)</td></tr>
<tr><td>ALTERNATE CRITERIA, for child >1 year old or ≤12 years old, at least three of the following:
• Fever (>38.4°C or >101.1°F) or hypothermia (<36.5°C or <97.7°F)
• Leukopenia (<4000 WBC/mm^3) or leukocytosis (≥15,000 WBC/mm^3)</td></tr>
</table>

	• New onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements • New onset or worsening cough, or dyspnea, apnea, or tachypnea. • Rales or bronchial breath sounds • Worsening gas exchange (e.g., O_2 desaturations [e.g., pulse oximetry <94%], increased oxygen requirements, or increased ventilator demand)

Table 3. Specific Site Algorithms for Pneumonia with Common Bacterial or Filamentous Fungal Pathogens and Specific Laboratory Findings (PNU2)

Radiology	**Signs/Symptoms**	**Laboratory**
Two or more serial chest radiographs with at least **one** of the following: • New or progressive and persistent infiltrate • Consolidation • Cavitation • Pneumatoceles, in infants ≤1 year old NOTE: In patients **without** underlying pulmonary or cardiac disease (e.g., respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary edema, or chronic obstructive pulmonary disease), one definitive chest radiograph is acceptable.	At least **one** of the following: • Fever (>38°C or >100.4°F) • Leukopenia (<4000 WBC/mm3) or leukocytosis (≥12,000 WBC/mm3) • For adults ≥70 years old, altered mental status with no other recognized cause *and* at least **one** of the following: • New onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements • New onset or worsening cough, or dyspnea or tachypnea • Rales or bronchial breath sounds • Worsening gas exchange (e.g., O2 desaturations [e.g., PaO2/FiO2 ≤240], increased oxygen requirements, or increased ventilator demand)	At least **one** of the following: • Positive growth in blood culture not related to another source of infection • Positive growth in culture of pleural fluid • Positive quantitative culture from minimally contaminated LRT specimen (e.g., BAL or protected specimen brushing) • ≥5% BAL-obtained cells contain intracellular bacteria on direct microscopic exam (e.g., Gram's stain) • Histopathologic exam shows at least **one** of the following evidences of pneumonia: o Abscess formation or foci of consolidation with intense PMN accumulation in bronchioles and alveoli o Positive quantitative culture of lung parenchyma o Evidence of lung parenchyma invasion by fungal hyphae or pseudohyphae

Table 4. Specific Site Algorithms for Viral, Legionella, and other Bacterial Pneumonias with Definitive Laboratory Findings (PNU2)

Radiology	**Signs/Symptoms**	**Laboratory**
Two or more serial chest radiographs with at least **one** of the following: • New or progressive and persistent infiltrate • Consolidation • Cavitation • Pneumatoceles, in infants ≤1 year old NOTE: In patients **without** underlying pulmonary or cardiac disease (e.g., respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary edema, or chronic obstructive pulmonary disease), one definitive chest radiograph is acceptable.	At least **one** of the following: • Fever (>38°C or >100.4°F) • Leukopenia (<4000 WBC/mm3) or leukocytosis (≥12,000 WBC/mm3) • For adults ≥70 years old, altered mental status with no other recognized cause *and* at least one of the following: • New onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements • New onset or worsening cough or dyspnea, or tachypnea • Rales or bronchial breath sounds • Worsening gas exchange (e.g., O2 desaturations [e.g., PaO2/FiO2 ≤240], increased oxygen requirements, or increased ventilator demand)	At least **one** of the following: • Positive culture of virus or *Chlamydia* from respiratory secretions • Positive detection of viral antigen or antibody from respiratory secretions (e.g., EIA, FAMA, shell vial assay, PCR) • Fourfold rise in paired sera (IgG) for pathogen (e.g., influenza viruses, *Chlamydia*) • Positive PCR for *Chlamydia* or *Mycoplasma* • Positive micro-IF test for *Chlamydia* • Positive culture or visualization by micro-IF of *Legionella spp*, from respiratory secretions or tissue. • Detection of *Legionella pneumophila* serogroup 1 antigens in urine by RIA or EIA • Fourfold rise in *L. pneumophila* serogroup 1 antibody titer to ≥1:128 in paired acute and convalescent sera by indirect IFA.

