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Antimicrobial resistance profiles in the paediatric burns unit at Chris Hani Baragwanath Academic Hospital

Moodley, Mahavishnu Morgan

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ANTIMICROBIAL RESISTANCE PROFILES IN THE PAEDIATRIC BURNS UNIT AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

Mahavishnu Morgan Moodley

A research report submitted to the faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Medicine in Medical Microbiology

Johannesburg, 2022

Supervisors:

1. **Dr Jeannette Wadula:** MD, DTM&H, PDIC, PDHSE, FCPath (Micro)

   Department of Clinical Microbiology and Infectious diseases
   Chris Hani Baragwanath Academic Hospital

2. **Dr Prenika Jaglal:** MBChB, DA (SA), MMed (Micro) and FCPath (Micro)

   Department of Clinical Microbiology and Infectious diseases
   Department of Chris Hani Baragwanath Academic Hospital

DECLARATION

I, Mahavishnu Morgan Moodley, declare that this Research Report is my own work. It is submitted for the Degree of Master of Medicine in Medical Microbiology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other university.



Signature of candidate

16th day of June 2022 in Soweto, Johannesburg

Supervisors:

1. Dr Jeannette Wadula: MD, DTM&H, PDIC, PDHSE, FCPath (Micro)



Signature: _____ Date__16-06-2022_____

2. Dr Prenika Jaglal: MBCHB, DA (SA), MMED (Micro), FCPath (Micro)



Signature: _____ Date__16-06-2022_____

ABSTRACT

Background

There has been a global concern regarding increasing colonization and/or infection of paediatric burns patients with multi-drug-resistant organisms, especially in Africa. Surveillance of antimicrobial resistance patterns enables clinicians to opt for the most appropriate empiric antimicrobial agent according to their pathogen profile.

Objective

This study sought to compile unit-specific antibiograms by comparing the frequency of organisms and resistance trends at the paediatric burns unit at Chris Hani Baragwanath Academic Hospital (CHBAH) from January 2015 to December 2019.

Methods

A retrospective, laboratory-based review was conducted of bacterial and fungal isolates including antimicrobial susceptibility testing (AST) data from blood cultures and tissue samples for the study period. We analysed the frequency of Enterobacterales, non-fermenters, Gram-positive organisms, and yeasts as a percentage of total positive blood cultures. A comparative analysis of resistance trends was performed between 2015, 2017, and 2019 for extended-spectrum beta-lactamases (ESBLs), carbapenem-resistant Enterobacterales (CRE), extreme drug-resistant (XDR) *Acinetobacter baumannii*, and methicillin-resistant *Staphylococcus aureus* (MRSA).

Results

For blood culture isolates, a statistically significant decrease in ESBL was noted with a rise in CREs. Majority of *A.baumannii* were XDR despite an appreciably decrease. A notable decrease in *S.aureus* and MRSA isolates with an increase in *C.auris* was observed.

Conclusion

The results of this study encourage review of current antimicrobial choices in the unit for empiric antibacterial cover.

Due to low numbers of yeasts, we cannot comment on institution of early antifungal strategies. We support reinforced infection prevention and control practices as well as antimicrobial stewardship initiatives.

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LIST OF ABBREVIATIONS

AMS – Antimicrobial Stewardship

AST – Antimicrobial Susceptibility Testing

CHBAH – Chris Hani Baragwanath Academic Hospital

CLSI – Clinical Laboratory Standards Institute

CNS – Coagulase-Negative Staphylococcus

CRE – Carbapenem-Resistant Enterobacterales

ESBL – Extended Spectrum Beta Lactamase

Imi-EDTA – Imipenem Ethylenediamine tetra-acetic acid

IPC – Infection Prevention and Control

ISO – International Organisation for Standardization

MDR – Multi-drug Resistant

MIC – Minimum Inhibitory Concentration

MRSA – Methicillin-Resistant *Staphylococcus aureus*

MSSA – Methicillin-Susceptible *Staphylococcus aureus*

NHLS – National Health Laboratory Services

SANAS – South African National Accreditation System

TBSA – Total Body Surface Area

VRE – Vancomycin-resistant Enterococci

XDR – Extreme drug Resistant

Note on the format of this Research Report

Prior to the undertaking of this project, a protocol describing the appropriate background literature and methodology that would be used was submitted to and approved by an assessor panel from the School of Pathology at the University of the Witwatersrand.

The project was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand and a copy of the approval letter can be found in the appendices.

The format of this Research Report is as stipulated by the Committee for Postgraduate studies, Faculty of Health Sciences at the University of the Witwatersrand. The format of the submissible article may differ from the rest of the research report to comply with the author's guidelines of the South African Journal of Plastic & Reconstructive Aesthetic Surgery and Burns (SAJPRASB), to which it is intended to be submitted.

1 Introduction

The number of paediatric burn patients is the highest in Africa with children younger than 5 years of age being greatest at risk and burns being ranked 5th among non-fatal childhood injuries [1,2]. The South African Medical Research Council approximates that 3.2% of the population are injured by burns yearly [3].

South Africa, considered a middle-income developing country, has heavily crowded informal settlements often with poor access to electricity [4]. A study by Parbhoo et al. at The Red Cross Children's Hospital in Cape Town revealed that the highest incidence of burns was among toddlers, with 83% of paediatric burns caused by hot liquid, followed by fire and electrical burns respectively [4].

Burns patients are inherently at risk of developing infections as the body's first line of defence, the skin, has been breached [5]. Despite noteworthy advances in the management of burn patients, infection poses a significant concern [6,7]. Following a burn incident, the wound is initially sterile. Within 48 hours, microbes from the skin, sebaceous glands, and hair follicles colonise the wound. Thereafter, gastrointestinal, and respiratory tract microbes as well as those from the environment colonise the wound. Studies have shown that Gram-positive organisms predominate in the first week following burns and Gram-negative organisms thereafter [7,8,9].

Infected burn wounds are associated with lengthier hospital stays and heightened morbidity and mortality [9]. Apart from burn wound sepsis, burn patients also develop infections elsewhere including bacteraemia, catheter-related infections, urinary tract infections, and pneumonia [6,10].

There has been an increase in antibiotic resistance trends among burns patients in recent years with an increased incidence of burns patients succumbing to drug-resistant bacterial infections [9,11]. Approximately 75% of all deaths in burns patients occur because of infection, and may be as high as 86% in some settings due to escalating resistance patterns [5,6] Burn patients are at increased risk of colonization or infection with multi-drug-resistant (MDR) pathogens which is an important determinant in their outcome [12,13]. Burn severity correlates closely with the development of multi-drug-resistant infections, with more MDR infections seen in patients with larger total body surface area (TBSA) involved [12]. MDR infections have

both clinical and financial implications with challenges in management [7]. Often, the use of broad-spectrum empiric antimicrobial agents to prevent MDR infections aggravates the vicious cycle of selective pressure and resistance development [12].

Antimicrobial agents are displaying reduced efficacy globally while limited newer agents are being developed, possibly leading us faster toward the 'post-antibiotic era' [14]. Growing evidence suggests that antimicrobial stewardship (AMS) programs are effective in enhancing compliance to antibiotic policy, reducing hospital stay or readmissions, and decreasing the incidence of *Clostridiodes difficile* infections. Several antimicrobial stewardship program interventions have shown improved outcomes on patient care, emphasizing the need for microbiological surveillance [12,15,16]. A core component of The National Antimicrobial Resistance Strategy Framework in South Africa, in line with conserving antimicrobial agents, is surveillance of antimicrobial resistance patterns [17]. Surveillance of antimicrobial susceptibility enables doctors to opt for the most appropriate antimicrobial agent [7]. An agent with suboptimal cover or to which the infecting pathogen is resistant can have dire patient consequences [18]. This needs to be balanced against the risks of using broad-spectrum antimicrobial agents [19].

An antibiogram is used mainly to monitor local susceptibility rates, assist in choosing appropriate empiric antimicrobial therapy, observe resistance patterns within units in a specified timeframe, and evaluate susceptibility rates across units and institutions [20]. Institution-wide antibiograms may have vital differences in susceptibility data when compared to unit-specific antibiograms [18]. An antibiogram specific to the burn unit is a useful aid in monitoring antimicrobial resistance trends and choosing appropriate empiric antimicrobial therapy.

2 Aim

The aim of this study was to determine the pathogen profile from blood cultures and tissue specimens at the Chris Hani Baragwanath Academic Hospital (CHBAH) paediatric burns unit between January 2015 and December 2019.

3 Objectives

The first study objective was to compile antibiograms specific for the paediatric burns unit based on positive blood culture isolates for the study period. The second

objective was to compare the frequency of organisms between the two periods 2015-2017 and 2018-2019 and to compare antimicrobial resistance trends between 2015, 2017, and 2019.

