An Audit of Blood Cultures Performed in an Emergency Department at a Johannesburg Academic Hospital

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment for the degree of MMed (Emergency Medicine)

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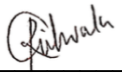
Declaration: Student's contribution to article

I, Bradley Rae, student number 0701910X, declare that this Research Report is my own work and that I contributed adequately towards research findings in this article stated below which are included in my Research Report. It is being submitted for the degree of MMed EM at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signature of Student_____ 

Date ___15/12/2020_____

Name of Primary Supervisor: ___Dr Radha Gihwala_____

Signature of Primary Supervisor_____ 

Date ____15/12/2020_____

Abstract

Background. Blood cultures (BCs) are the standard test for detecting bacteraemia but have come under scrutiny on their usefulness in Emergency Departments (EDs) as they have a low yield, tend not to alter patient management and may be subject to high contamination rates especially in resource limited settings. Identifying patients most at risk of bacteraemia may improve the usefulness of BCs as investigations. We aim to describe and compare clinical and demographic characteristics of patients in whom BCs where taken as well as validate scoring systems predicting bacteraemia.

Methods. A retrospective observational, descriptive and comparative study. Reports from all BCs performed in the ED in 2017 were requested from the National Health Laboratory Service (NHLS). Data from all positive BCs were used to audit cultured organisms and their sensitivity and resistance patterns. Secondly, clinical and laboratory data from 206 consecutively selected patients (103 positive and 103 negative BC results) were used to calculate the Shapiro score, a prediction tool for bacteraemia, and the Systemic Inflammatory Response Syndrome (SIRS) criteria.

Results There was a total of 4011 BCs performed in 2017. There were 715 (17.8%) positive BCs, of which pathogens were cultured in 400 (10.0%) BCs and 315 (7.9%) BCs cultured known contaminants. *Streptococcus Pneumoniae* was the highest pathogen load (n=108, 24.3%) and was 94.4% sensitive to co-amoxiclav. A positive Shapiro score and SIRS criteria increased the likelihood of a positive BC by 5.6 and 2.3 times, respectively. Positive HIV status, rigors, pulse rate > 115bpm, deranged mentation, white cell count (WCC) > 18 ($x10^9$cells/L) and creatinine > 177 (µmol/L) were all risk factors for a positive BC.

Conclusion. There was a low yield of positive BCs from the ED and using the SIRS criteria or the whole or components of the Shapiro score would improve the pre-test probability of a positive BC result in patients with suspected sepsis.

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Abbreviations

BCs	Blood Cultures
CAP	Community Acquired Pneumonia
CNS	Coagulase Negative Staphylococcus
CRP	C-Reactive Protein
EDs	Emergency Departments
GCS	Glasgow Coma Scale
HIV	Human Immuno-deficiency Virus
HJH	Helen Joseph Hospital
NHLS	National Health Laboratory Service
PCT	Procalcitonin
qSOFA	quick Sequential Organ Failure Assessment
SIRS	Systemic Inflammatory Response Syndrome
WCC	White Cell Count

Chapter 1: Original research article:

An Audit of Blood Cultures in an Emergency Department at a Johannesburg Academic Hospital

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Introduction

Sepsis is a global health concern with ever increasing mortality in the developing world and high rates among patients who are immunocompromised [1]. Blood cultures (BCs) are the gold standard test for detecting bacteraemia in patients with suspected sepsis [2]. They are a useful tool to identify the causative organism and to guide antibiotic therapy [3].

The taking of routine BCs in Emergency Departments (EDs) has come under much scrutiny in recent years. There are concerns that BCs may not change the management of patients in the ED as they are prone to high rates of contamination and that the yield may be extremely low in certain pathological conditions such as community acquired pneumonias (CAP) [3-6]. Furthermore, since the BC must be performed in a sterile manner, it is a time consuming investigation which often leads to clinicians working in busy EDs to perform them rather poorly [7].

The yield of BCs is low with rates of positive BCs generally falling between 5 to 14%. Of these, there is up to a 56% chance of false positive results, decreasing the specificity of BCs [8,9]. False positive BC rates should ideally be limited to 2 to 3% of all BCs if they are being performed correctly [7,10-12].

Apart from using the correct procedure to take BCs the key to success in achieving higher true positive and lower false positive rates also lies in increasing the pre-test probability by identifying the patient population most likely to have bacteraemia [7,8,13,14]. Some prediction tools exist to predict the likelihood of bacteraemia, for example, the Shapiro score [13]. The score achieved a sensitivity of 98% in its validation studies, and has also been used in combination with other markers of sepsis such as procalcitonin (PCT) to further increase its specificity [15]. These scores however have not yet been well validated in the developing world [13,15-17]. Additionally, other screening tools for sepsis may be better, such as the Systemic Inflammatory Response Syndrome (SIRS) criteria, to identify patients at risk of bacteraemia [18].

Furthermore, the value of BC audits cannot be overstated. They guide empiric antibiotic therapy, monitor common pathogen resistance patterns, and identify rates of BC contamination [19].

We think BCs can be useful tools in detecting bacteraemia but are best used in the right patient population with the right indication and performed in the correct manner. The aim of this study is to perform an audit on BCs that were taken at an ED in Johannesburg, South Africa. The Shapiro score and SIRS criteria are calculated using patient demographics, vital signs and blood results, to determine if these scores will increase the pre-test probability of a positive BC in our setting. Secondly, we want to describe the common bacterial isolates of BCs performed in the ED and their sensitivities to commonly used empiric antibiotic(s) as well as BC contamination rates.

Materials and Methods

This is a retrospective observational, cross-sectional descriptive and comparative study which was conducted in the ED of the Helen Joseph Hospital (HJH), a tertiary level academic institution in Johannesburg that provides services to approximately 60 000 people annually. The centre includes most major disciplines and specialties, except for obstetrics & gynaecology and paediatrics. Therefore, only BCs from adult patients were included in the study.

Ethical approval to conduct this study was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (ref. no. M180265). Permission was also sought through the National Laboratory Health Service (NHLS) for the use of their data.

A list of all BCs which were performed in the ED from 1 January 2017 to 31 December 2017 was requested from the NHLS. Two separate data sheets were provided: one with the positive BCs as well as their sensitivities to antibiotics. The other data sheet was a list of 1000 negative BC results generated by the NHLS Data Warehouse. The list of all positive BCs was used to calculate a more accurate true positive and false positive BC rate, as well as better identify sensitivities of the organisms which were cultured. The resistance rates of the commonly used antibiotics in the ED were also reviewed. The likely false positive BC results were separated to review the possible impact of future clinical course if these organisms were cultured and then treated.

Two further lists were created, one of which was the positive BC list which excluded the usual contaminant organisms[20], and the other was a randomly generated (every alternate) list of a matching cohort from the 1000 negative BCs. These lists were submitted to the HJH Records Department to obtain the full report.

The first 100 (minimum) files from each of the positive and negative lists which had a complete set of data needed to calculate the Shapiro score and SIRS criteria were selected and all information captured electronically.

Using the NHLS list of positive BCs, an anonymous summary was made of all doctors who performed ten or more BCs. True positive and false positive BC rates were identified to better describe the shortfalls in respect to the taking of a BC and contamination rates.