Footnotes to Algorithms:

Occasionally, in nonventilated patients, the diagnosis of healthcare-associated pneumonia may be quite clear on the basis of symptoms, signs, and a single definitive chest radiograph. However, in patients with pulmonary or cardiac disease (for example, interstitial lung disease or congestive heart failure), the diagnosis of pneumonia may be particularly difficult. Other noninfectious conditions (for example, pulmonary edema from decompensated congestive heart failure) may simulate the presentation of pneumonia. In these more difficult cases, serial chest radiographs must be examined to help separate infectious from noninfectious pulmonary processes. To help confirm difficult cases, it may be useful to review radiographs on the day of diagnosis, 3 days prior to the diagnosis and on days 2 and 7 after the diagnosis. Pneumonia may have rapid onset and progression, but does not resolve quickly. Radiographic changes of pneumonia persist for several weeks. As a result, rapid radiographic resolution suggests that the patient does not have pneumonia but rather a noninfectious process such as atelectasis or congestive heart failure

<u>Surgical Site Infection (SSI)</u>

<u>DIP/DIS-Deep incisional surgical site infection</u>

Deep incisional SSI must meet the following criterion:

Infection occurs within 30 or 90 days after the NHSN operative procedure (where day 1 = the procedure date) according to the list in Table 12

and

involves deep soft tissues of the incision (e.g., fascial and muscle layers)

and

patient has at least one of the following:

a. purulent drainage from the deep incision

b. a deep incision that spontaneously dehisces or is deliberately opened by a surgeon, attending physician** or other designee and is culture-positive or not cultured

and

patient has at least one of the following signs or symptoms: fever (>38°C); localised pain or tenderness. A culture-negative finding does not meet this criterion.

c. an abscess or other evidence of infection involving the deep incision that is detected on direct examination, during invasive procedure, or by histopathologic examination or imaging test.

** The term attending physician for the purposes of application of the NHSN SSI criteria may be interpreted to mean the surgeon(s), infectious disease, other physician on the case, emergency physician or physician's designee (nurse practitioner or physician's assistant).

Comments

There are two specific types of deep incisional SSIs:

1. Deep Incisional Primary (DIP) – a deep incisional SSI that is identified in a primary incision in a patient that has had an operation with one or more incisions (e.g., C-section incision or chest incision for CBGB)

2. Deep Incisional Secondary (DIS) – a deep incisional SSI that is identified in the secondary incision in a patient that has had an operation with more than one incision (e.g., donor site [leg] incision for CBGB)

Reporting instructions

• The type of SSI (superficial incisional, deep incisional, or organ/space) reported should reflect the deepest tissue layer involved in the infection: o Report infection that involves the organ/space as an organ/space SSI, whether or not it also involves the superficial or deep incision sites.

o Report infection that involves the superficial and deep incisional sites as a deep incisional SSI.

o Report infection that involves the superficial and deep incisional sites as a deep incisional SSI.

<u>Organ/space surgical site infection</u>

Organ/Space SSI must meet the following criterion:

Infection occurs within 30 or 90 days after the NHSN operative procedure (where day 1 = the procedure date)

and

infection involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure

and

patient has at least 1 of the following:

a. purulent drainage from a drain that is placed into the organ/space

b. organisms isolated from an aseptically-obtained culture of fluid or tissue in the organ/space

c. an abscess or other evidence of infection involving the organ/space that is detected on direct examination, during invasive procedure, or by histopathologic examination or imaging test

and

meets at least one criterion for a specific organ/space infection site

Comments

Because an organ/space SSI involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure, the criterion for infection at these body sites must be met in addition to the organ/space SSI criteria. For example, an appendectomy with subsequent subdiaphragmatic abscess would be reported as an organ/space SSI at the intraabdominal specific site (SSI-IAB) when both organ/space SSI and IAB criteria are met.

Reporting instructions

• If a patient has an infection in the organ/space being operated on, subsequent continuation of this infection type during the remainder of the surveillance period is considered an organ/space SSI, if organ/space SSI and site-specific infection criteria are met.

• Report mediastinitis following cardiac surgery that is accompanied by osteomyelitis as SSI-MED rather than SSI-BONE.

• If meningitis (MEN) and a brain abscess (IC) are present together after operation, report as SSI-IC. Similarly, if meningitis and spinal abscess (SA) are present together after an operation, report as SSI-SA.

• Report CSF shunt infection as SSI-MEN if it occurs within 90 days of placement; if later or after manipulation/access, it is considered CNS-MEN and is not reportable under this module.