4 Methods

4.1 Study setting

Chris Hani Baragwanath Academic Hospital is a tertiary-level hospital situated in Soweto, Johannesburg. It has a dedicated paediatric burns unit with 19 regular and 7 intensive-care beds. The causes of burns seen at the facility are hot water, fire, and electrical burns. Current empiric antibiotic regimens used in the paediatric burns unit depend on duration of hospital stay. If within 3 days of admission, Co-Amoxyclav is started to cover community-associated infections. From day 4 onwards or if escalating therapy, meropenem and vancomycin are commenced to cover healthcare-associated infections. All antibiotics are started after blood cultures and other relevant site-specific cultures are obtained.

4.2 Study design

A retrospective, laboratory-based review was conducted of bacterial and fungal isolates and antimicrobial susceptibility (AST) data from blood cultures and tissue samples for the period January 2015 to December 2019. Clinical samples were tested at the SANAS-accredited National Health Laboratory Services (NHLS) microbiology laboratory situated at CHBAH.

Blood cultures were obtained from patients in the ward who were suspected of having sepsis. Blood was collected in BacT/Alert bottles which were then loaded into the blood culture instrument (bioMerieux). When a bottle flagged positive (i.e. growth detected), the bottle was removed, and processed according to the local laboratory's standard operating protocols.

Tissue was collected in saline in a universal container from patients who were systemically septic, had septic wounds undergoing debridement, or were scheduled for graft procedures. Tissue was processed according to the local laboratory's standard operating protocols.

For Gram-positive cocci in clusters, identification was made by use of catalase, DNAse agar, and Staphaurex (Thermo Fischer). Identification of Gram-positive cocci in pairs or chains was made using catalase, the bile esculin test, bacitracin and optochin discs, PYR (Hardy Diagnostics), and Streptex (Thermo Fischer). Gram-negative bacilli were further identified using oxidase and Analytical Profile Index (API) 20E or 20NE (bioMerieux) and, if needed, Microscan (Beckman Coulter). Fungi were identified using the germ tube test and Vitek2 (bioMerieux) or Auxacolor systems (Auxacolor, Sanofi, Pasteur, Paris, France).

Antimicrobial susceptibility testing was performed according to the Kirby-Bauer method and in line with the Clinical and Laboratory Standards Institute (CLSI) recommendations, and interpretation of results were as per CLSI breakpoints [(21)]. If needed, Epsilometer/E-tests (bioMerieux) may have been done to determine minimum inhibitory concentrations (MIC). Detection of carbapenem-resistant Enterobacterales (CRE) was initially done using the modified Hodge and imipenem-ethylenediamine tetra-acetic acid (imi-EDTA) tests, but the laboratory has since shifted to using the Resist-4 O.K.N.V. (Coris Bioconcept) kit.

Data for the study period and specimen types was requested from the National Health Laboratory Services data warehouse. CLSI M39-A4 recommendations were adhered to when compiling the antibiograms [(22)]. Thus, only the first isolate of a given species per patient per calendar year was included regardless of body site, antimicrobial susceptibility profile, or other phenotypic characteristics. Preference was also given to the first blood culture in cases where multiple blood and tissue specimens were collected on the same day. Surveillance cultures were excluded.

Enterobacterales with minimum inhibitory concentrations (MIC) showing reduced susceptibility to any of the routinely tested carbapenems were included as carbapenem-resistant Enterobacterales (CRE).

4.3 Statistical analysis

Data analysis was performed using Microsoft Excel for tabulation and generating graphs. STATA software was used in comparative analysis to calculate *p*-values which were reported as two-tailed, with values <0.05 considered statistically significant.

Data was sorted into tables for Enterobacterales, non-fermenters (*Acinetobacter* spp. and *Pseudomonas* spp.), Gram-positive organisms, and yeasts. For the blood cultures, the percentage susceptibility to the various antimicrobial agents was calculated. For tissue samples, only predominant organisms, and their resistance profiles (in percentages) were reported.

The percentage of total positive blood cultures per year was calculated for Enterobacterales, non-fermenters, Gram-positive organisms, and yeasts. The percentage resistance was calculated for both blood and tissue cultures as follows: % *Staphylococcus aureus* that were methicillin-resistant *Staphylococcus aureus* (MRSA); % *Enterococcus* spp. that were vancomycin-resistant enterococci (VRE), % Enterobacterales that were AmpCs, extended-spectrum beta lactamases (ESBL), or CRE; % *Acinetobacter* spp. that were MDR or extreme drug-resistant (XDR); and % *Pseudomonas* spp. that were MDR or XDR.

To assess whether there were statistically significant differences for the organism types across the study period, the periods 2015-2017 and 2018-2019 were compared and *p*-values calculated. Regarding antimicrobial resistance, 2015 was compared to 2017 and 2019 with *p*-values calculated. The most common resistance profiles were included: ESBL and CRE for Enterobacterales, XDR for *Acinetobacter* spp., and MRSA.

4.4 Ethical approval

The study was approved by the University of the Witwatersrand's Human Research Ethics Committee (protocol number M210952).

5 Results

A total of 2549 patients were admitted to the unit during the study period with an average of 510 admissions annually. Blood and tissue cultures for the study period totalled 1918 and 395 episodes respectively. Following removal as per exclusion criteria, 1511 blood and tissue cultures were included in the study.

Blood culture isolates in descending order for all the years analysed were Gram-positive organisms, non-fermenters, Enterobacterales, and yeasts. (Figure 1 and Table 1). Tissue culture isolates in descending order for all the years analysed were non-fermenters, Enterobacterales, Gram-positive organisms, and yeasts. (Table 1).

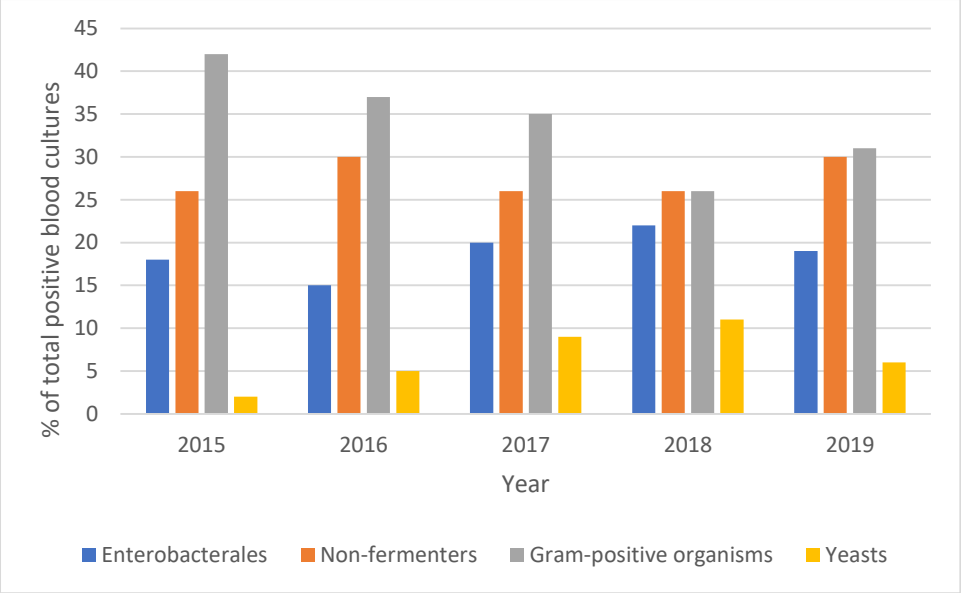

Figure 1: Organism type as a percentage of total positive blood cultures, 2015-2019

Table 1: Organism type as a percentage of total positive blood and tissue cultures

	Organism	Percentage of total positive blood cultures (%)				
		2015	2016	2017	2018	2019
Blood cultures	Enterobacterales	18	15	20	22	19
	Non-fermenters	26	30	26	26	30
	Gram-positive organisms	42	37	35	26	31
	Yeasts	2	5	9	11	6
	Organism	**Percentage of total positive tissue cultures (%)**				
		2015	**2016**	**2017**	**2018**	**2019**
Tissue cultures	Enterobacterales	32	16	25	17	27
	Non-fermenters	36	54	48	50	44
	Gram-positive organisms	20	22	21	26	22
	Yeasts	0	0	0	2	1

5.1 Blood culture isolates

Enterobacterales

Enterobacterales were the third most isolated organisms from blood cultures for all the years studied. As a proportion of total positive blood cultures, equal numbers of Enterobacterales were noted for 2015-2017 and 2018-2019 (n=118 for both periods, p=1.000). (Table 2). *Klebsiella* spp. was the predominant species from blood cultures in all years (Figure 2). A modest increase in *Klebsiella* spp. was observed from the period 2015-2017 and 2018-2019 (p=0.4982) (Table 2). Enterobacterales in lesser

proportions include *Enterobacter* spp., *Escherichia coli*, *Serratia* spp., *Salmonella* spp., and *Citrobacter* spp. (Figure 2).

The most common resistance mechanism was AmpC production for all years studied except in 2015 where ESBL was more prevalent (Table 3). The percentage of Enterobacterales that were ESBL-producers had decreased in all years when compared to 2015 with the lowest ESBL rates noted in 2016. Comparing 2015 to 2017 and 2019, a statistically significant decrease in ESBL was seen (p=0.0024 and p=0.0004 respectively). Carbapenem resistance increased appreciably in 2017 and 2019 when compared to 2015 (p=0.010 and p=0.0003 respectively) (Table 4).