The data were electronically captured and analysed using SPSS Statistics v22 (IBM, Armonk, NY). The biographical information of the patients in the study were presented descriptively using frequencies and percentages for all categorical variables and means and standard deviations (SDs) for all numerical variables. The Pearson's chi-square test of association or T-Test was performed to examine for associations between the BC results and various other clinical results. Binomial logistic regression modelling was done to determine the extent to which a positive BC could be predicted using The Shapiro Score and SIRS criteria. The corresponding Exp(B) values represent the adjusted odds ratios for predicting a positive BC from each of these scores. A p-value < 0.05 indicated statistical significance.

Results

There was a total of 4011 BCs performed at the HJH ED in 2017. Positive BCs were found in 715 (17.8%) cases and represented 806 cultured organisms (as several BCs cultured more than one organism) with 400 BCs likely to be true positive representing 481 (59.7%) likely pathogens. *Streptococcus Pneumoniae* (n=108, 22.5%) was the most commonly isolated pathogen.

Organisms Cultured

Figure 1 shows the pathogenic organisms cultured. There were 481 cultured organisms from the 400 positive BCs. Almost half of the organisms cultured identified *S. Pneumonia, E. Coli* and *S. Aureus* as the causative organisms. Within the sample of positive BCs, there was an unusually large series of *Serratia Marcescens* (n=42, 8.8%) organisms which were cultured. The majority of these *S. Marcescens* cultures (n=39, 93%) also cultured additional organism(s) many of them other virulent pathogens, such as *Pseudomonas Aeruginosa* (n=28, 72%), *Enterococcus* species (n=23, 59%), *Klebsiella Pneumoniae* (n=3, 7.7%) and various combinations of the above pathogens with three or more organisms being cultured in 19 (45%) of these BCs. Several of these *Serratia* BCs were cultured in a consecutive fashion. Nine of the 42 *S. Marcescens* BCs were taken by the same doctor, with three other doctors culturing three or more *S. Marcescens* BCs in a consecutive manner. Additionally, there were four instances where there were BCs taken from two different patients within six hours of each other with the same or remarkably similar organism profiles.

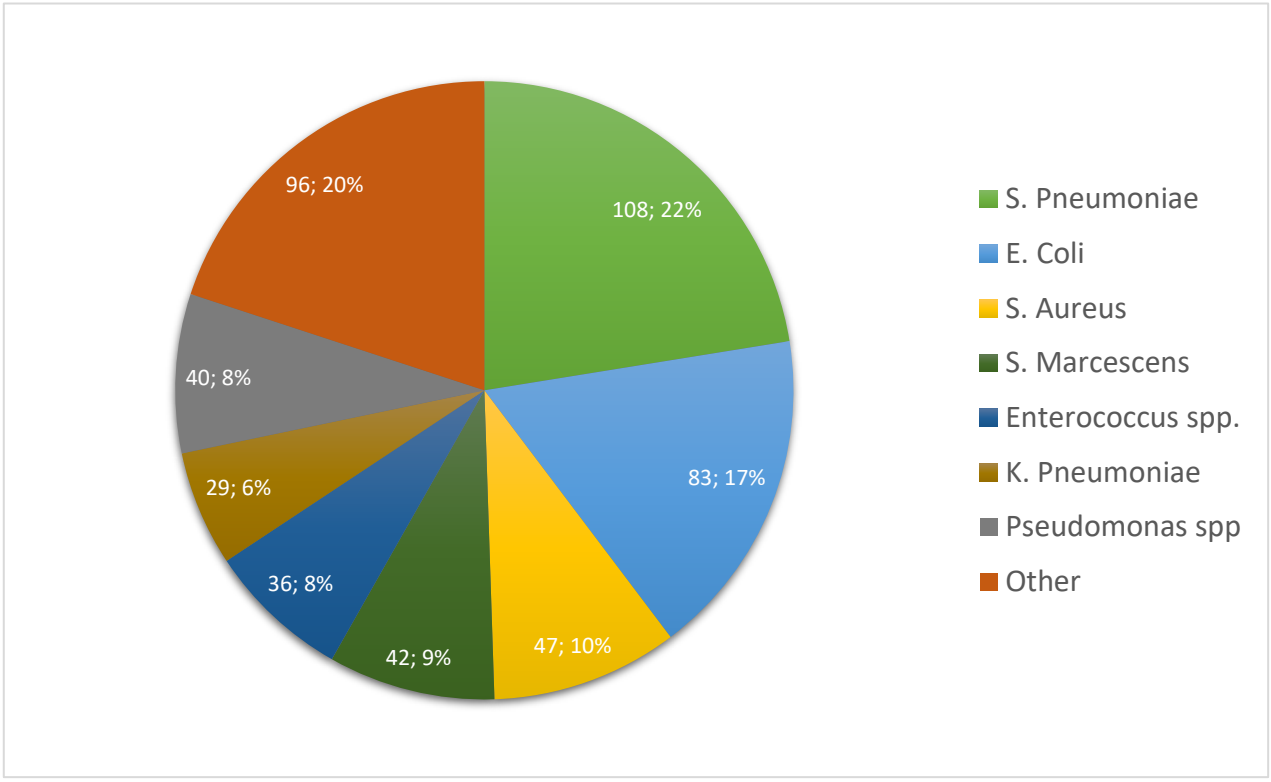

Figure 1: Pathogenic organisms cultured (n=481)

The number of BCs culturing suspected contaminates within the sample was 315 (44% of the positive BCs and 7.9% of all BCs performed). Of these BCs, 246 (75.7%) cultured Coagulase Negative Streptococcus (CNS). The resistance rates of the most frequently isolated pathogens to the commonly used antibiotics co-amoxiclav and

ceftriaxone are shown in figure 2. Notably the resistance rates to the clustered groups of all contaminants as well as the Serratia Marcescens cluster of BCs were very high (up to 80%).