• The term attending physician for the purposes of application of the NHSN SSI criteria may be interpreted to mean the surgeon(s), infectious disease, other physician on the case, emergency physician or physician's designee (nurse practitioner or physician's assistant).

<u>SIP/SIS-Superficial incisional surgical site infection</u>

Superficial incisional SSI must meet the following criterion:

Infection occurs within 30 days after any NHSN operative procedure (where day 1 = the procedure date), including those coded as 'OTH'*

and

involves only skin and subcutaneous tissue of the incision

and

patient has at least 1 of the following:

a. purulent drainage from the superficial incision

b. organisms isolated from an aseptically-obtained culture of fluid or tissue from the superficial incision

c. superficial incision that is deliberately opened by a surgeon, attending physician** or other designee and is culture-positive or not cultured

and

patient has at least one of the following signs or symptoms of infection: pain or tenderness; localised swelling; redness; or heat. A culture negative finding does not meet this criterion

d. diagnosis of superficial incisional SSI by the surgeon or attending physician** or other designee (see reporting instructions).

***http://www.cdc.gov/nhsn/XLS/ICD-9-cmCODEScurrent.xlsx**

** The term attending physician for the purposes of application of the NHSN SSI criteria may be

interpreted to mean the surgeon(s), infectious disease, other physician on the case, emergency

physician or physician's designee (nurse practitioner or physician's assistant).

Comments

There are two specific types of superficial incisional SSIs:

1. Superficial Incisional Primary (SIP) – a superficial incisional SSI that is identified in the primary incision in a patient that has had an operation with one or more incisions (e.g., C-section incision or chest incision for CBGB)

2. Superficial Incisional Secondary (SIS) – a superficial incisional SSI that is identified in the secondary incision in a patient that has had an operation with more than one incision (e.g., donor site [leg] incision for CBGB)

__Urinary Tract Infection (UTI)__

Table 5. Urinary Tract Infection Criteria

Criterion	**Urinary Tract Infection (UTI)**
	Symptomatic Urinary Tract Infection (SUTI) Must meet at least *1* of the following criteria:
1a	Patient had an indwelling urinary catheter in place for >2 calendar days, with day of device placement being Day 1, and catheter was in place on the date of event *and* at least 1 of the following signs or symptoms: fever (>38°C); suprapubic tenderness*; costovertebral angle pain or tenderness* *and* a positive urine culture of ≥105 colony-forming units (CFU)/ml with no more than 2 species of microorganisms. Elements of the criterion must occur within a timeframe that does not exceed a gap of 1 calendar day between two adjacent elements. ---OR--- Patient had an indwelling urinary catheter in place for >2 calendar days and had it removed the day of or the day before the date of event *and* at least 1 of the following signs or symptoms: fever (>38°C); urgency*; frequency*; dysuria*; suprapubic

	tenderness*; costovertebral angle pain or tenderness* *and* a positive urine culture of ≥105 colony-forming units (CFU)/ml with no more than 2 species of microorganisms. Elements of the criterion must occur within a timeframe that does not exceed a gap of 1 calendar day between two adjacent elements. ***With no other recognized cause**
1b	Patient did not have an indwelling urinary catheter that had been in place for >2 calendar days and in place at the time of or the day before the date of event *and* has at least 1 of the following signs or symptoms: fever (>38°C) in a patient that is ≤65 years of age; urgency*; frequency*; dysuria*; suprapubic tenderness*; costovertebral angle pain or tenderness* *and* a positive urine culture of ≥105 CFU/ml with no more than 2 species of microorganisms. Elements of the criterion must occur within a timeframe that does not exceed a gap of 1 calendar day between elements two adjacent elements. *With no other recognized cause
2a	Patient had an indwelling urinary catheter in place for >2 calendar days, with day of device placement being Day 1, and catheter was in place on the date of event *and* at least 1 of the following signs or symptoms: fever (>38°C); suprapubic tenderness*; costovertebral angle pain or tenderness* *and* at least 1 of the following findings: a. positive dipstick for leukocyte esterase and/or nitrite b. pyuria (urine specimen with ≥10 white blood cells [WBC]/mm3 of unspun urine or >5 WBC/high power field of spun urine) c. microorganisms seen on Gram's stain of unspun urine *and* a positive urine culture of ≥103 and <105 CFU/ml with no more than 2 species of microorganisms. Elements of the criterion must occur within a timeframe that does not exceed a gap of 1 calendar day between two adjacent elements. --OR--- Patient with an indwelling urinary catheter in place for >2 calendar days and had it removed the day of or the day before the date of event *and* at least 1 of the following signs or symptoms: fever (>38°C); urgency*; frequency*; dysuria*; suprapubic tenderness*; costovertebral angle pain or tenderness* *and*