Table 2: Comparison of frequency of organisms between 2015-2017 and 2018-2019 on blood cultures

Organism type	**Total number of isolates (*n*) 2015-2019**	**2015-2017**	**2018-2019**	***p***
Gram-negative organisms	575	297	278	0.2625
Enterobacterales	**236**	**118**	**118**	**1.000**
Klebsiella spp.	109	52	57	0.4982
Other Enterobacterales	127	66	61	0.5304
Non-fermenters	**339**	**179**	**160**	**0.1445**
Acinetobacter spp.	208	103	105	0.8445
Pseudomonas spp.	131	76	55	0.0095
Gram-positive organisms	412	249	163	<0.001
Coagulase-negative Staphylococci	141	82	59	0.0062
Staphylococcus aureus	138	90	48	<0.001
Enterococcus spp.	104	52	52	1.000
Streptococcus pyogenes	29	25	4	<0.001
Yeasts	86	37	49	0.0673
Candida albicans	10	3	7	0.0736
Candida parapsolosis	19	5	14	0.0035
Candida auris	53	25	28	0.56
Other *Candida* spp.	4	4	0	0.0047

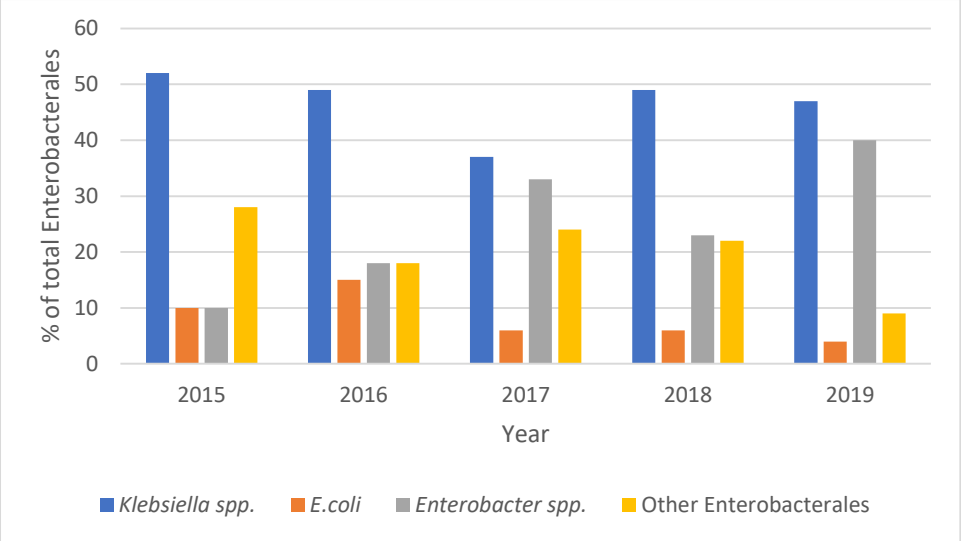

Figure 2: Organism type as a percentage of total Enterobacterales on blood cultures

Table 3: Percentage resistance for Gram-negative organisms on blood cultures

Organism	Number of isolates	Percentage resistance (%)				
		AMP C	ESBL	CRE	MDR	XDR
Enterobacterales	31	19	42	3	-	-
	33	24	12	21	-	-
	54	33	22	17	-	-
	73	29	23	22	-	-
	45	33	19	19	-	-
***Acinetobacter* spp.**	25	-	-	-	0	100
	36	-	-	-	6	92
	42	-	-	-	7	81
	57	-	-	-	5	77
	48	-	-	-	-	92
***Pseudomonas* spp.**	19	-	-	-	0	16
	29	-	-	-	3	0
	28	-	-	-	0	0
	29	-	-	-	0	3
	26	-	-	-	4	0

Table 4: Comparison of resistance mechanisms between 2015, 2017, & 2019 on blood cultures

Enterobacterales					*Acinetobacter* spp.		*S.aureus*	
Year	ESBL	*p*	CRE	*p*	XDR	*p*	MRSA	*p*
2015	42	0.0024	3	0.0010	100	<0.001	73	0.0001
2017	22		17		81		46	
2015	42	0.0004	3	0.0003	100	0.0039	73	0.0177

2019	19		19		92		57	

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184 Table 5: Gram-negative antibiogram (blood cultures)

ORGANISM	*n*	Percentage susceptibility (%)												
		AMP	AUG	TZP	CTX	CAZ	CEP	ETP	IMI	MERO	GENT	AMIK	CIP	STX
***Klebsiella* spp.**	16	-	19	69	25	25	25	100	100	100	38	94	56	13
	16	-	19	38	31	31	31	50	75	81	38	94	56	31
	20	-	35	45	35	40	40	55	60	70	45	70	45	40
	36	-	17	44	25	25	28	58	61	64	28	83	58	28
	21	-	38	48	43	43	43	62	67	57	57	86	52	33
Escherichia coli	3	0	67	67	67	67	67	100	100	100	67	100	67	33
	5	0	80	80	100	100	100	100	100	100	100	100	100	60
	3	33	67	100	100	100	100	100	100	100	100	100	100	33
	4	0	25	100	100	100	100	100	100	100	75	100	100	0
	2	0	100	100	100	100	100	100	100	100	100	100	100	100
***Enterobacter* spp.**	3	-	-	100	67	67	67	67	100	100	100	100	100	100
	6	-	-	100	100	100	100	100	100	100	100	100	100	100
	18	-	-	89	78	89	94	100	100	94	94	100	89	67
	17	-	-	71	65	65	71	82	100	100	71	100	94	71
	18	-	-	83	72	72	78	94	94	94	83	100	89	61
Other Enterobacterales	9	0	56	100	100	100	100	100	100	100	78	78	89	67
	6	33	67	100	100	100	100	100	100	100	67	83	100	50
	13	0	23	100	46	46	92	100	100	100	77	85	77	15
	16	13	31	100	94	100	100	100	100	100	100	100	100	100
	4	0	50	100	75	75	100	100	100	100	100	100	100	0
***Acinetobacter* spp.**	25	-	-	0	-	20	0	-	0	0	16	16	12	0
	36	-	-	3	-	17	6	-	3	3	14	11	14	3
	42	-	-	12	-	14	10	-	12	12	19	36	17	5
	57	-	-	18	-	23	18	-	14	16	26	37	28	16

	48	-	-	8	-	19	8	-	8	8	25	35	27	83
***Pseudomonas* spp.**	19	-	-	79	-	89	79	-	79	81	84	84	79	-
	29	-	-	86	-	90	86	-	90	90	76	100	100	-
	28	-	-	96	-	100	100	-	86	89	96	100	86	11
	29	-	-	90	-	97	90	-	48	48	93	100	93	7
	26	-	-	96	-	100	100	-	42	27	92	96	81	96

Key:

n=number of isolates; AMP=Ampicillin; AUG=Co-Amoxyclav; TZP=Piperacillin-Tazobactam; CTX=Ceftriaxone; CAZ=Ceftazidime; CEP=Cefipime; ETP=Ertapenem; IMI=Imipenem; MERO=Meropenem; GENT=Gentamycin; AMIK=Amikacin; CIP=Ciprofloxacin; STX=Co-Trimoxazole

Non-fermenters

Acinetobacter spp. and *Pseudomonas* spp. were the second most common isolated organisms from blood cultures for all the years studied (Figure 1 and Table 1). Among the non-fermenters, *Acinetobacter* spp. predominated for all the years analysed (Figure 3). Although a statistically significant decrease in XDR *Acinetobacter* spp. was noted when 2015 was compared to 2017 and 2019 (p <0.001 and p=0.0039 respectively) (Table 4), the % *Acinetobacter* spp. that were XDR remained high for all years studied with all isolates in 2015 being XDR (Table 3). In contrast, fewer *Pseudomonas* spp. isolates were considered XDR with majority susceptible to piperacillin-tazobactam, ceftazidime, and cefepime. A reduced susceptibility to imipenem and meropenem was noted from 2017 onwards (Table 5).