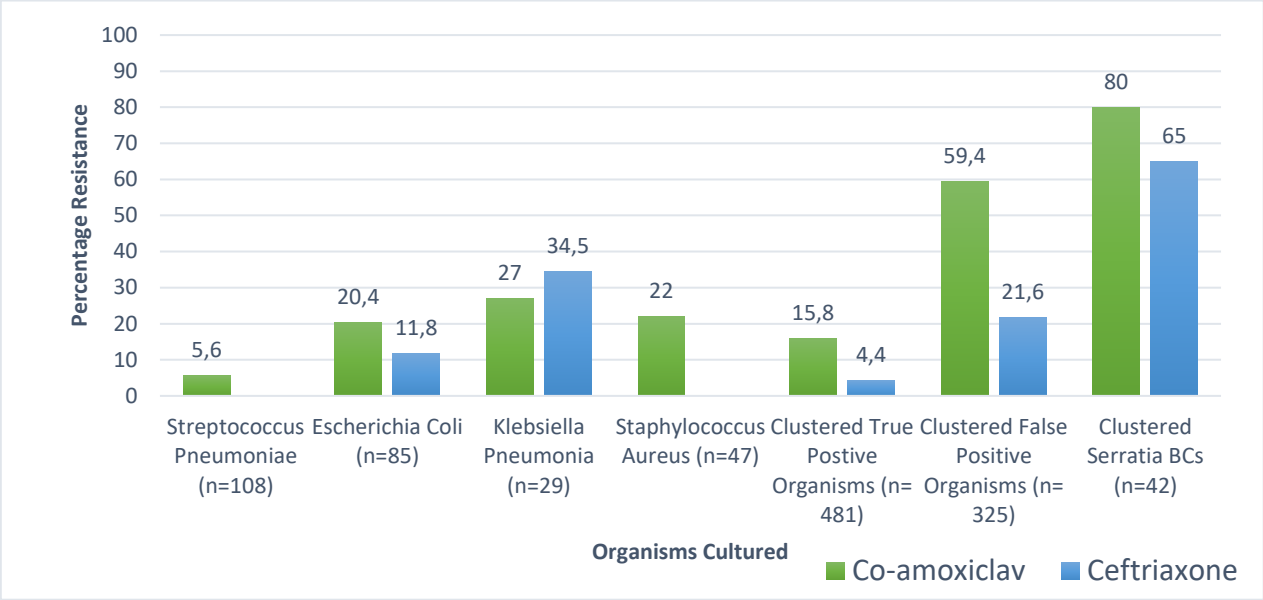

Figure 2: Organism resistance rates to commonly used antibiotics in the ED

For all the BCs which tested positive, an anonymous summary was formulated of all the Doctors who performed 10 or more BCs within the study period (Mean number 19 BCs during review period). The contamination rates as well as the incidence of *S. Marcescens* in BCs are shown in figure 3. One doctor achieved a true positive rate (pathogens found in BCs) of 94% and one doctor was responsible for 21.4% of all the *S. Marcescens* BCs. A total of 70% of doctors had contaminants in 50% or more of the BCs taken.

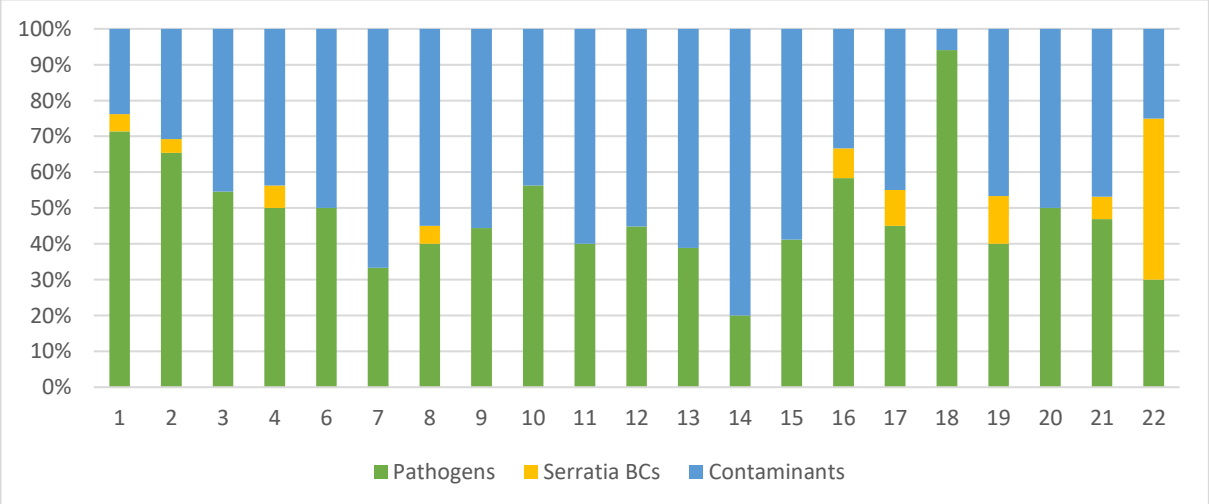

Figure 3: Percentage positive and negative BC rates of Doctors who performed 10 or more BCs during the period of review

Clinical prediction scores and clinical parameters analysis

This study reviewed a total of 206 patient files (103 negative and 103 positive BCs). Of the positive BCs, 16 (15,5%) were deemed likely to be false positive based on both the organism(s) cultured and patients' clinical characteristics and were excluded from the positive BC data set. This decision was discussed with and supported by a specialist Microbiology clinician.

Of the remaining 190 patient records, 101 (53%) were female and the mean (SD) age was 42(5.5) years. Of the 190 cases, the most likely source of sepsis in half of these BCs was the respiratory system (Table 1).

Overall, 56% of the patients in the study were HIV positive. The percentage of HIV positive patients who had a positive and negative BCs was 58% and 42% respectively, among the HIV negative patients 31% of the BCs were positive and 69% negative. Patients who were HIV positive were significantly more likely to have a positive BC (p=0.01).

Table 1: Organ Systems suspected as source of sepsis and the most commonly isolated organisms from each category

Organ system	n (%)	Organism (%)
Respiratory	95 (50.0)	S. Pneumoniae (61), E. Coli (15), Salmonella (13)
Neurological	34 (17.9)	S. Pneumoniae (50), E. Coli (22), C. Neoformans (11)
Gastrointestinal	27 (14.2)	E. Coli (38), S. Pneumoniae (31)
Urinary	25 (13.2)	E. Coli (75), Salmonella (10)
Skin	8 (4.2)	S. Aureus (100)
Gynaecological	3 (1.6)	Nil Positive BC
ENT	4 (2.1)	S. Aureus (50), S. Pneumoniae (50)
Other	17 (8.9)	S. Aureus (100)
Unknown	7 (3.7)	S. Aureus (43), E. Coli (29)
Multisystem involvement	30 (15.8)	S. Pneumoniae (44), E. Coli (38)

The Shapiro score was found to be positive in 68% and 32% of the positive and negative BC data sets, respectively. The sensitivity of the Shapiro score for a positive BC was 69% and the specificity was 72%. Despite these relatively low values a

positive Shapiro score was found to have a significant association with positive BCs (Wald chi-square=28.76, *p*=0.01), with an adjusted odds ratio = 5.6 for positive BCs.

A positive SIRS (two or more positive criteria) was also shown to be a predictor for a positive BC (Wald chi-square=7.21, *p*=0.01) with an adjusted odds ratio = 2.3 that a non-negative SIRS will yield a positive BC. Additionally, the SIRS criteria had a sensitivity of 73% and a specificity of 46% in predicting a positive BC. Table 2 highlights the association of each of the clinical parameters to positive BCs.

Table 2: Shapiro Score parameters and mean clinical parameters and their association with positive and negative BCs (n=190).

Shapiro Score Parameters	**BC Positive**	**BC Negative**	**P Value.**
Chills	55%	41%	0.04
Endocarditis	1%	0%	0.28
Vomiting	29%	22%	0.31
Temperature > 38.3˚C	10%	6%	0.36
Systolic BP < 90mmHg	8%	6%	0.54
WCC > 18 (x10^9/L)	24%	6%	0.01
Platelet count < 150 (x10^9/L)	20%	11%	0.09
Creatinine > 177µmol/L	33%	6%	0.01
Clinical and Laboratory parameters	**BC Positive Mean (SD)**	**BC Negative Mean (SD)**	**P Value**
Temperature (˚C)	36.9 (0.84)	36.8 (0.84)	0.28
Pulse (bpm)	114.9 (26.3)	105.9 (23.4)	0.01
Systolic BP (mmHg)	119.7 (21.81)	120.2 (24)	0.88
Diastolic BP (mmHg)	74.5 (16)	75.8 (18)	0.63
Glasgow Coma Scale (GCS)	14.4 (1.5)	14.9 (0)	0.01
Respiratory Rate (bpm)	22.4 (6.9)	20.7 (5)	0.06
WCC (x10^9/L)	13.8 (8.26)	9.5 (5)	0.01
Platelets (x10^9/L)	266.7 (169)	287.8 (140.8)	0.36
Urea (mmol/L)	11.9 (9.92)	6.7 (5.8)	0.01
Creatinine (µmol/L)	178.5 (167)	98.8 (111)	0.01
CRP (mg/L)	216.8 (95.8)	100 (83.5)	0.01
HIV Positive	70%	44%	0.01
SIRS Criteria*	**BC Positive (%)**	**BC Negative (%)**	**P Value.**
Positive SIRS	65 (71)	54 (54)	0.025
Negative SIRS	27 (29)	46 (46)	

*SIRS Criteria: Temperature ≥ 38˚C or <36˚C, Pulse >90bpm, Respiratory Rate >20bpm, White cell count >12x10^9/L or <4 x10^9/L; At least two criteria needed for a positive SIRS

There were a number of factors which were significantly increased in those with positive BCs compared to negative BCs: presence of chills, positive HIV status, and

increased WCC, pulse rate, CRP, creatinine and urea levels. Patients with a positive BC also had a significantly lower Glasgow Coma scale.