	at least 1 of the following findings: a. positive dipstick for leukocyte esterase and/or nitrite b. pyuria (urine specimen with ≥10 WBC/mm3 of unspun urine or >5 WBC/high power field of spun urine c. microorganisms seen on Gram's stain of unspun urine *and* a positive urine culture of ≥103 and <105 CFU/ml with no more than 2 species of microorganisms. Elements of the criterion must occur within a timeframe that does not exceed a gap of 1 calendar day between two adjacent elements. ***With no other recognized cause**
2b	Patient did not have an indwelling urinary catheter, that had been in place for >2 calendar days and in place at the time of, or the day before the date of event *and* has at least 1 of the following signs or symptoms: fever (>38°C) in a patient that is ≤65 years of age; urgency*; frequency*; dysuria*; suprapubic tenderness*; costovertebral angle pain or tenderness* *and* at least 1 of the following findings: a. positive dipstick for leukocyte esterase and/or nitrite b. pyuria (urine specimen with ≥10 WBC/mm3 of unspun urine or >5 WBC/high power field of spun urine c. microorganisms seen on Gram's stain of unspun urine *and* a positive urine culture of ≥103 and <105 CFU/ml with no more than 2 species of microorganisms. Elements of the criterion must occur within a timeframe that does not exceed a gap of 1 calendar day between two adjacent elements. *With no other recognized cause
3	Patient ≤1 year of age with** or without an indwelling urinary catheter has at least 1 of the following signs or symptoms: fever (>38°C core); hypothermia (<36°C core); apnea*; bradycardia*; dysuria*; lethargy*; vomiting* *and* a positive urine culture of ≥105 CFU/ml with no more than 2 species of microorganisms. Elements of the criterion must occur within a timeframe that does not exceed a gap of 1 calendar day between two adjacent elements. *With no other recognized cause ** Patient had an indwelling urinary catheter in place for >2 calendar days, with day of device placement being Day 1, and catheter was in place on the date of event
4	Patient ≤1 year of age with** or without an indwelling urinary catheter has at least 1 of the following signs or symptoms: fever (>38°C core); hypothermia (<36°C core); apnea*; bradycardia*; dysuria*; lethargy*; vomiting* *and*

	at least 1 of the following findings: a. positive dipstick for leukocyte esterase and/or nitrite b. pyuria (urine specimen with ≥10 WBC/mm3 of unspun urine or >5 WBC/high power field of spun urine c. microorganisms seen on Gram's stain of unspun urine *and* a positive urine culture of between ≥103 and <105 CFU/ml with no more than two species of microorganisms. Elements of the criterion must occur within a timeframe that does not exceed a gap of 1 calendar day between two adjacent elements. *With no other recognized cause ** Patient had an indwelling urinary catheter in place for >2 calendar days, with day of device placement being Day 1, and catheter was in place on the date of event.

Infection-related Ventilator-Associated Complication (IVAC)

Patient meets criteria for VAC

and

on or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, the patient meets both of the following criteria:

1. Temperature > 38 °C or < 36°C, OR white blood cell count ≥ 12,000 cells/mm3 or ≤ 4,000 cells/mm3.

and

2. A new antimicrobial agent(s)* is started, and is continued for ≥ 4 calendar days.

*See Table 15 for eligible agents.

Possible VAP – Possible Ventilator-Associated Pneumonia

Patient meets criteria for VAC and IVAC

and

on or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, ONE of the following criteria is met:

1) Purulent respiratory secretions (from one or more specimen collections)

• Defined as secretions from the lungs, bronchi, or trachea that contains > 25 neutrophils and < 10 squamous epithelial cells per low power field [lpf, x100].

• If the laboratory reports semi-quantitative results, those results must be equivalent to the above quantitative thresholds.

• See additional instructions for using the purulent respiratory secretions criterion in the VAE Protocol.

