An 8-year retrospective review of pyogenic liver abscesses at Groote Schuur Hospital, Cape Town, South Africa

Dr Nieleshen Govender

GVNNIE001

THESIS SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

In fulfilment of the requirements for the degree:

Masters in Medicine (MMed) in Surgery

Department of Surgery

Faculty of Health Sciences

University of Cape Town

Supervisor: Professor JC Kloppers

Department of Surgery, Faculty of Health Science, University of Cape Town

Date of submission: 15 August 2022

Table of Contents

Declaration

I, **NIELESHEN GOVENDER** hereby declare that the work on which this dissertation/thesis is based, is my original work (except where acknowledgements indicate otherwise). This thesis/dissertation has been submitted to the Turnitin module and I confirm that my supervisor has seen my report and any concerns revealed by such have been resolved with my supervisor.

Neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: …Signed by candidate…

Date: 04/08/2022 ……..……

Acknowledgement and Contributions

I would like to thank the following people for their instrumental help, support and guidance:

Prof. JC Kloppers[1], my supervisor, for his vision and vigor as a leader.

Prof. E Jonas[1], for inspiring and editing this dissertation.

Prof. Dlamini[3], for his guidance in infectious diseases and microbiology.

Prof. JEJ Krige[1], for establishing the registry.

Dr O Chihaka[1], for collection of data and building a registry.

Dr L Raphael[1], for data collection.

Dr KJ Gqada[1], for data collection.

Dr K Naicker[2], my wife, for everything, including but not limited to editing, data collection, statistical analysis, quality assurance and her unwavering support.

To my family and friends, I stand on the shoulders of giants.

Affiliations:

University of Cape Town Health Sciences Faculty and Groote Schuur Hospital, Anzio Road, Observatory, Cape Town, South Africa.

- [1] Surgical Gastroenterology Unit, Division of General Surgery.
- [2] Mayosi Research Group, Department of Medicine.
- [3] Infectious Diseases Unit.

List of Tables

Literature Review

Publication Ready Manuscript

List of Figures

Literature Review

Publication Ready Manuscript

Abbreviations

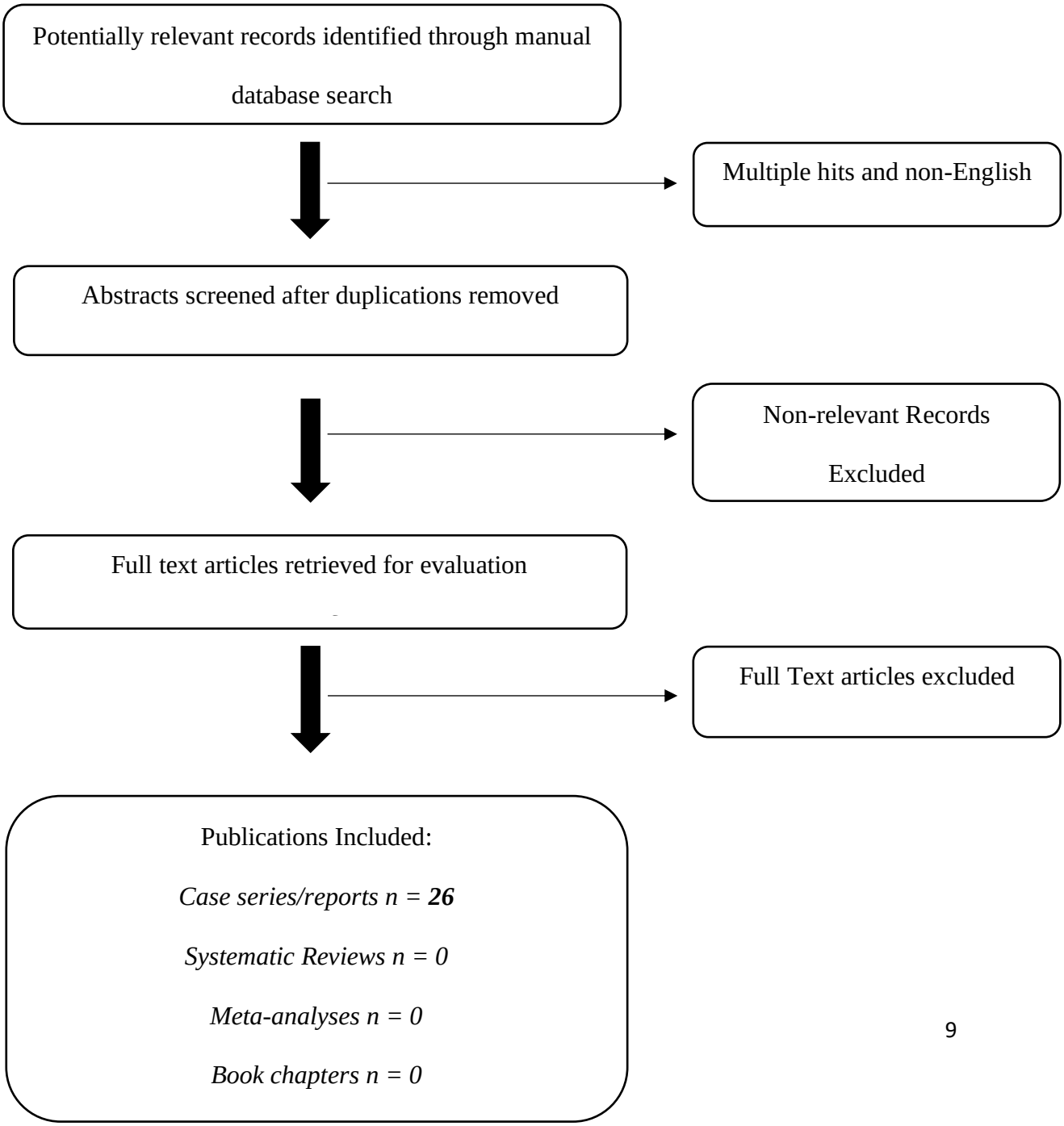
CE-CT	Contrast-Enhanced Computed Tomography
GSH	Groote Schuur Hospital
HIV	Human Immunodeficiency Virus
NTUH	National Taiwan University Hospital
OSD	Open Surgical Drainage
PLA	Pyogenic Liver Abscess
TB	Tuberculosis
US	Ultrasound
USA	United States of America