Discussion

Less than 18% of all BCs were positive and almost half of those had cultured contaminant organisms. The suspected source of sepsis was most commonly the respiratory system and HIV positive patients were significantly more likely to have a positive BC. *S. Pneumoniae* was the most common organism cultured followed by E. Coli, with resistance rates to co-amoxiclav of 5.6% and 20.4% respectively. There are unacceptably high rates of contaminated BCs sent from this ED. A positive Shapiro score as well as positive SIRS were significantly predictive of positive BCs.

In this ED, a positive HIV status is a risk factor for blood stream infection with a high risk of a positive BC. The HIV population are at particular risk for developing bacteraemia and with such a high prevalence of HIV in sub-Saharan Africa, this may suggest that knowledge of a positive HIV status with signs of infection should influence the decision to perform a BC on this population [21].

Of the organisms which were cultured in the ED, *S. Pneumonia*, *S. Aureus* and *E. Coli* accounted for 49.5% of all pathogens (true positive BCs). This is in contrast with another ED in Cape Town, South Africa where *E. Coli*, *K. Pneumoniae* and *S. Pneumoniae* were the top three organisms cultured [17]. This previous study was conducted in 2015 and our results highlight the importance of regular institutional BC audits for the development of microbiograms to find the most probable causative organisms, as prevalence of these organisms may vary between demographic areas and over time and will influence the choice of empiric antibiotics [19].

In this study, a large proportion of patients had suspected respiratory system involvement. As *S. Pneumoniae* is the most common causative pathogen of pneumonias worldwide [23], our study, as expected, revealed that *S. Pneumonia was* cultured in 61% of all positive BCs where the respiratory organ system was suspected to be infected. With *S. Pneumoniae* in our setting being mostly (94.4%) sensitive to co-amoxiclav, which would be the first choice for empirical therapy, the value of BCs for uncomplicated CAP remains questionable. This study, however, was not powered to review if the BC result would alter the management in these patients.

The true positive rate of BCs in this study (9.9%) falls in line with the 8-14% highlighted by previous studies [12], however the high rates of contamination are a concern. Ideally false positive rates should be 2-3% of all BCs taken if performed in the correct sterile manner [7]. This study had contamination rates at 7.9%, with Coagulase Negative *Staphylococcus* being the primary culprit in over 75% of cases. This contrasts with another study in a South African ED which showed a contamination rate of only 2.6% [17]. Poor technique in busy and overcrowded EDs is likely to be a significant contributing factor [24]. Only one physician achieved a success rate of 94% for true positive vs likely contaminant BCs. This highlights the need for review with quality improvement and education in the performance of BCs in the ED. Some techniques to improve the quality of the BCs include the use of dedicated phlebotomists defining a standardized yet simple technique of taking a BC, and instituting quality assurance measures to reduce these high contamination rates [7,25].

The *S. Marcescens* series of BC results pose a diagnostic challenge. Although *S. Marcescens* can be a rare opportunistic infection with a prevalence of only 1-2% of nosocomial infections, the organism is known to colonize damp wet areas such as hospitals and bathrooms [26]. This study showed a growth rate of *S. Marcescens* of 10.5% of the true positive BCs. The majority (93%) of the BCs cultured more than one organism which is a feature suggestive of contaminated BCs [20]. Many of these other organisms such as *Enterococcus spp.* and *P. Aeruginosa* can also colonize hospitals [27,28]. The rather peculiar pattern of *S. Marcescens* growth only for certain doctors raises suspicion of not only persistently poor technique in taking of the BCs but also possible colonization of these organisms within certain areas in the ED. Often these organisms become very resistant to antibiotics when colonizing hospitals [29] and if these cultures were treated, 80% of them would require an escalation of antibiotics as most of the *S. Marcescens* organisms as well as several of the *P. Aeruginosa* and *K. Pneumoniae* organisms which were co-cultured with S. Marcescens were resistant to co-amoxiclav. If the *S. Marcescens* cultures are to be considered contaminated specimens, the rate of contamination would increase to 49.9% of the positive BCs or 8.9% of all BCs taken which is excessive.

The Shapiro score may be useful in predicting bacteraemia. The sensitivity of the Shapiro score in this study (69%) was not as good as the original derivation (98%) or

validation studies (97%) [13,16]. This may be due to the lack of data on percentage bands (a bio-marker suggestive of infection) in this study as a full blood count differential was not a routine test performed in this ED. Additionally the Shapiro score was derived and validated in a first world setting. Despite this, the results of this study suggest that the Shapiro Score may have some value in predicting bacteraemia. A simpler (and more practical) prediction tool may be the SIRS criteria, which in defining sepsis has been replaced in the Sepsis-3 guidelines [1], but is still accepted in low to middle income countries with limited resources as a predictive tool for sepsis and septicaemia [22].

The difference in CRP levels in this study was statistically significant with mean levels in the negative and positive BC group 100mg/L and 218.6mg/L (p=0.01) respectively. However, CRP has previously been stated as being of little value in predicting bacteraemia as defining an absolute cut-off value has yet to be established with highly variable levels between patient populations, different sources of infection and co-morbid states [30]. Furthermore, CRP peaks 2 to 4 days after onset of infection or inflammation, so in isolation is of limited use in the ED [30]. The best utilization of CRP in predicting bacteraemia may be its use in conjunction with other parameters.

Perhaps deriving some of the components of the Shapiro score and/or SIRS criteria to devise a clinical score to predict bacteraemia in our setting may be of some use. Of the clinical parameters to consider, renal function, WCC, CRP, pulse rate, GCS, HIV status and the presence of chills/rigors seemed to be of most value. Difficulties with blood tests may arise however, with slow laboratory turnaround time and lack of point of care testing in many EDs. Clinical evaluation may be the best and most practical way of determining who to perform a BC on. A previous study on the indications for BCs recommended that, in low to middle income countries, using a raised temperature of >38˚C (or hypothermia) with either the qSOFA (quick Sequential Organ Failure Assessment as defined in Sepsis-3) criteria or suspicion of severe infection may be better but this was subject to the authors' clinical experience [22]. The qSOFA score uses a systolic BP of <100mmHg, a respiratory rate > 22 bpm and decreased GCS to predict patients with suspected sepsis. However, in this study, of these suggested parameters only a decreased GCS was found to be predictive of positive BC. We would recommend adding the presence of chills/rigors, HIV status and high pulse rate as additional criteria to be used in resource limited settings.