OR

2) Positive culture (qualitative, semi-quantitative or quantitative) of sputum*, endotracheal aspirate*, bronchoalveolar lavage*, lung tissue, or protected specimen brushing*

**Excludes the following:*

• Normal respiratory/oral flora, mixed respiratory/oral flora or equivalent

• *Candida* species or yeast not otherwise specified

• Coagulase-negative *Staphylococcus* species

• *Enterococcus* species

Probable VAP

Patient meets criteria for VAC and IVAC

and

On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, ONE of the following criteria is met:

1) Purulent respiratory secretions (from one or more specimen collections—and defined as for possible VAP)

and

one of the following:

• Positive culture of endotracheal aspirate*, ≥ 105 CFU/ml or equivalent semi-quantitative result

• Positive culture of bronchoalveolar lavage*, ≥ 104 CFU/ml or equivalent semi-quantitative result

• Positive culture of lung tissue, ≥ 104 CFU/g or equivalent semi-quantitative result

• Positive culture of protected specimen brush*, ≥ 103 CFU/ml or equivalent semi-quantitative result

**Same organism exclusions as noted for Possible VAP.*

OR

2) One of the following (without requirement for purulent respiratory secretions):

• Positive pleural fluid culture (where specimen was obtained during thoracentesis or initial placement of chest tube and NOT from an indwelling chest tube)

• Positive lung histopathology

• Positive diagnostic test for Legionella spp.

• Positive diagnostic test on respiratory secretions for *influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus, rhinovirus, human metapneumovirus, coronavirus*

Secondary Bloodstream Infection (BSI) Guide (not applicable to Ventilator-associated Events)

What is the meaning of the statement "not related to infection at another site" in relation to a positive blood culture?

The purpose of using the CDC/NHSN infection criteria is to identify and consistently categorize infections that are healthcare-associated into major and specific infection sites or types. LCBI criteria include the caveat that the organism(s) cultured from the blood cannot be related to infection at another site (i.e., must be a primary BSI). One must be sure that there is no other CDC-defined primary site of infection that may have seeded the bloodstream secondarily; otherwise the bloodstream infection may be misclassified as a primary BSI or erroneously associated with the use of a central line, i.e., called a CLABSI. For locations participating in in-plan VAE surveillance, refer to the VAE chapter for specific guidance on assigning a secondary BSI to a VAE.

Below are listed several scenarios that may occur with guidance on how to distinguish between the primary or secondary nature of a BSI, along with the definition of "matching organisms", and important notes and reporting instructions.

1. **Blood and site-specific specimen cultures match for at least one organism**: In a patient suspected of having an infection, blood and a site-specific specimen are collected for culture and both are positive for at least one matching organism. If the site-specific culture is an element used to meet the infection site criterion, then the BSI is considered secondary to that site-specific infection. a. Example: Patient meets HAI criteria for a symptomatic urinary tract infection (suprapubic tenderness and >105 CFU/ml of *E. coli*) and blood culture from the same date grows *E. coli*. This is an HAI SUTI with a secondary BSI and the reported organism is *E. coli*.

b. Example: Patient meets HAI criteria for a symptomatic urinary tract infection (suprapubic tenderness and >105 CFU/ml of *E. coli*) and blood culture from the same date grows *E. coli* and *P. aeruginosa*. This is an HAI SUTI with a secondary BSI and the reported organisms are *E. coli* and *P. aeruginosa*, since *P. aeruginosa* is a logical pathogen for this site of infection.

c. Example: Patient meets HAI criteria for a symptomatic urinary tract infection (suprapubic tenderness and >105 CFU/ml of *E. coli*) and blood culture from the same date grows *E. coli* and *S. epidermidis*. This is an HAI SUTI with a secondary BSI and the reported organism is only *E. coli*, since the single common commensal *S. epidermidis* positive blood culture by itself does not meet BSI criteria.