Chapter 1 : Literature review

Literature Search Strategy

A structured literature appraisal was performed searching PubMed, an electronic database. The search terms “liver abscess”, “hepatic abscess”, “pyogenic liver abscess” and “pyogenic hepatic abscess” was used. Only human studies were used. References were examined and ratified.

Figure 1. Algorithm for Literature Search



Background

Pathophysiology

A pyogenic liver abscess (PLA) is the most common abdominal solid organ abscess[1]. The incidence of PLA worldwide is estimated at 2.3-17.59 per 100 000 annually[2-6]. It is a potentially fatal disease with a mortality rate of 2-30%[7]. The liver is frequently exposed to bacterial loads through various sources. Normally, it is able to clear this. When the liver is unable to clear the bacteria, a PLA occurs. When a bacterial inoculum invades liver tissue, this results in an infiltration of neutrophils and thus the formation of an organised abscess. PLA are usually the result of spread of infection from the biliary tree, portal vein, hepatic arteries, infective contiguous collections in the abdomen or trauma. Risk factors for PLA include Human Immunodeficiency Virus (HIV), diabetes mellitus, hepato-biliary disease including liver transplantation and diseases of the pancreas[2-4].

Clinical Presentation

Patients usually present with fever (90%), and abdominal symptoms (50-75%). Commonly, right upper quadrant pain is experienced. Guarding and rebound tenderness may or may not be appreciated[8]. Septic features and abdominal symptoms particularly in the region of the right upper quadrant should raise suspicion of a PLA.

Diagnosis

Diagnosis is made by history, clinical examination, blood investigations and radiographic imaging. Computed tomography and ultrasound are the preferred diagnostic modalities[9]. Early diagnosis and treatment is fundamental for favourable patient outcomes[10].

Management

A surgeon's natural reaction to an abscess is to consider draining it. Drainage of larger abscesses and antibiotic therapy form the basis of treatment[11]. Drainage decompresses tissue, provides pain relief and allows better perfusion and delivery of the antibiotic to the affected site. Percutaneous catheter drainage is the preferred choice of drainage in most patients. Open surgery or laparoscopy should be reserved for unsuccessful percutaneous drainage or to treat the primary cause (e.g. appendicitis)[2, 12, 13].