This retrospective analysis of BCs performed in the ED further highlights some of the concerns surrounding them as a diagnostic tool. Although BCs may be valuable in identifying the causative organism in bacteraemia and guiding antibiotic therapy, this study found that the contamination rates were almost as high as the true positive BC rates. This may imply that a large population of our patients in the ED are at risk of an unnecessary escalation of antibiotics based on a (often) poorly performed test. By reducing the number of negative results by more astute patient selection and reducing the number of contaminated specimens by improving the technique of taking BCs, perhaps we could improve the utility of the BCs as a decision-making tool. The use of predictive scores such as the Shapiro or SIRS criteria would significantly improve the true positive BC rate.

Limitations

There are several limitations. The study was limited to one institution. One of the components of the Shapiro score, Percentage bands (a marker of immature white blood cells within a blood count differential), was not routinely tested at this ED and therefore this parameter was excluded from the data. For the purpose of identifying true clinical characteristics of patients likely to have bacteraemia, only true pathogens were used in the positive sample group. Labelling of certain bacteria as contaminants may be deemed presumptuous as even CNS may cause pathology in rare cases. The sample size is small, and a larger prospective trial may better identify the usefulness of these prediction scores. The taking of BCs in this study was not standardized and subject to the clinician treating the patient.

Conclusion

Blood cultures are diagnostic tools which should not be performed without first considering pre-test probability, the possibility of a positive result changing the clinical course and measures which should be taken to prevent specimen contamination. If empirical antibiotic therapy is to be used routinely it is also important to repeat blood culture audits regularly to determine if pathogens and their sensitivity to antibiotics have changed.

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Chapter 2: Protocol

An Audit of Blood Cultures Performed in an Emergency Department at a Johannesburg Academic Hospital

Dr Bradley Rae

Student Number: 0701910X

Protocol for:

Masters of Medicine

Emergency Medicine

Supervisors

Dr Radha Gihwala

Dr Alison Bentley

Expanded Literature Review

Blood cultures (BCs) are performed regularly in Emergency Department (EDs) in patients with presumed infection. They are used to detect the presence of bacteraemia in patients with signs and symptoms of an infection. These signs and symptoms include, but are not limited to: fever, rigors, tachycardia, hypotension and raised white cell count[1]. Infection may also affect a particular organ system producing more specific symptoms such as cough, diarrhoea or dysuria[2]. The aim of BCs are to identify the causative organism with a view to select the most appropriate antibiotic to treat the infection.

The decision on whom to perform a BC may vary between institutions based on local resource availability, local guidelines, and the experience of the treating physician. Recommendations include any patient with fever, history of fever or hypothermia together with any one of; hypotension, confusion, increased respiratory rate or suspicion of severe localized or systemic infection. More specifically BCs are indicated in any patient with suspected bloodstream infection[3].

Some policies, however, have recommended far more liberal use of BCs. One such policy is based on the Joint Commission and the Centres for Medicare and Medicaid Services guidelines which address the treatment of community acquired pneumonia (CAP). The guidelines include several measures to address the quality of care of patients with CAP and one of these measures includes the routine use of BCs in all patients before the commencement of antibiotics[4]. This policy has been implicated in the increased use of BCs for patients with CAP from 29.4% of patients in 2002 to 51.1% of patients in 2010[5]. Currently, in South Africa, indications for BCs include all patients with clinical features of sepsis, suspicion of infective endocarditis, pyrexia of

unknown origin, unexplained leucocytosis or leukopenia or any suspected systemic or localised bacterial or fungal infection[2]. Thus, there can be confusion for doctors due to inconsistent guidelines.

BCs will either yield a positive or negative (no growth) result. Positive BCs can be further subdivided into true-positive in which the cultured organism is a blood-borne pathogen or false-positive where the cultured organism is a contaminant or a non-pathogen[6]. The decision to differentiate contamination from true bacteraemia is multifactorial. These factors include identity of the organism cultured, number of positive BC sets, time to growth, quantity of growth, clinical and laboratory data and source of infection[7]. Organisms cultured which are most commonly classified as contaminants are *Coagulase-Negative Staphylococcus* species, *Corynebacterium* species and *Alpha*- or *Gamma-haemolytic Staphylococcus* species to name a few[8].

True positive BC results should represent at least 8-14% of total BCs collected if there is correct clinical evaluation and if the correct technique for BC sampling is employed [9]. Furthermore, false positive results should represent 2-3% of all BCs if performed in the correct sterile manner[10].

An important factor in achieving high rates of true positive BCs is adopting the correct technique. Guidelines on the optimal technique of taking BCs include collecting the blood in a sterile manner and taking 2 to 3 sets (a set contains one aerobic and one anaerobic bottle) of BCs with 10 to 20mls of blood in each BC bottle. This increases the sensitivity of the BCs as well as decreases the time to identification of the responsible organism. Ideally different puncture sites should be used for each set of BCs as this increases their specificity[2]. Ideally the BCs should be taken before the

administration of antibiotics as antibiotics have been shown to reduce the yield of BCs by up to 50%[11]. Thus, timing and technique are crucial in taking a BC.

Management decisions are often dependant on the BC results which aim to guide antibiotic therapy[9]. Often patients are initiated on a broad-spectrum antibiotic based on local microbial sensitivities and the choice of antibiotic is narrowed subsequently based on the sensitivity of the cultured organism[12]. BCs which are positive in certain patient populations may have a major impact on the patient's clinical outcome. Patients with a true positive BC result are 12 times more likely to die during hospitalization[6]. Thus, BCs may also be helpful for prognostication.

Controversies

The majority of BCs are often done in under-resourced and over-crowded environments which may lead to increased contamination rates. ED overcrowding is associated with a negative impact on clinical care and also associated with increased rates of BC contamination[13]. Hence, BCs taken in South African EDs, often prone to overcrowding or a high workload may be inadequately performed and at a higher risk of yielding contaminated results[14,15]. As a result, these patients are at risk of being subjected to further invasive and non-invasive investigations, unnecessary hospital admissions and an increase in the average length of hospital stay[7]. This is because often the BCs or other tests may need to be repeated to ensure that the organism is in fact a contaminant to obtain diagnostic certainty.

Coagulase Negative Staphylococcus, the most common contaminant in BCs which is a usual skin commensal, can also cause bacteraemia in rare causes but usually in patients with infective carditis or in patients with large indwelling intravascular catheters[6].

Both the patient and the hospital incur the unnecessary costs of over-investigation[8]. Currently at the National Health Laboratory Service (NHLS), a public health laboratory service in South Africa, the cost of a single BC with no growth is R48.16. However, should an organism be cultured, true pathogen or contaminant, to determine the microbial sensitivity the cost escalates to R310.69. Thus, a large cost may be incurred by the hospital for exceptionally low yield benefit.

Furthermore, BCs may be performed on the wrong patient population. Young patients presenting to the ED with CAP may have a prevalence of bacteraemia of as low as 0.11% resulting in over 900 BCs needed before a single positive BC result is achieved[16]. Similarly, patients with localized cellulitis also have very low pre-test probability for bacteraemia (2%) making the utility of BCs somewhat questionable[17]. Conversely, diabetic patients or patients with a suspected biliary tract infection may be at 3 and 8 times higher risk for bacteraemia respectively[12]. And patients with HIV infection are also at an increased risk of bacteraemia depending on their degree of immunosuppression[18]. Therefore, careful patient selection may increase pre-test probability of a positive BC result.