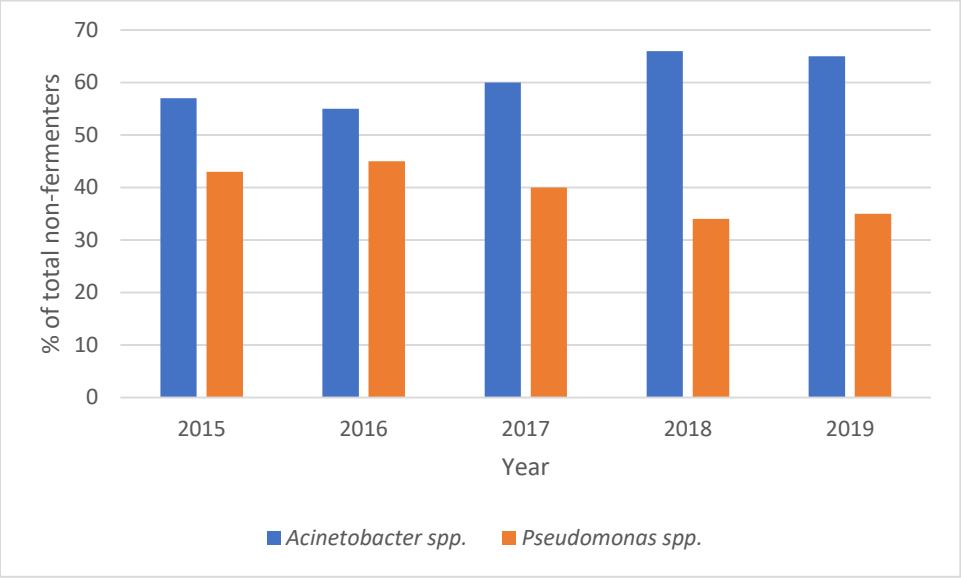

Figure 3: Organism type as a percentage of total non-fermenters on blood cultures

Gram-positive organisms

Gram-positive organisms were the most isolated organisms from blood cultures for all years studied (Figure 1 & Table 1). Coagulase-negative staphylococci (CNS) was most prevalent among the Gram-positive organisms on blood cultures for the years 2015, 2018, and 2019. For 2016 and 2017, *S.aureus* predominated (Figure 4) with all isolates susceptible to vancomycin and linezolid for the study period (Table 7). A notable decrease in the number of *S.aureus* was observed when comparing 2015-2017 and 2018-2019 (p<0.001). MRSA also decreased when comparing 2015 to 2017 and 2019 (p=0.0001 and p=0.0177 respectively) (Table 4).

Among the *Enterococcus* spp., *Enterococcus faecalis* was most prevalent for all years studied. The number of isolates from blood cultures that were *Enterococcus* spp. were equal for the periods 2015-2017 and 2018-2019 (p=1.000). Vancomycin-resistant enterococci were detected from 2017 onwards (Table 6).

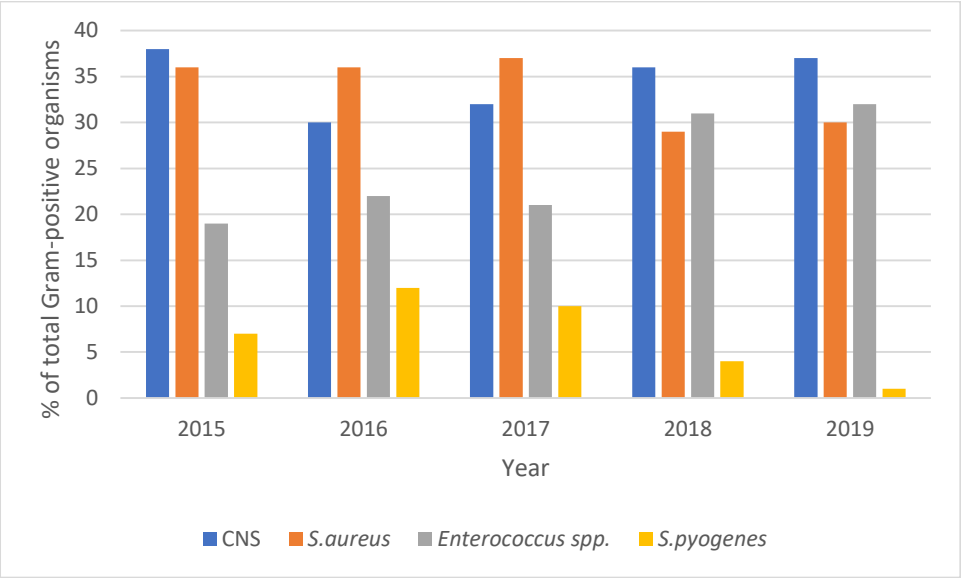

Figure 4: Organism type as a percentage of total Gram-positive organisms on blood cultures

Table 6: Percentage resistance of Gram-positive organisms on blood cultures

Organism	Number of isolates	Percentage resistance (%)	
		MRSA	VRE
Staphylococcus aureus	26	73	-
	29	55	-
	35	46	-
	25	56	-
	23	57	-
***Enterococcus* spp.**	14	-	0
	18	-	0
	20	-	5
	27	-	4
	25	-	4

223 Table 7: Gram-positive antibiogram (blood cultures)

Organism	*n*	Percentage susceptibility (%)											
		CLOX	PEN/AMP	ERY	CLIN	VANC	LIN	STX	RIF	CTX	CIP	FUS	GENT
CNS	27	22	-	26	52	100	100	15	56	-	33	70	52
	25	12	-	12	48	100	100	28	64	-	52	88	56
	30	23	-	17	57	100	100	27	73	-	50	83	20
	31	13	-	19	32	100	100	16	45	-	39	68	52
	28	29	-	21	46	100	100	21	39	-	39	89	39
Staphylococcus aureus	26	27	-	27	73	100	100	27	85	-	31	96	27
	29	31	-	45	66	100	100	52	90	-	52	90	45
	35	54	-	54	89	100	100	51	94	-	54	94	51
	25	44	-	44	68	100	100	60	84	-	60	80	40
	23	43	-	43	65	100	100	43	96	-	57	96	48
Enterococcus faecalis	10	-	100	-	-	100	100	-	-	-	-	-	80
	10	-	100	-	-	100	100	-	-	-	-	-	60
	11	-	100	-	-	100	100	-	-	-	-	-	82
	20	-	100	-	-	100	100	-	-	-	-	-	85
	17	-	100	-	-	100	100	-	-	-	-	-	82
Enterococcus faecium	4	-	0	-	-	100	100	-	-	-	-	-	100
	8	-	0	-	-	100	100	-	-	-	-	-	100
	9	-	22	-	-	89	100	-	-	-	-	-	67
	7	-	14	-	-	86	100	-	-	-	-	-	71
	8	-	0	-	-	88	100	-	-	-	-	-	75
Streptococcus pyogenes	5	-	100	100	100	100	100	-	-	60	-	-	-
	10	-	100	90	90	100	100	-	-	90	-	-	-
	10	-	100	100	100	100	100	-	-	100	-	-	-
	3	-	100	100	100	100	100	-	-	100	-	-	-

	1	-	100	100	100	100	100	-	-	100	-	-	-

Key:

n=number of isolates; CLOX=Cloxacillin; PEN/AMP= Penicillin/Ampicillin; ERY=Erythromycin; CLIN=Clindamycin; VANC=Vancomycin; LIN=Linezolid; STX=Co-Trimoxazole; RIF=Rifampicin; CTX=Ceftriaxone; CIP=Ciprofloxacin; FUS=Fusidic acid; GENT=Gentamycin

Yeasts

The minority of positive blood cultures were yeasts accounting for only 86 isolates over the total study period (Figure 1 and Table 1). The increase in yeasts and, particularly *Candida auris*, documented between 2015-2017 and 2018-2019 was not statistically significant (p=0.0673 and p=0.56 respectively) (Figure 5 and Table 2).

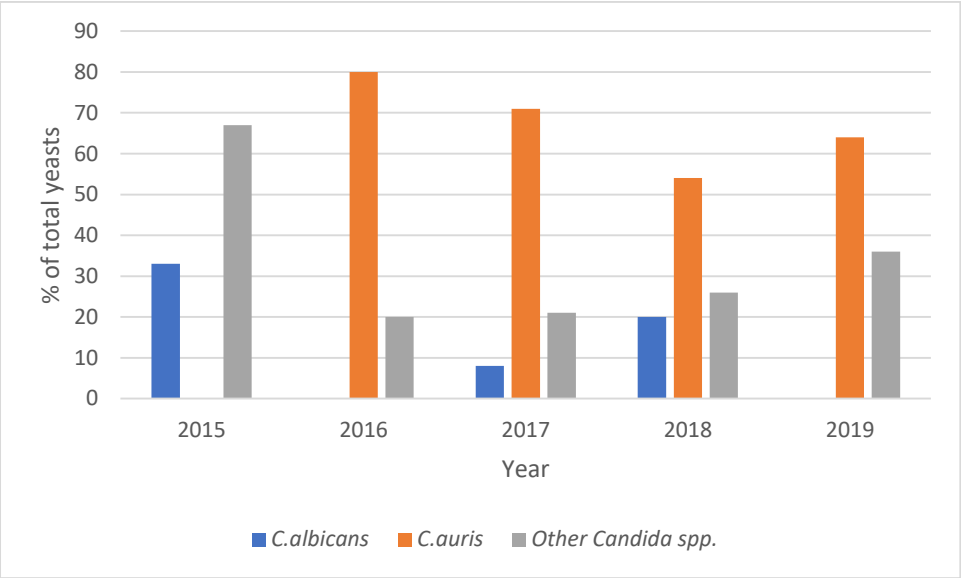

Figure 5: Organism type as a percentage of total yeasts

5.2 Tissue isolates

Tissue culture isolates in descending order for all the years analysed were non-fermenters, Enterobacterales, Gram-positive organisms, and yeasts. (Table 1). *Pseudomonas* spp. was the most isolated organism on tissue culture in all years except 2017 when *Acinetobacter* spp. predominated, all of which were XDR in all years except 2019 (Figure 6 and Table 8). After the non-fermenters, the Enterobacterales were most isolated on tissue with *Klebsiella* spp. prevailing in most years. ESBLs were the highest in 2015 with the highest CREs noted in 2017 (Table 8). In contrast to blood culture isolates, Gram-positive organisms featured less frequently in tissue isolates with *S.aureus* being most isolated. Higher numbers of MRSA were noted from 2017 onwards (Table 8). Yeasts were the least isolated on tissue culture with most years having no yeasts isolated.