Microbiology

Several pathogens are responsible for PLA. There is a high variability in these pathogens. A great variety of organisms exist due to the heterogeneity of sources of infection. Poor interventional or sampling technique can result in inadequate culture substrate and therefore not accurately reflect the causative organism. Antibiotics are generally started empirically before the causative organism(s) are identified. A partially treated abscess may not yield enough bacteria for a positive culture[14]. Multiple organisms have been identified as causative organisms in specific populations. Enteric gram-negative bacilli such as *Escherichia coli* and *Klebsiella pneumoniae* have been found to be the most common causative organisms worldwide[15]. *Klebsiella pneumoniae* is becoming a frequent cause of PLA in Asia. It is due to two serotypes of *Klebsiella Pneumoniae* strains, K1 and K2. It is also a frequent manifestation in diabetic patients[16]. A nationwide study conducted in the United States of America (USA) showed that *Streptococci* was the most common causative organism of PLA[5].

Antibiotic therapy should be broad enough to cover the common causative organisms[10]. In lower to middle income countries, empiric antibiotic protocols target both amoebic and

pyogenic causes of PLA. Developing an empiric antibiotic protocol is encumbered by lack of a local microbiome profile. Consequently, protocols are not tailored to the local bacterial environment and taken from protocols of other regions where different microbiomes are prevalent[14].

Pharmacotherapy

Once PLA is diagnosed, antibiotics should be started after blood cultures are taken and before drainage procedures are undertaken[17]. Four to six weeks of antibiotic therapy is recommended parenterally. If adequate drainage of the abscess occurs then two to four weeks of antibiotics is suggested[18]. Empiric antibiotics should cover Gram positive and Gram negative organisms as well as anaerobes. Amoxicillin-Clavulanic acid, Piperacillins, Tazobactam, and third generation Cephalosporins in conjunction with an Aminoglycoside are suggested. Metronidazole provides cover for some anaerobes and also provides cover if an amoebic abscess is suspected. Various regimens have been used: a third or later generation cephalosporin with Metronidazole if an amoebic abscess is suspected; beta-lactam-beta-lactamase inhibitor (e.g. Piperacillin-Tazobactam) with/without Metronidazole; Ampicillin plus Gentamycin with/without Metronidazole; Fluoroquinolone with/without Metronidazole and a Carbapenem with/without Metronidazole. Patients who do well on treatment, have improved clinically and have adequately drained the abscess, can finish the antibiotic course with the appropriate oral antibiotics[19-21].

Literature review

Global Research

A paucity of data on PLA exists in sub-Saharan Africa. Gonzalez et al conducted a study from 2001-2015 to look at the geographical distribution of PLA. The study also reviewed the various study designs of research conducted on PLA. Furthermore, it aimed to identify areas of possible future research [1]. It determined the top 16 countries that have produced research on PLA. None of these countries are on the African continent[1].

Table 1: Top 15 Countries producing research on PLA.

Country	Number of documents published
Taiwan	71
United States	39
China	29
South Korea	21
Japan	19
India	13
Spain	11
Italy	8
Turkey	7
United Kingdom	6
Germany	6
Singapore	6
Australia	5
France	5
Brazil	5
Canada	5

Taiwan has published the most documents on PLA[1]. A study conducted by Tsai et al reviewed the Taiwanese National Health Insurance database as well as the central referral hospital of the country, National Taiwan University Hospital (NTUH), and concluded that the incidence was 17.59 per 100 000 in 2004. A total of 506 cases from NTUH were reviewed. NTUH is a central referral hospital and possibly only reflects complicated referred cases. Simple cases that had an uncomplicated course may not have been analysed[6].

Establishing an accurate incidence in the USA is difficult. Huang et al conducted a study that looked at 233 patients over a 42 year period at only one centre[2]. Kaplan et al reviewed patients from 1999-2003 at only one centre[4]. A larger, more representative study by Meddings et al reviewed 17787 patients on a national database admitted with PLA. However this only represented 20% of private acute care hospitals where most patients had medical insurance. These studies were limited in providing an accurate assessment of the incidence in the varying socio-economic levels in the entire population[5]. A comparison between the United States and Asian countries shows that PLA are found worldwide but the varying incidence in different areas is significant.

Management

Percutaneous catheter drainage and extended duration of antibiotic therapy are the mainstays of treatment[11]. Commencing an antibiotic regimen that provides treatment to the local causative organisms is vital for good outcomes for patients[10]. The antibiotic regimens have been developed according to organisms affecting countries outside of Africa. We employ these regimens into our practice but they are not specific to the causative organisms of the South African population. This is due to the lack of data within this country[1].