Often, patient outcomes may not be influenced in the ED setting based on the BC result. This is because BCs in our setting take hours to days to yield a positive identification of organism. Also, sometimes fewer than 2% of BC results will cause a change in the management of ED patients[19]. Without compromising patient care, immunocompetent patients with common illnesses such as urinary tract infections, cellulitis and CAP may not require a BC[20]. Additionally, causative organisms from more localised infections can be better identified using more direct culture mediums. For example a urine culture will be more sensitive in culturing the causative organism

in urinary tract infections or pyelonephritis, a pus culture will be more useful in abscesses and induced sputum in CAP[20].

Ultimately, the performance and interpretation of BCs falls to the treating clinician. And with such variations in indications for BCs, there seems to be some discrepancy in whom a BC should be taken. Additionally, the signs of infection listed above may not be present or may be present in varying combinations, making the decision to perform a BC somewhat challenging. Furthermore, the interpretation of results may also be challenging, especially in the case of an organism being cultured which was not expected or does not typically cause the source of infection. Since the decision to conclude a BC result as false positive is so multifactorial, escalation or de-escalation of antibiotics based on these uncertain results may have negative consequences which could involve either the worsening of the patients' condition or poor antibiotic stewardship.

Prediction Models

There are prediction models which assist in improving the likelihood of yielding a positive BC in these patients. One such model which is of use in EDs is the score developed by Shapiro et al. The Shapiro score, which has a sensitivity of 98% in its validation studies, uses various demographic, clinical and laboratory parameters to identify which patients should have a BC taken[1].(Appendix A) The Shapiro score has been used in conjunction with other clinical parameters such as procalcitonin, a biomarker suggesting bacterial infection, to further elevate its usefulness. A positive Shapiro score as assessed as greater than three positive points together with a PCT >0.25µg/L would decrease the number of negative results by 41.7% and still identify 96.1% of positive BCs[21].

Another score which screens for severe sepsis in the ED (as well as having prognostication value) is the quick Sepsis Related Organ-dysfunction Score (qSOFA). The qSOFA looks at altered mental status, respiratory rate greater than 22 breaths/min and a systolic blood pressure less than 100mmHg to quickly screen for patients who are likely to have poorer outcomes in sepsis. The qSOFA was coined in the Sepsis-3 guidelines, and has been considered to provide greater prognostic predictive validity than the older Systemic Inflammatory Response Syndrome (SIRS) criteria used in the past[22]. The SIRS criteria (Appendix B) however, may be more useful in screening for those patients who may benefit from a BC as it is more specific than qSOFA [3,23]. Use of these scores may help reduce the high number of false positive results, prevent unnecessary costs in investigating patients not at risk of bacteraemia, and may help BCs become better diagnostic tools. However, many of these prediction models have not been well validated in low to middle income countries[3].

Blood Culture Audits

BC audits are important in creating local guidelines for appropriate empiric antibiotics. They also identify outbreaks of nosocomial infections, patterns of resistance and rates of contamination. Common positive bacterial isolates often differ between areas. Common bacterial isolates from BCs in an audit from over 200 hospitals in the United States of America included, *Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella pneumonia* and *Enterococcus faecium*[24]. Whereas in Nigeria, at a single hospital. the most commonly isolated organisms from an audit at a single tertiary hospital were *Salmonella enterica*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Escherichia coli* and *Mycobacterium tuberculosis*[25]. *Escherichia coli*, *Klebsiella Pneumoniae* and *Streptococcus Pneumoniae* were the

most common bacterial isolates identified in a BC study conducted in an ED in Cape Town[12].

BC audits are also useful to identify pitfalls in the performance of taking BCs. Contamination rates in African settings have been reported to be as high as 10.4%[26]. Rationale for these high rates of contamination are under-resourced settings and taking BCs in a non-sterile manner as many of these contaminant organisms are usual skin commensals. After the performance of BC audits, quality assurance measures can be implemented to ensure that these contamination rates decrease. Some of these measures which may decrease BC contamination rates in the ED include improving available equipment, educating staff or personnel who perform BCs on the correct technique, developing simplified standardized techniques on performing BCs or hiring dedicated phlebotomists to take the BCs. All these measures have been shown to reduce contaminated results, reduce hospitals costs and hospital length of stay[8,27-29].

Along with skin commensals, BCs may also be contaminated with hospital commensals. BCs which yield either multiple organisms or organisms not consistent with the patient's presenting source of infection are a major diagnostic dilemma. Organisms such as *Pseudomonas Aeruginosa*, *Enterococcus Faecalis, Serratia Marcescens, Klebsiella Pneumonia* may cause severe sepsis and septic shock in hospitalized patients and may result in high rates of mortality, making the decision to discard suspicious BCs with these organisms as false positive highly controversial[9]. The only clues that these BCs may in fact be false positive is that these organisms rarely cause community acquired infections, the patient is clinically too well to be suffering bacteraemia from that particular organism (warranting the question why the BC was performed in the first place), and finally that the BC yields several of these

organisms, as this also supports contamination of the specimen over true pathogens. These scenarios are challenging and will inevitably result in escalation of antibiotics, further blood tests and increased length of hospital stay[7].

Conclusion

With such controversy surrounding indications for BCs as well as the clinical impact in the ED, and taking into consideration our resource-stretched and overcrowded environments, further research is needed into establishing improved local guidelines to facilitate the decision of when to perform BCs on patients in South African EDs, as well as which patients will most benefit from a positive BC result.

Study Aims and Objectives

The aim of this study is to understand the blood culture environment of the ED at Helen Joseph hospital and better identify the patients presenting to the ED who will benefit from BCs by use of the triage vital signs, patient presentation, blood results and demographics. The Shapiro score and SIRS Criteria will be used to predict the likelihood of positive BC in the context of South African Emergency Departments. Secondary aims will be to identify which organisms are cultured in BC performed at the Helen Joseph ED, their frequency and sensitivity to the commonly used broad-spectrum antibiotics such Co-Amoxiclav (Augmentin®) and Ceftriaxone (Rocephin®).

Primary objectives

1. To describe the demographic and clinical characteristics of patients who had BC drawn on presentation to the Emergency department.
2. To compare demographic and clinical characteristics between those patients with positive versus those with negative BC results

3. To compare the validity of scoring systems suggesting bacteraemia such as the Shapiro score and qSOFA with rate of positive BC

Refer appendix C for data collection sheet

Secondary objectives

1. To describe the organism profile of the blood cultures performed in the ED
2. To describe the antibiotic sensitivity rate of Co-Amoxiclav and Ceftriaxone to the organisms cultured in the ED.

Methodology

Study design

This is a retrospective, observational, cross-sectional descriptive and comparative study.

Study Site and Population

Helen Joseph Hospital (HJH) ED is part of a tertiary level academic institution that provides services to approximately 60 000 people annually. Sixty to seventy percent of patients are medical and the vast majority are adults, owing to a mother and child hospital nearby.

An application will be made to the NHLS Data Warehouse for a collated spreadsheet of all consecutive patients that had BCs drawn on presentation at the HJH ED during the period 1 January 2017 to 31 Dec 2017 which will be included in the study. The anticipated number of patients to be included within this timeframe is roughly 800 - 1000. The period of the study may need to be increased if the sample size of positive BC does not reach 100.