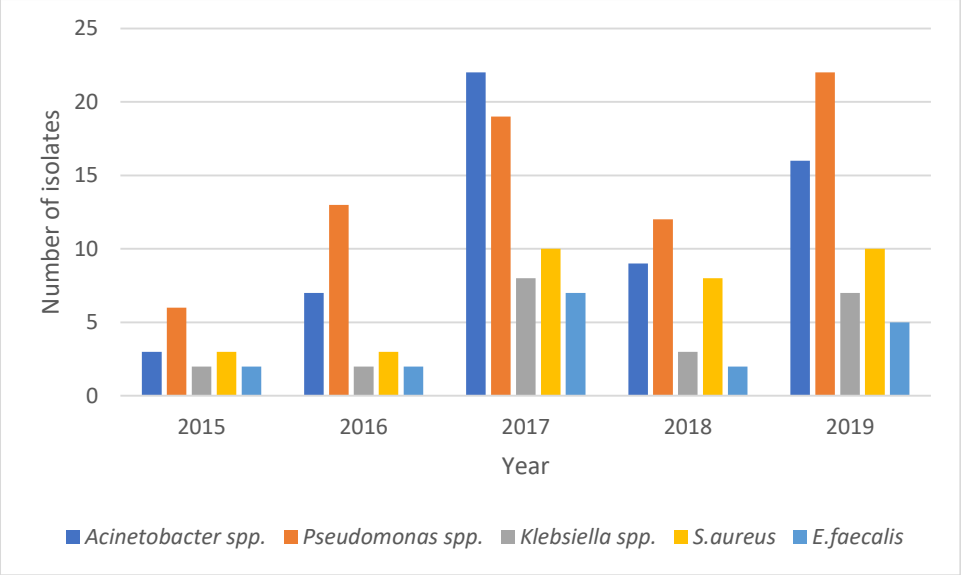

Figure 6: Top five organisms isolated on tissue cultures

Table 8: Organism type and percentage resistance for tissue cultures

Organism	Number of isolates	Percentage resistance (%)			
		ESBL	CRE	XDR	MRSA
Enterobacterales	8	38	13	-	-
	6	0	0	-	-
	21	24	14	-	-
	7	14	43	-	-
	23	30	4	-	-
***Acinetobacter* spp.**	3	-	-	100	-
	7	-	-	100	-
	22	-	-	100	-
	9	-	-	100	-
	16	-	-	69	-
S.aureus	3	-	-	-	0
	3	-	-	-	33
	10	-	-	-	60
	8	-	-	-	75
	10	-	-	-	80

6 Discussion

Different healthcare settings have differing bacteriological and susceptibility profiles [7]. Even within institutes, units may have disparate antibiograms, highlighting the need for unit-specific susceptibility profiles [18]. This study is the first to describe the antimicrobial susceptibility profiles of blood and tissue cultures from the paediatric

burns unit at CHBAH and provides valuable information of epidemiological significance.

A retrospective review by Moffa et. al. [19] at West Penn Burn Center over a 12-month period showed that Gram-positive organisms feature prominently in the first 4 days post-burn. From day 5 onwards, Gram-negative organisms and *Candida* spp. become more prevalent. It should be noted that this study did not take into consideration the time of obtaining cultures relative to duration of admission, an important determinant in terms of type of organism isolated.

Gram-positive organisms were the most isolated for all the years analysed of which coagulase-negative staphylococci predominated for all years except in 2016 and 2017 where *S.aureus* was more common. CNS are part of the normal skin flora and, as such, may be implicated as a coloniser or a true cause of infection, a distinction that may be difficult and warrant clinical correlation. Gram-positive preponderance in this study is in keeping with findings from a retrospective study by Asena et al. [5] among paediatric burn patients which revealed that the most commonly occurring bacterial growth was CNS. Gram-positive dominance was also reported in a prospective study conducted by Fekih Hassen et al. in Tunisia over a 30-month period, where *S.aureus* was the most common organism comprising 93.8% methicillin-susceptible *S.aureus* (MSSA) [23]. This is unlike our study where, although a significant decrease in MRSA was noted when 2015 was compared to 2017 and 2019, MRSA was predominant in all years except 2017. Other studies have also noted higher rates of MRSA among paediatric burns patients [8,24,25].

In contrast to our findings, Bhat and Vasaikar reported Gram-negative prevalence with fewer CNS in their study conducted on burn wound specimens in the Eastern Cape [24] with majority of Gram-negative isolates being *Klebsiella pneumoniae* and high rates of ESBL similar to other studies [5,10,11,23]. Dissimilarly, our study noted a statistically significant decrease in ESBL when 2015 was compared to 2017 and 2019. The reason for the decrease is not known. Though this may seem encouraging, the increase in CREs is concerning. This could be, in part, due to the use of meropenem as an empiric antimicrobial choice for patients who require escalation of therapy or develop sepsis from day 4 of admission onward.

The non-fermenters were the second-most-commonly-isolated organisms from blood cultures with *Acinetobacter* spp. being the most common non-fermenter for all the years analysed. Alarmingly, even though a significant decrease in XDR was noted when 2015 was compared to 2017 and 2019, the majority of *Acinetobacter* spp. were XDR in all years studied. A study by Bayram et al. on wound swabs revealed 93% of *Acinetobacter baumannii* to be MDR [11]. Our finding of *Acinetobacter* spp. being more common than *Pseudomonas aeruginosa* is unlike several other studies where *P.aeruginosa* was the most commonly isolated organism [7,9,25].

Vinaik et. al. reported an increase in fungal infections in burns patients due to the widespread use of antimicrobial agents with the majority of infections due to *Candida albicans* [12]. Relatively low numbers of yeasts were noted in this study across all years analysed. Of concern is the shift from *Candida albicans* to non-albicans Candida, a finding reported in the same study [12] and, particularly, *Candida auris* which is considered MDR.

7 Recommendations

The use of Co-Amoxyclav as an empiric antimicrobial choice for sepsis occurring from days 1-3 of admission may not be adequate to cover most organisms isolated from blood cultures due to the high incidence of resistant Gram-negative and Gram-positive pathogens for all the years analysed. This, however, should be viewed with caution as the timing of the blood cultures relative to admission is not known. In addition, if meropenem is recommended as an empiric antimicrobial choice earlier on (before day 4 of admission), it may contribute to increased numbers of CREs [26]. Though newer agents have shown promise in treating MDR Gram-negative organisms [27], these are not yet available at CHBAH.

The use of piperacillin-tazobactam combined with amikacin as empiric antimicrobial agents for Gram-negative sepsis may be more appropriate as a carbapenem-sparing option. Our data shows that it will offer better antimicrobial cover for the most likely Gram-negative organisms than the current empiric choice used in the unit. For Gram-positive cover, vancomycin is appropriate given the high incidence of MRSA. Due to low numbers of yeasts isolated across the years analysed, this study cannot make recommendations regarding early antifungal strategies. It is likely that the consideration for initiation of an antifungal agent would have to be individualised.

We recommend paediatric infectious diseases consultation for management of patients in this unit. A study conducted in China by Tang et al. revealed that involvement of infectious diseases physicians in the management of patients with bacteraemia had a significantly lower mortality risk and encouraged appropriate antimicrobial use [28]. In addition, we recommend institution of AMS initiatives, including the use of dedicated prescription charts, weekly AMS ward rounds, and post-prescription review and feedback. These measures have been shown in previous studies to enhance stewardship without adversely affecting patient outcomes [14,15,29]. Lastly, we recommend reinforcement of infection prevention and control measures including standard and contact precautions, and scrupulous wound care, all of which have been shown to decrease the incidence of infection and reduce mortality [14,30]. A likely challenge in implementing these recommendations is a paucity of financial and human resources, a concern shared in other studies [14,29].