2. **Blood and site-specific specimen cultures do not match**: There are two scenarios that can occur when a patient suspected of having an infection has blood and a site-specific specimen cultured but the organisms do not match. a. If the site-specific culture is an element used to meet the infection site criterion and the blood isolate is also an element used to meet another criterion at the same infection site, then the BSI is considered secondary to that site-specific infection. i. Example: Postoperative patient becomes febrile and complains of nausea and abdominal pain. Blood and an aseptically-obtained T-tube drainage specimen are collected for culture. A CT scan done that day shows fluid collection suggestive of infection. Culture results show *Escherichia coli* from the purulent drainage specimen but the blood grows *Bacteroides fragilis.* Because the patient meets IAB criteria by positive site-specific culture (IAB criterion 3a) and by positive blood culture as an element of a different criterion of the same infection site (IAB 3c), the blood is considered a secondary BSI to an IAB and both organisms would be listed as the IAB infection pathogens. No primary BSI would be reported.

b. If the site-specific culture is an element used to meet the infection site criterion and the blood isolate is not, then the BSI is considered a primary infection.

i. Example: Postoperative patient has an intraabdominal abscess (IAB) noted during reoperation and purulent material is obtained at that time which grows *Escherichia coli*. The patient spikes a fever two days later and blood culture shows *Bacteroides fragilis*. Because the organisms from the site and blood cultures do not match, and no site-specific criterion that includes positive blood culture as an element is met, both a site-specific infection (criteria 1 and 2) and a primary BSI would be reported.

ii. Example: Unconscious ICU patient with a Foley catheter and central line for past 4 days spikes a fever; blood, urine and sputum specimens are collected for culture. The urine culture grows >100,000 CFU/ml of *Escherichia coli*, blood culture grows Enterococcus faecium, and sputum shows oral flora only. Because the organisms from the urine and blood cultures do not match, and a UTI criterion that includes positive blood culture as an element is not met, both a SUTI (SUTI criterion 1a) and a primary BSI would be reported. This infection does not meet the ABUTI criterion since that requires at least one matching uropathogen organism in urine and blood in an asymptomatic patient.

3. **No site-specific specimen culture, only a positive blood culture**: In a patient suspected of having an infection, if the only specimen cultured is blood and it grows a logical pathogen for the suspected body site of infection, and a site-specific infection criterion is met, an element of which may or may not include a positive blood culture, the BSI is considered secondary to that site-specific infection. a. Example: Postoperative patient has an abscess in the small bowel noted during reoperation. The only specimen cultured is blood which grows *B. fragilis*. Because gastrointestinal tract infection (GIT) criterion 1 is met with the surgically-identified abscess alone and because *B. fragilis* is a logical pathogen for this site of infection, the BSI is considered secondary to a GIT and *B. fragilis* is listed as the GIT infection pathogen.

b. Example: Patient has a positive blood culture with *E. coli* proximal in time with fever, abdominal pain, and CT scan evidence of intraabdominal abscess (IAB). This patient meets IAB criterion 3c, which includes a positive blood culture as one of its elements. The BSI is considered secondary to the IAB and *E. coli* is listed as the IAB infection pathogen.

4. **Negative site-specific specimen culture with positive blood culture**: In a patient suspected of having an infection, if a specimen from the suspected site of infection is cultured and yields no growth, but a blood specimen collected as part of the infection work-up is positive, that BSI is only considered a secondary BSI if another of the site-specific criteria that includes positive blood culture as an element is met. Otherwise, the BSI is considered a primary BSI, even if another criterion for that site is met and the blood isolate is a logical pathogen for the infection. a. Example: Patient has purulent material from the IAB space cultured and it yields no growth. The patient also has fever, abdominal pain, a positive blood culture with *Pseudomonas aeruginosa*, and radiographic evidence of IAB infection. This patient does not meet IAB criterion 1 (positive culture from purulent material) but does meet IAB criterion 3c, an element of which is a positive blood culture (signs/symptoms plus positive blood culture plus radiographic evidence). This BSI is considered secondary to the IAB and *P. aeruginosa* is listed as the IAB infection pathogen.

b. Example: Postoperative knee replacement patient with a central line spikes a fever; blood and knee joint fluid are cultured. Only the blood cultures from at least two separate blood draws are positive for *S. epidermidis*. No other JNT infection criteria are met. This BSI should be reported as a CLABSI.

c. Example: Patient has a central line in place for 10 days. Patient complains of knee joint tenderness and limited range of motion. CT scan findings suggest joint (JNT) infection but culture of a needle-aspirated joint fluid is negative. However, a blood culture from the same time period grows *S. aureus*. While this patient does not meet JNT criterion 1 (positive joint fluid culture), he does meet JNT criterion 3d (signs/symptoms plus positive laboratory test on blood [blood culture]). Since a positive blood culture is part of the criterion met for JNT infection, this BSI is considered secondary to the JNT infection and not reported as a CLABSI. *S. aureus* is reported as the pathogen for the JNT infection.