Paediatric patients (age < 14) will be excluded from the study.

Data Collection

A list of all BCs which were performed in the HJH ED during the study period will be obtained from the NHLS Data Warehouse.

A summary of all positive BCs will be made followed by sorting the positive BCs into true positive and suspected contamination by means of the type of organisms cultured. Contaminated results will be excluded from the data set to validate the Shapiro score and SIRS criteria.

A list of approximately 300 to 400 patients who had true positive BC results will then be submitted to records to obtain the patient data required. The first 100 (minimum) patients to have the full data set needed to obtain the Shapiro score and SIRS criteria will then be used. As it is expected that there will be more negative than positive BC results another random list (e.g. every 5^{th} result) comprising of 300 to 400 negative BC results will be made, and the first 100 (minimum) patient files with the complete set of data to calculate the Shapiro score and SIRS criteria will also be obtained.

All data needed from the files will be collected on a data collection sheet (Appendix C). The data needed will be that to assess the validity of the Shapiro and SIRS criteria and to compare both of those scores with the BC positivity rate.

All data will be captured directly into Microsoft Excel. Anonymity will be maintained through a separate list of patient details and blood culture numbers which will be allocated a unique study number and will be kept securely on a password-protected computer.

Ethics

Ethics clearance will be obtained from the Human Research Ethics Committee of the Faculty of Health Sciences of the University of Witwatersrand. Permission to conduct research will be obtained from the Chief Executive Officer (CEO) at HJH and the NHLS.

Statistical analysis

The data captured onto the Excel spreadsheet will then be further analysed. Positive or negative Shapiro and SIRS criteria for each patient will be determined according to criteria.

Frequency (percentage) will be calculated for the entire data set as well as for the groups of true positive, false positive and negative BC results for comparison. The descriptive analysis will also make use means/medians with SD or ranges as appropriate for normally distributed and skewed numerical data. The Chi-squared test and Fisher's exact test will be used to assess the relationships between categorical variables of the Shapiro score between positive and negative BC. Sensitivity and specificity of the blood cultures versus the scores will be done using Chi squared tests. A similar process using Chi squares will be done for categorical variables.

Association of variables including those included in the Shapiro score to BC positivity and negativity will be calculated. Validation of the Shapiro score and association of the SIRS criteria to BC positivity will be determined.

Problems / Biases / Limitations

Anticipated problems include failure to trace the patient files needed from records. The ED is generally busy by nature and the condition of the patient at the time of arrival

may have prevented complete recording of all required and relevant data. This may make the decision to label a BC result as a false positive challenging. Tracing other blood results may prove challenging if only a BC was performed without other blood tests.

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Appendix A – Shapiro score

Major Criteria

- Suspected endocarditis
- Temperature > 39.4˚C
- Indwelling vascular catheter

Minor Criteria

- Age > 65
- Temperature 38.3˚C – 39.4˚C
- Presence of chills
- Presence of vomiting
- Systolic BP < 90mmHg
- White cell count > 18 cellsx10^9/L
- Platelets < 150 cellsx10^9/L
- Creatinine > 177µmol/L

Positive Score if one major or two minor criteria present.

Appendix B: SIRS criteria

Criteria

- Temperature ≥ 38˚C or <36˚C
- Heart rate >90/min
- Respirations >20/min or PaCO2 <32mmHg
- White blood cell count >12x10^9/L or <4 x10^9/L

At least two criteria needed for a positive SIRS

Appendix C: Data Collection Sheet:

DATA FIELD	INFORMATION
Study Number	
Date of admission	
Patient Characteristics:	
Age / Gender	years ☐ M ☐ F
Previous Medical History	☐ HIV ☐ DM ☐ OTHER:_____
Suspected organ system involved	☐ Resp ☐ Urinary ☐ Skin/Soft Tiss. GIT ☐ ☐ Gynae ☐ CNS ☐ Other Unknown ☐ Detail of other: ……
Indwelling vascular catheters	☐ Renal line/ Shunt ☐ Central line ☐ None
Suspicion of endocarditis	☐ Yes ☐ No
Vomiting	☐ Yes ☐ No
Chills / Rigors	☐ Yes ☐ No

Vitals:			
Pulse rate	bpm	Blood pressure	/ mmHg
Temperature	°C	GCS	/15
Respiratory rate	bpm		

Blood culture			
Result	☐ Positive ☐ False Positive ☐ Negative	Organisms:	Sensitivity: ☐ Co-amoxiclav ☐ Cephtriaxone

Other blood results	
FBC	WCC: Plts: Neutrophil%: Bands:
U&E	Urea: Creatinine:
CRP	

Complications/Other information:

Appendix D: Ethics approval

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr Bradley Rae

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180265

NAME: (Principal Investigator)	Dr Bradley Rae
DEPARTMENT:	Emergency Medicine Helen Joseph Hospital
PROJECT TITLE:	An audit of blood cultures performed in an emergency deparment at a Johannesburg academic hospital
DATE CONSIDERED:	23/02/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Radha Gihwala and Dr Alison Bentley
APPROVED BY:	Prof C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	14/05/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193 University of the Witwatersrand. 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 resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in April and will therefore be due in the month of April each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 19/05/2018

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

DECLARATION:

Adherence to HREC (Medical) Ethics Application Terms and Conditions

I, the undersigned, hereby declare that I have not collected data/ done secondary data analysis or any other form of research, prior to obtaining clearance certificate from the HREC (Medical) for study no: M180265.

I have read and understood the terms and conditions on page 8-9 of the HREC (Medical) application form. I confirm that it is my responsibility to ensure that I have received final HREC (Medical) Clearance before commencing any research.

Bradley Rae

Name, Surname and Signature

Student/Staff no if applicable: 0701910X

Date: 15/07/2020

Radha Gihwala

Name, Surname and Signature

Supervisor (if applicable)

Date: 15/07/2020

Chapter 3: Turn-it-in report

Turnitin Originality Report

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An Audit of Blood Cultures Performed in an Emergency Department at a Johannesburg Academic Hospital

Chapter 4: Author guidelines for the journal: Cureus

Submitting an Article

Authors must complete the following steps in order to submit an article draft for peer review. Authors may save and exit the submission process at any time by clicking “Exit” in the top right corner of the page.

Important: Cureus operates a merit-based publication system, in which we publish all articles that satisfy Cureus editorial requirements and contain no fraudulent or dangerous science. It is the submitting author’s responsibility to meet us halfway by submitting an article draft that meets all listed editorial requirements.

1. Getting Started

Are you submitting on behalf of a channel? Are you entering a competition? Designate your article as a channel and/or competition article here, then choose the article type (original, review, case report, technical report, editorial). It’s important to make sure this information is correct as it cannot be changed after moving on to the Title, etc. section.

2. Title, etc.

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Enter the article title in Title Case. Do not enter the title in all caps. Beginning with this step, you may preview your draft at any time to see how the published version will be displayed.
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Enter your article abstract. Abstracts are limited to 3,500 characters. Subheaders are permitted in original article abstracts only.

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Select up to three article categories. (You must select at least one.)

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Add at least one and up to ten keyword to your article. Keywords will allow your article to be more easily searchable when published.