8 Study limitations

This study has several important limitations. We only analysed blood and tissue cultures but burns patients may have other sources of infection such as catheter-related infections, urinary tract infections, and pneumonia. Although the study is over a significant period (2015-2019), several organisms were below the CLSI target of a minimum of 30 isolates per species. Thus, the results of this study should be viewed with restraint. Other limitations are largely due to the retrospective nature of the study. Clinical information, key to directing antimicrobial choices, was not available. The primary site of infection (in the case of blood cultures) was not known. The timing of cultures in relation to duration of admission was not known. Distinguishing community-associated from hospital-associated infections was not possible. Findings could not be correlated to the clinical condition of the patient. As such, some isolates may be considered contamination in an otherwise well patient. It could not be determined if patients were on antimicrobial agents when cultures were collected – this would influence microbiological yield. The amount of blood in culture bottles is important. This information was not available. It was also assumed that aseptic techniques were employed during microbiological sampling. It was not known whether the tissue specimens were collected at in theatre or in the ward and how these specimens were collected. At the laboratory, consumable stockouts, fallen antimicrobial discs for AST, or erroneous omission in reporting meant that not all

relevant antibiotics may have been documented on the TrakCare laboratory information system. Although most of the yeasts other than *Candida albicans* with high MICs to fluconazole were referred for further testing on the suspicion of possible *C.auris*, there were some isolates that were mistakenly not referred. Similarly, some *Saccharomyces cerevisiae* identified on tissue cultures, suggestive of possible *C.auris,* were not referred for confirmation of identification. Details entered on the TrakCare system are assumed to be correct with possible discrepancies in hospital numbers not taken into consideration.

9 Conclusions

Infections in paediatric burns patients is a serious concern and may lead to adverse patient outcomes. The selection of the most appropriate empiric antimicrobial agent is an important consideration in the management of these patients. Our study revealed that the current empiric antimicrobial regimens in the unit need to be reviewed periodically. We recommend piperacillin-tazobactam with amikacin and vancomycin as empiric antimicrobial agents to cover the most likely bacterial organisms isolated from a bloodstream infection. Additionally, attention to IPC practices and provision of AMS activities need to be constantly reinforced due to the high burden of MDROs in the paediatric burns unit.

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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

CANDIDATE'S SURNAME: Moodley		FIRST NAME/S: Mahavishnu Morgan	STUDENT NUMBER: 0603769D
CURRENT QUALIFICATIONS: MBChB, DTM&H			
TEL:	CELL: 078 758 1884	E-MAIL: mahavishnu.moodley@nhls.ac.za	FAX:
DEGREE FOR WHICH PROTOCOL IS BEING SUBMITTED: MMed Microbiology			
PART-TIME OR FULL-TIME: Full-time			
FIRST REGISTERED FOR THIS DEGREE:	TERM : July		YEAR: 2018
DEPARTMENT: Clinical Microbiology and Infectious Diseases			
TITLE OF PROPOSED RESEARCH: Antimicrobial Resistance Profiles in the Paediatric Burns Unit at Chris Hani Baragwanath Academic Hospital			
CANDIDATE'S SIGNATURE:			DATE: 07-04-2021
SUPERVISOR 1 (NAME & SURNAME): Dr Jeannette Wadula			% Supervision: 50
SUPERVISOR'S QUALIFICATIONS: MD, DTM&H, PDIPC, PDHSE, FCPath (Micro)			
SUPERVISOR'S DEPARTMENT: Clinical Microbiology and Infectious Diseases			
SUPERVISOR'S ADDRESS / TEL / E-MAIL: jeannette.wadula@nhls.ac.za 082 803 5699			
SUPERVISOR 2 (NAME & SURNAME): Dr Prenika Jaglal			% Supervision: 50
SUPERVISOR'S QUALIFICATIONS: MBChB, DA (SA), MMed (Micro), FCPath (Micro)			
SUPERVISOR'S ADDRESS / TEL / E-MAIL: prenika.jaglal@nhls.ac.za 079 873 1429			
SUPERVISOR 3 (NAME & SURNAME):			% Supervision
SUPERVISOR'S QUALIFICATIONS			
SUPERVISOR'S ADDRESS / TEL / E-MAIL:			

SYNOPSIS OF RESEARCH: (Brief summary of proposed research project; between 200-300 words only; with sub-headings: an introduction and justification for study, aim/s, proposed methodology and expected outcome/s)
[Use reverse side of this page if more space is required]

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SYNOPSIS OF RESEARCH CONTINUED

Introduction:
The South African Medical Research Council approximates that 3.2% of the population are injured by burns yearly. The number of paediatric burn patients is the highest in Africa with children younger than 5 years of age being greatest at risk. Paediatric burns in the South African context is largely related to vulnerable children dwelling in unregulated living spaces.
Managing paediatric burns patients is often complicated and associated with high morbidity and mortality. Compared to non-infected burn wound patients, infected burn wounds are associated with lengthier hospital stays and heightened morbidity and mortality.
Burn patients receive antimicrobial agents throughout their admission, increasing the risk of colonization or infection with MDR pathogens. Colonization with MDR organisms is an important determinant in the outcomes of burns patients.
Different healthcare settings have differing bacteriological and susceptibility profiles. An antibiogram is an intervallic consolidation of an institution or unit's antimicrobial susceptibility data based on isolates submitted for testing to the microbiology laboratory. Its utility is mainly to monitor local susceptibility rates, assist in choosing appropriate empiric antimicrobial therapy, observing resistance patterns within units in a specified timeframe, and evaluating susceptibility rates across units and institutions.

Aim:
The aim of this study is to review the antimicrobial resistance profiles for the Paediatric Burns Unit at CHBAH for the period January 2015 to December 2019.

Methods:
This study is a retrospective laboratory-based review of blood cultures and tissue samples from January 2015 to December 2019.

Data Analysis:
The National Health Laboratory Services (NHLS) CDW will be requested to provide data which will then be analysed using Microsoft Excel spreadsheets. Duplicates will be removed according to exclusion criteria.

Statistical Analysis:
A biostatistician will be consulted as needed.

11 March 2019/MP

Antimicrobial Resistance Profiles in the Paediatric Burns Unit at Chris Hani Baragwanath Academic Hospital

Dr Mahavishnu Morgan Moodley

Student Number: 0603769D

MMed in Medical Microbiology

Supervisors:

1. Dr Jeannette Wadula - MD, DTM&H, PDIPC, PDHSE, FCPath (Micro)
2. Dr Prenika Jaglal - MBChB, DA (SA), MMed (Micro), FCPath (Micro)

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Abbreviations:

AMR – Antimicrobial Resistance

AMS – Antimicrobial Stewardship

CAI – Community-Associated Infections

CDW – Corporate Data Warehouse

CHBAH – Chris Hani Baragwanath Academic Hospital

CLSI – Clinical Laboratory Standards Institute

CNS – Coagulase-Negative Staphylococcus

CRE – Carbapenem-Resistant Enterobacterales

ESBL – Extended Spectrum Beta Lactamase

GNB – Gram-Negative Bacilli

HAI – Healthcare-Associated Infections

ICU – Intensive Care Unit

Imi-EDTA – Imipenem Ethylenediamine tetra-acetic acid

IPC – Infection Prevention and Control

ISO – International Organisation for Standardization

LMIC – Low-to-Middle-Income Countries

MDR – Multi-drug Resistant

MIC – Minimum Inhibitory Concentration

MRSA – Methicillin-Resistant *Staphylococcus aureus*

MSSA – Methicillin-Susceptible *Staphylococcus aureus*

NHLS – National Health Laboratory Services

PDR – Pan-drug Resistant

SANAS – South African National Accreditation System

TBSA – Total Body Surface Area

UTI – Urinary Tract Infection

WHO – World Health Organization

XDR – Extreme drug Resistant

Introduction:

The South African Medical Research Council approximates that 3.2% of the population are injured by burns yearly [1]. Children are particularly at risk, with burns being ranked 5th among non-fatal childhood injuries [2]. The number of paediatric burn patients is the highest in Africa with children younger than 5 years of age being greatest at risk [3].

South Africa, considered a middle-income developing country, has heavily crowded informal settlements often with poor access to electricity [4]. A study by Parbhoo et al. at The Red Cross Children's Hospital in Cape Town revealed that the highest incidence of burns was among toddlers, followed by babies younger than 1 year [4]. 83% of paediatric burns were caused by hot liquid, followed by fire and electrical burns [4].

An estimated 180 000 deaths occur annually because of burns, most of which take place in low-to-middle-income countries (LMIC) [2]. Approximately 75% of all deaths in burns patients occur because of infection and may be as high as 86% in some settings due to escalating resistance patterns [5,6].

Despite noteworthy advances in the management of burn patients, infection poses a significant concern [6,7]. Burns patients are inherently at risk of developing infections as the body's first line of defence, the skin, has been breached, contributing to the immunocompromising effects [8].

Almost inevitable, burn wounds are colonised by microbes [5]. Breached skin in burn patients is replaced by a proteinaceous, avascular environment that is conducive to microbial colonization and growth [9].

Following a burn incident, the wound is initially sterile. Within 48 hours, microbes from the skin, sebaceous glands, and hair follicles colonise the wound. Thereafter, gastrointestinal, and respiratory tract microbes, as well as those from the environment, colonise the wound. Studies have shown that Gram-positive organisms predominate in the first week following burns and Gram-negative organisms thereafter [7,10,11].

Infected burn wounds are associated with lengthier hospital stays and heightened morbidity and mortality [11]. A study by Amado et al., looking at morbidity and mortality among paediatric burn patients in Mozambique revealed that wound infections and sepsis account for 58% and 27% of complications, respectively. All deaths reported in their study were because of septic shock [3].