A **matching organism** is defined as one of the following:

1. If genus and species are identified in both cultures, they must be the same. a. Example: A blood culture reported as *Enterobacter cloacae* and an intraabdominal specimen of *Enterobacter cloacae* are matching organisms.

b. Example: A blood culture reported as *Enterobacter cloacae* and an intraabdominal specimen of *Enterobacter aerogenes* are NOT matching organisms as the species are different.

2. If the organism is less definitively identified in one culture than the other, the identifications must be complementary. a. Example: A surgical wound growing *Pseudomonas* spp. and a blood culture growing *Pseudomonas aeruginosa* are considered a match at the genus level and therefore the BSI is reported as secondary to the SSI.

b. Example: A blood culture reported as *Candida albicans* and a urine culture reported as yeast are considered to have matching organisms because the organisms are complementary, i.e. Candida is a type of yeast.

APPENDIX 6. COMPLEXITY CATEGORIES OF CARDIOTHORACIC SURGICAL PROCEDURES

(Levy, Ovadia et al. 2003)

Table 1 *Complexity categories of cardiothoracic surgical procedures*

Category 1	Category 2	Category 3	Category 4
Patent ductus arteriosus closure weight >1500 g	Multiple VSD	Blalock–Taussing/other shunts	Patent ductus arteriosus < 1500 g
Coarctation of aorta repair	Tetralogy of Fallot with transannular patch	Complete A–V canal repair	Aortic arch anomaly repair
Blalock–Henlon septectomy	Bidirectional Glenn anastomosis	Tetralogy of Fallot (with right ventricular to pulmonary conduit	Banding of pulmonary artery
Aortic valvulotomy	Aortopulmonary window repair	Tetralogy of Fallot with other intracardiac procedures	Waterstone or central shunts
Vascular ring repair	Aortic root repair	Reconstruction of right ventricular outflow tract with or without shunt	Pulmonary valvotomy (not open heart)
Atrial septal defect (ASD), secundum ASD	Mitral valve repair	Fontan operation/total cavo-pulmonary deviation	Other ops for CHF without extra corporeal
Cortriatriatum or supravalvular mitral stenosis	Rastelli repair/intraventricular tunnel repair	Ebstein malformation repair	Total anomalous pulmonary venous connection
Single VSD		Aortoventriculoplasty	Truncus arteriosus repair
VSD and aortic incompetence		Aortic valvotomy, open	Anomalous left coronary from pulmonary artery
Tetralogy of Fallot without transannular patch		Mitral valve replacement	Aortic valve replacement (other)
Pulmonary valvotomy		Arterial switch with or without other cardiac procedures	Other ops for left ventricular outlet obstruction
Coronary fistula closure		Other op for CHF with extra corporeal	Hypoplastic left heart of aortic atresia (Norwood, other)
Aortic valve replacement			Mitral valve replacement, creation or enlargement of ASD
Aortic stenosis (subvalvular, supravalvular)			Mustard/Senning repair of transposition of great arteries
Cardiac arrhythmia surgery			LV–PA conduit with or without other cardiac procedures
			Other procedures for transposition of great arteries or double outlet of right ventricle or Septation (primary or staged), single ventricle procedures
			Other procedures for single ventricle

APPENDIX 7. SYSTEMS OF ASSESSING QUALITY OF CARE IN PAEDIATRIC PATIENTS FOR CARDIAC SURGERY

Several groups have proposed **systems of assessing quality of care** by assigning surgical cardiac operations risk score or grouping operations of similar risk into categories. Two such systems, namely the Aristotle Basic Complexity (ABC) score and the Risk Adjustment for Congenital Heart Surgery (RACHS-1), were developed. Briefly, the Aristotle score reflects the potential for mortality, potential for morbidity, and technical difficulty for each operation.

Scoring systems such as the Paediatric Index of Mortality (PIM) score allows the assessment of severity of illness and mortality risk adjustment in heterogeneous groups of patients in an objective manner. The PIM scoring system has been developed and carefully validated in tertiary PICUs (van Keulen, Polderman et al. 2005, Slater, Shann et al. 2003).

Our institution (RCWMCH) uses two scoring systems in cardiac surgery patients. The cardiothoracic team assign an Aristotle score to each operation and when admitted to PICU a PIM2 score is assigned. These scoring systems may then be used to conduct audits into quality of care of cardiac surgery patients in the PICU.