3. Authors

Add any additional co-authors (including email addresses and complete affiliation including location). Review articles, case reports, technical reports and editorials may feature a maximum of five authors. (Original articles do not have an author limit.) Each

additional entry must include an email address and affiliation with location included. Medical students should list the article category as their department (e.g. neurosurgery, family medicine, etc.). When adding authors who already have confirmed Cureus accounts, no author information may be entered or changed, however, each co-author must update his/her profile to ensure a complete name and affiliation is listed.

There is only one primary (first) author. The submitting author is listed as the primary author by default; this can be changed by dragging and dropping the authors into the desired order.

4. Disclosures

Please provide all relevant information pertaining to any human or animal subjects and disclose any relevant conflicts of interest (COI). You may also add acknowledgements at this time.

In the event that human or animal subjects are included in the article, please provide the relevant IRB names and approval numbers and confirm that informed consent was obtained or waived.

The submitting author is responsible for including all co-author COI and disclosure information. Are you unsure about potential conflicts of interest among your co-authors? You can send an email request for this information directly to your co-authors from inside the submission process.

Conflicts of interest may involve 3rd party payment or service for any aspect of the submitted work, relevant financial activities outside the submitted work, patents that could be considered broadly relevant to the work and any relationships not covered previously.

Based on the provided information and disclosures, Cureus will automatically generate an Ethics Statement and Conflict of Interest Disclosures to be included alongside the published article. Please see the Publication Ethics and Conflicts of Interest sections of the Author Guide to view a detailed breakdown of required statements and disclosures.

5. Article

Enter the main article content here. Article sections will vary depending on the article type selected earlier in the submission process. We do not recommend composing your article directly in the text field. Instead, compose your article in the word processor of your choice and then copy and paste your article text into the appropriate section. Please do not include section names (e.g. Introduction, Materials & Methods, Results, etc.) as these are added automatically.

All articles must adhere to Cureus formatting styles - no paragraph indentations, only one line return after each paragraph and only one space between sentences. Please remove any text styling before copying and pasting your text into the appropriate field.

Numbers 1-9 should be spelled out except in cases of measurement. (e.g. 7 mm) Numbers higher than nine should be entered numerically. (10, 100, 463, 1,932, etc.)

Citations: References should be cited using square brackets. These must be placed at the end of the sentence before the period. For example: This is an example sentence [1]. If multiple references are cited in one sentence, please list them as follows: [1-4], [1,3], [5,9-12], etc. Footnotes are not permitted. Citations are not permitted in figure, table, video or interactive model titles. They should instead be included in the media legend or table cells.

Media: Media is not permitted in the abstract, introduction or conclusions section of any article type. The only exception is the introduction section of a review article. Each article is permitted up to 25 media items.

To add media to your article first place your cursor in the desired location in the article section text field and click one of the Insert Figure, Table, Video or Interactive Model buttons on the article section toolbar. You will then be prompted to upload the figure, paste or create the table or paste the video or interactive model URL and add a title and optional legend.

Please visit our Media Guide for detailed instructions on adding each media type as well as examples of unacceptable media.

Subheaders: Cureus allows for three levels of subheaders. Both types of subheaders should be followed by a line return before the next paragraph begins.

Major subheaders should be formatted using the subheader style found in the “Styles” dropdown menu. Major subheaders should be in sentence case, i.e. the first word should be capitalized and all other words should be in lowercase, except proper nouns and acronyms/initialisms (such as GBM, SRS, etc.).

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6. References

Creating references is simple with our automated converting tool. Simply copy and paste your reference list from a text document and select “Convert references.” We’ll do our best to detect each reference type based on its formatting.

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For more detailed instructions, please view the References section.

References

Reference Limits

The maximum allowed number of references varies by article type:

- Review articles: 50 references
- Original articles: 30 references
- Technical reports: 20 references
- Case reports: 20 references
- Editorials: 5 references

Adding DOIs

The DOI (digital object identifier) is a string of numbers that uniquely identifies a published article. The DOI is permanently assigned to an article and provides a persistent link to current information about that article, including location. This enables readers to find the online article irrespective of any subsequent changes in the web site structure, in the management responsibility of the journal in which it was first published, or the location of the website on which the journal is hosted.

Cureus requires DOI numbers, when available, to be included in all references. If a DOI was not assigned, then try to find a link to the published paper and add the URL to the corresponding field in the reference

If you have a PubMed ID, but no DOI, you can try searching for the DOI using this tool.

Citing Unpublished Material

Material that has not yet been accepted for publication should be noted as “unpublished data” and should not be included in the reference list. The reference list should only include publications cited within the article text.

All material included in the reference list must have been previously published in citable journals or books. If you wish to reference material that does not meet this specification, such as an abstract without DOI, poster, unpublished data or personal communication, please include the citation within the text of your article.

To cite an abstract without DOI, poster or other unpublished material in the body of your article, please use the following format: (Type of unpublished material: Author names. Title in Title Case. Meeting Title (if applicable); Date). If needed, repeated subsequent citations for the same item should be shortened to include first author name and date as follows: (Type of unpublished material: First author name, date).

Citing References

References should be cited using square brackets. These should be placed at the end of the sentence before the period. For example: This is an example sentence [1]. If multiple references are cited in one sentence, please list them as follows: [1-4], [1,3], [5,9-12], etc. Footnotes are not permitted.

Please number references in the order in which they are mentioned in the text; they should not be alphabetized. All co-authors must be cited when creating a reference. If more than seven authors, insert “et al.” after the first three authors. Author names should be formatted as seen in the examples below.

Additional Requirements

Journal names should be abbreviated according to the Index Medicus system. For more information, please refer to the International Committee of Medical Journal Editors: Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals.

Please adhere to the following requirements for each reference type. Submissions that do not follow these requirements will not be published. Please pay particular attention to the following:

- All references must return a positive result when clicked.
- Do not reference a website that no longer exists. (Defunct journals may still be referenced.)
- When referencing a book (chapter or whole), editors (if available), publisher and publisher location must be listed.
- When referencing a journal article, only the first letter of the first word should be capitalized. (Note: Book titles should be listed in title case, i.e. the first letter of each word is capitalized.)
- Website references must include an access date and the name of the citation (i.e. not just the URL).
- List only the volume number of the journal. Issue and supplement numbers are not needed. If referencing a book chapter, please include the edition and volume numbers.
- Please list the page numbers of the cited chapter or article.
- The DOI number should be added to the end of the reference, if available. The “DOI” abbreviation should not be included.

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Electronic journal articles:

Huynen MMTE, Martens P, Hilderlink HBM: The health impacts of globalization: a conceptual framework. Global Health. 2005, 1:14-16. Accessed: January 25, 2012. http://www.globalizationandhealth.com/content/1/1/14.

Article within a journal

Koonin EV, Altschul SF, Bork P: BRCA1 protein products: functional motifs. Nat Genet. 1996, 13:266-267.

Website

New child vaccine gets funding boost. (2001). Accessed: March 21, 2001: http://news.ninemsn.com.au/health/story_13178.asp

Book chapter, or article within a book

Schnepf E: From prey via endosymbiont to plastids: comparative studies in dinoflagellates. In Origins of Plastids. Lewin RA (ed): Chapman and Hall, New York; 1993. 2:53-76.

Whole issue of journal

Ponder B, Johnston S, Chodosh L (Eds): Innovative oncology. In Breast Cancer Res 1998, 10:1-72.

Complete book

Margulis L: Origin of Eukaryotic Cells. Yale University Press, New Haven; 1970.

Book with institutional author

Advisory Committee on Genetic Modification: Annual Report. London; 1999.

End