Apart from burn wound sepsis, burn patients also develop infections elsewhere. In the first week following the burn incident, skin and soft tissue infections tend to dominate, followed by bacteraemia, catheter-related infections, urinary tract infections, and pneumonia [6,12].

There has been an increase in bacterial antimicrobial resistance trends amongst burns patients in recent years [9]. A retrospective analysis was conducted by Bhat and Vasaikar in Eastern Cape, South Africa on burn wound specimens which reported that 57.5% of *Staphylococcus aureus* were methicillin-resistant (MRSA), while extended-spectrum beta-lactamase (ESBL) producers were detected in 32.14% of *Klebsiella pneumoniae*, 11% of *Klebsiella oxytoca*, and 5.1% of *Escherichia coli* [5]. den Hollander et al. describes the increased incidence of fatal sepsis as worrisome with many burn patients succumbing to drug-resistant bacterial infections [13].

Epidemiology of Burn Wound Infections:

Different healthcare settings have differing bacteriological and susceptibility profiles [7].

A retrospective study by Asena et al. [8] among paediatric burn patients revealed that the most commonly occurring bacterial growth was coagulase-negative staphylococci (CNS). Gram-positive dominance was also reported in a prospective study conducted by Hassen et al. in Tunisia over a 30-month period, where *S.aureus* was the most common organism comprising 93.8% methicillin-susceptible *S.aureus* (MSSA) [14]. This is dissimilar to other studies, where higher rates of methicillin-resistant *S.aureus* (MRSA) were noted [5,7,8,15].

High rates of ESBL were documented in studies from different settings [5,8,9,12,14]. Gram-negative bacilli (GNB) predominance was reiterated in a study in Southeast China by Li et al., where GNB accounted for 57.6% of pathogenic strains, with the most common bacteria being *Acinetobacter baumannii* (17.6%) resistant to ceftazidime, imipenem and meropenem in >80%, 58.5% and 83.3% of isolates respectively [12]. The finding of *A.baumannii* as the most common isolate and *P.aeruginosa* as the second most common isolate was reported by Bayram et al. in their retrospective study in Turkey, where 93% of the *A.baumannii* and 43% of the *P.aeruginosa* were considered multi-drug resistant (MDR) [9]. MDR is defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories. Extreme-drug resistance (XDR) is defined as non-susceptibility to all but two or fewer categories of antimicrobial agents. Pan-drug resistance (PDR) is defined as non-susceptibility to all agents in all antimicrobial categories [16].

The finding of *P.aeruginosa* as the most common organism isolated was reiterated in several Indian studies [7,11,15]. A retrospective analysis by Singh et al. [7] found a 15.2% occurrence of MDR *P.aeruginosa*.

A retrospective study at a burns unit in Italy revealed a frequent occurrence of nosocomial pathogens causing burn wound infections, particularly carbapenem-resistant *A.baumannii* (27%), carbapenem-resistant *P.aeruginosa* (25%), and MRSA (26%) [6]. The incidence of infections was 27%, 40%, and 43.8% on days 7, 14 and 28 of admission, respectively, congruent with the notion that longer hospital stay is associated with more infections.

An increase in fungal infections in burns patients is noted due to the widespread use of antimicrobial agents. The majority of infections are due to *Candida albicans*, but one must bear in mind possible non-albicans Candida and other fungi including *Aspergillus* species and *Fusarium* species [17]. Apart from bacterial and fungal infections that occur in burn patients, reactivation of latent viral infections, either systemically or close to the wound, is also a concern [18].

Antimicrobial Resistance (AMR):

The World Health Organisation (WHO) has acknowledged that MDR pathogens undermine the efforts taken to prevent and treat bacterial infections [19]. AMR occurs as a result of an array of biological, pharmacological, and societal variables that occur globally, and LMIC are seeing a more rapid rise in AMR [19].

The risk factors for the development of MDR infections present in other patient populations are also relevant to the burn patients, including the use of urinary catheters, endotracheal intubation, and prior use of antimicrobial agents [20].

Burn patients are at increased risk of colonization or infection with MDR pathogens which is an important determinant in their outcome [17,19]. Burn severity correlates closely with the development of MDR infections, with more MDR infections seen in patients with larger total body surface area (TBSA) involved [17].

MDR infections have both clinical and financial implications with challenges in management [7]. Often, the use of broad-spectrum empiric antimicrobial agents to prevent MDR infections aggravates the vicious cycle of selective pressure and resistance development [17]. MDR strains of certain isolates may establish themselves in the hospital environment and spread between patients [7].

Antimicrobial Stewardship (AMS):

AMS may be defined as the rational and judicious use of antimicrobial agents by instituting a series of logical steps at an individual, national, and global level, thereby enhancing the responsible use of antimicrobial agents [16]. Global usage of antimicrobial agents has increased by 36% between 2000 and 2010 [21]. Antimicrobial agents are displaying reduced efficacy globally while limited newer agents are being developed, possibly leading us faster toward the 'post-antibiotic era' [22]. A core component of The National AMR Strategy Framework in South Africa, in line with conserving antimicrobial agents, is surveillance of antimicrobial resistance patterns [23].

Growing evidence suggests that AMS programs are effective in enhancing compliance to antibiotic policy, reducing hospital stay/readmissions, and decreasing the incidence of *Clostridiodes difficile* infections. Several AMS program interventions

have shown improved outcomes on patient care, emphasizing the need for microbiological surveillance [17,24,25].

Antibiogram – Why is it needed?

An antibiogram is an intervallic consolidation of an institution or unit's antimicrobial susceptibility data based on isolates submitted for testing to the microbiology laboratory. Its utility is mainly to monitor local susceptibility rates, assist in choosing appropriate empiric antimicrobial therapy, observing resistance patterns within units in a specified timeframe, and evaluating susceptibility rates across units and institutions [26].

Surveillance of antimicrobial susceptibility enables doctors to opt for the most appropriate antimicrobial agent [7]. An agent with a suboptimal cover or to which the infecting pathogen is resistant can have dire patient consequences [27]. This needs to be balanced against the risks of using broad-spectrum antimicrobial agents [28]. The global rise in antimicrobial resistance has confounded this decision. Commencement of empiric antimicrobial agents should be directed by patient-related factors (age, renal function, medications) and knowledge of the pathogens most implicated within the unit [29].

Institution-wide antibiograms may have vital differences in susceptibility data when compared to unit-specific antibiograms as reflected by a study by Binkley et al. [27]. An antibiogram specific to the burn unit is a useful aid in monitoring antimicrobial resistance trends and choosing appropriate empiric antimicrobial therapy.

Aims:

This study aims to review the bacterial and fungal antimicrobial resistance profiles for the Paediatric Burns Unit at CHBAH for the period January 2015 to December 2019.

Study Objectives:

1. To compile unit-specific antibiograms based on positive blood and tissue culture specimens comparing the prevalence of bacterial and fungal isolates including their antimicrobial resistance trends
2. To compare the frequency of organisms and resistance trends between the periods January 2015-June 2017 and July 2017-December 2019

METHODS:

Study Setting:

The Chris Hani Baragwanath Academic Hospital is a tertiary institution situated in Soweto, Johannesburg. It is the third-largest hospital complex globally, with more than half its admissions being emergencies [30]. A dedicated paediatric burns unit has 19 regular and 7 ICU beds. The average admission between the period January 2015 to December 2019 was 42 patients per month, with an average of 8 admissions to ICU per month. An average of 2 deaths per month occurred during this period. The majority of paediatric burns seen at the unit are caused by hot liquids, followed by flame and electrical burns.

Current empiric antibiotic regimens used in the paediatric burns unit depend on the duration of hospital stay. If within three days of admission, Co-Amoxyclav is started to cover community-associated infections (CAI). From day four onwards or if escalating therapy, meropenem and vancomycin are commenced to cover healthcare-associated infections (HAI). All antibiotics are started after blood and other relevant cultures are obtained.

Study Design:

This study is a retrospective laboratory-based review of blood cultures and tissue samples from January 2015 to December 2019.

Laboratory Methods:

The Microbiology Laboratory at CHBAH is accredited by the South African National Accreditation System (SANAS) according to International Organization for Standardization (ISO) 15189 standard and subscribes to the guidelines of the Clinical Laboratory Standards Institute (CLSI) [31].

Blood cultures are obtained from burns patients who are suspected of having sepsis. Tissue is collected from burns patients who are systemically septic, have septic wounds undergoing debridement, or are scheduled for graft procedures. Both specimen types are processed according to the local laboratory's standard operating protocols.

Inclusion Criteria:

Blood and tissue samples from the paediatric burns unit at CHBAH obtained between January 2015 and December 2019 will be included. Only the first isolate of a given species per patient per calendar year regardless of body site, antimicrobial susceptibility profile, or other phenotypic characteristics will be included. This is in keeping with CLSI M39-A4 recommendations for compiling a cumulative antibiogram to guide clinical decisions about empiric antimicrobial therapy of initial infections [35]. If multiple blood and tissue culture specimens are collected on the same day from the same patient and cultures the same organism, preference will be given to the first blood culture.

Exclusion Criteria:

In line with CLSI M39-A4 recommendations [35], patients with repeat isolates of the same species regardless of body site will be considered a single episode if within the same calendar year. Surveillance cultures will be excluded.

Data Analysis:

Relevant data according to the data collection sheet (appendix 1) will be requested from the National Health Laboratory Services (NHLS) Corporate Data Warehouse (CDW) for two 30-month periods, January 2015-June 2017 and July 2017-December 2019. Data analysis will be performed using Microsoft Excel. Organisms will be sorted into separate tables for Gram-positive organisms, Gram-negative organisms, and yeast. Duplicates will be removed according to the exclusion criteria.

Categorical data will be summarised by frequency and percentage. The total number of isolates per organism will be added and the frequency calculated as a measure of the total number of positive cultures in the data series over the study period. The percentage susceptibility to each of the routinely tested antimicrobial agents at CHBAH will be calculated according to Gram-positive, Gram-negative, and fungal panels. Results will be tabulated as percentage susceptibility per antimicrobial agent. The frequency and resistance trends of organisms will be compared between two 30-month periods, namely January 2015 to June 2017 and July 2017 to December 2019. Trends will be ranked according to prevalence.

Enterobacterales with minimum inhibitory concentrations (MIC) showing reduced susceptibility to any of the routinely tested carbapenems will be included as CRE [31].

Statistical Analysis:

Descriptive statistics will be used to summarise the data. Due to the categorical nature of the data, Fisher's exact test with a 2X2 contingency table will be utilised to

808 determine if statistical significance exists between the two comparative periods for
809 the frequency of organisms and resistance patterns. Two-tailed *p*-values will be
810 reported, with values <0.05 considered statistically significant. GraphPad (GraphPad
811 Software, USA) will be used for this purpose. A biostatistician will be consulted as
812 needed.

813 **Limitations:**

814 The retrospective nature of the study has several limitations:

815 • Clinical information, key to directing antimicrobial choices, is not available.
816 The primary site of infection (in the case of blood cultures) is not known.
817 • The timing of cultures in relation to the duration of admission is not known.
818 Distinguishing community-associated from hospital-associated infections will
819 not be possible.
820 • Findings cannot be correlated to the clinical condition of the patient. As such,
821 some isolates may be considered contamination in an otherwise well patient.
822 • It cannot be determined if patients were on antimicrobial agents when cultures
823 were collected – this would influence microbiological yield.
824 • The amount of blood in culture bottles is important. This information is not
825 available. It is also assumed that aseptic techniques were employed during
826 microbiological sampling.
827 • It is not known whether the tissue specimens were collected at debridement in
828 theatre or the ward and how these specimens were collected.
829 • Details entered on the TrakCare system are assumed to be correct. Possible
830 discrepancies in hospital numbers are not taken into consideration.

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Timeline:

MONTH/YEAR	APR 2021	MAY 2021	JUN 2021	JUL 2021	AUG 2021	SEP 2021	OCT 2021	NOV 2021	DEC 2021	JAN 2022	FEB 2022
Literature Review											
Protocol Preparation											
Protocol Assessment											
Ethics Application											
Data Collection											
Data Analysis											
Write-up											
Submission											

Ethics:

Approval from HSREC and the CEO of CHBAH will be sought. No patient particulars, identification, or clinical details will be included.

Funding:

The Department of Clinical Microbiology and Infectious Diseases (CMID) at the University of the Witwatersrand will fund the printing and publishing costs.

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Appendix

Data Collection Sheet 1 – January 2015-June 2017:

Episode No.	Hospital No.	Specimen Collection Date	Blood culture	Tissue culture	Organism	Resistance profile: Antimicrobial agent	Study number

Data Collection Sheet 1 – January 2015-June 2017:

Episode No.	Hospital No.	Specimen Collection Date	Blood culture	Tissue culture	Organism	Resistance profile: Antimicrobial agent	Study number

Acknowledgements:

Dr Ronell Parkhust (CHBAH paediatric burns unit) provided background information on the unit as well as data regarding admissions and mortality.

UNIVERSITY OF THE
WITWATERSRAND
JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

24 August 2021
Person No: 0603769D
PAG

Mr MSM Moodley
P O Box 2077
Verulam
Greytown
3250
South Africa

Dear Mr Mahavi Moodley

Master of Medicine in Microbiological Pathology: Approval of Title

We have pleasure in advising that your proposal entitled *Antimicrobial Resistance Profiles in the Paediatric Burns Unit at Chris Hani Baragwanath Academic Hospital* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

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UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Dr MM Moodley

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M210952

NAME: (Principal Investigator)	Dr MM Moodley
DEPARTMENT:	School of Pathology Dept of Clinical Microbiology & Infectious Diseases Medical School University
PROJECT TITLE:	*Antimicrobial resistance profiles in the Paediatric Burns Unit at Chris Hani Baragwanath Academic Hospital*
DATE CONSIDERED:	2021/10/01
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Dr J Wadula
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2021/12/08

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Philip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report** When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in September and therefore reports and re-certification will be due in the month of **September** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical)

Signature of Principal Investigator _____ Date _____

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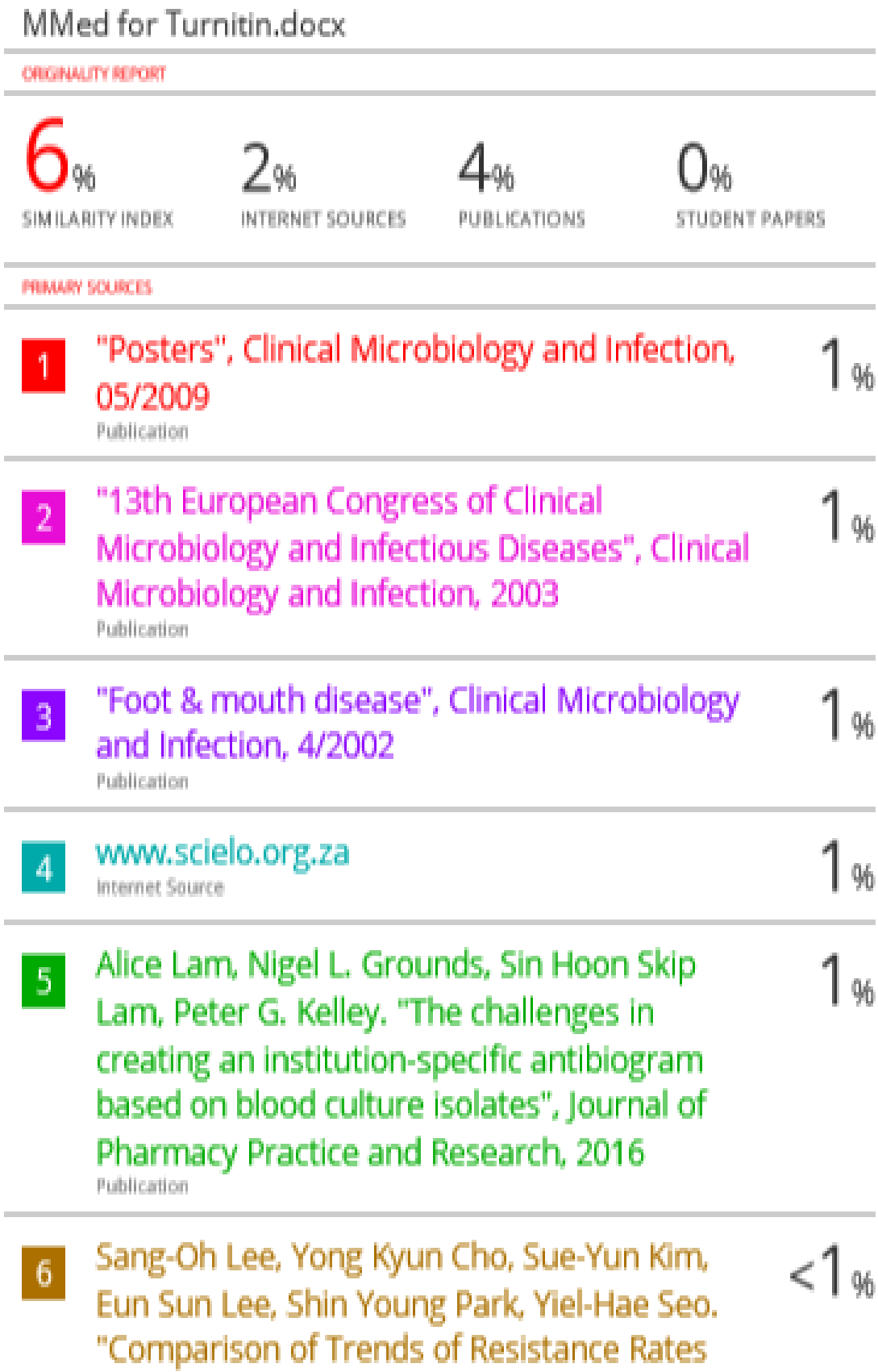

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