Microbiology

PLA is caused by a variety of different organisms. The pathogens differ due to the varying routes of infection. There are several confounding issues in determining an accurate picture of the microbiology of PLA. PLA are mostly polymicrobial[2]. On most occasions a patient has received antibiotics before pus from the PLA is obtained. All these variables confound and possibly misrepresent the true bacterial profile. This could mislead a clinician's choice in an appropriate antibiotic. It also poses a selection bias in that the bacterium cultured could represent a resistant organism that has been exposed to antibiotics. Furthermore susceptible organisms might not culture positive as they have been treated before culture. A patient may be started on antibiotics long before the abscess is drained and cultured. This is due to the fact that percutaneous drainage is only available at certain centres in South Africa. A patient treated in the periphery could experience a delay in culture of the PLA due to poor access to healthcare. Referral or lack thereof and delays in access to healthcare might prolong the use of an inappropriate antibiotic. These are all factors that obscure the microbiome that needs to be targeted as well as create resistance in the causative organisms. Identifying an accurate picture of the causative organisms would lead to appropriate antibiotic use and good adherence to antibiotic stewardship.

The causative organisms differ according to geographic locations. According to Khim et al, the predominant organism in the USA was found to be *Streptococcus milleri* followed by *Klebsiella pneumoniae*. Whereas *Klebsiella pneumoniae* is the most common causative organism in South Korea and Taiwan[14]. In the United Kingdom, a study conducted on 132 patients with PLA by Neill et al, found that *Escherichia coli*(21, 15.9%) and *Klebsiella* species (21, 15.9%) were the most commonly cultured organisms. *Streptococcus milleri* was found to be cultured in 19 (14.4%) of the PLA[22]. This study is a reflection of only one centre in the

United Kingdom. A study by Osman et al [23] demonstrates the microbiological profile in New Zealand. It looked at a small number (n=57) of patients retrospectively from 2005 to 2014. *Klebsiella pneumoniae* was the commonest organism cultured. It is notable that 13 patients (23%) returned to hospital within 30 days for further antimicrobial therapy/percutaneous drainage and re-imaging. This highlights the morbidity of PLA and the importance of appropriate treatment. There is a dearth of local sub-Saharan literature on PLA. A paediatric study conducted in South Africa by Hendricks et al showcased the epidemiological characteristics of PLA in the Western Cape. They looked at children under 13 years of age diagnosed with PLA clinically or by ultrasound that were admitted to Red Cross and Tygerberg Hospitals between January 1983 and December 1992. Of these, 57 patients were identified with PLA, 43 with culture positives and 14 with culture negatives that were diagnosed as a PLA. It was found on blood culture and pus swab culture that 36 (85%) of PLA were due to *Staphylococcus aureus*. The rest cultured *Bacteroides fragilis* [3(7%)], *Klebsiella* [1(2%)], *Propionibacterium* [1(2%)], *Salmonella* Group B [1(2%)], and *Serratia marcescens* [1(2%)]. The study also looked at amoebic abscesses(n=25). Secondary infection of these amoebic abscesses occurred in 5 patients. Three of these were due to *Staphylococcus aureus*. The article suggests the high incidence of *Staphylococcus aureus* PLA is due to a common community acquired infection in lower socio-economic communities[24].

A case report by Gordan et al described the unsuccessful course of a septic patient that presented to Chris Hani Baragwanath Hospital. Blood culture revealed a *Klebsiella pneumoniae* bacteraemia. The case report highlights the importance of being mindful of *Klebsiella pneumoniae* as the cause of the cryptogenic PLA in this patient. This article questions whether cryptogenic invasive *Klebsiella pneumoniae* LA (CIKPLA) is an emerging disease in South Africa[25]. The article also recommends intravenous cephalosporins for a

period of three weeks as well as drainage of the abscess. This recommendation comes from a study by Casella et al in Italy that was based on only two patients successfully treated on this regimen[26].

Pharmacotherapy and Intervention

Antibiotics and percutaneous drainage are the foundation of treatment for PLA. An antibiotic is instituted first before other strategies of care are initiated. An antibiotic is available far more freely than a percutaneous drain. Therefore the choice of antibiotic is vital for a favourable outcome. Empiric antibiotics should be tailored to the common causative organisms. A review article in 2015 proposes that antibiotic choice should be directed at microbes typically cultured with action against Gram positive and negative bacteria. An aminoglycoside should be used in conjunction with this. Metronidazole should form part of the regimen in providing cover against anaerobic organisms if there is no cover by the other agent. Importantly, Metronidazole can be commenced if an amoebic abscess is suspected[19]. This does not provide a direct antibiotic regimen that is specific to Sub-Saharan Africa highlighting the importance of profiling the local causative organisms of PLA.

A study that looked at percutaneous catheter drainage versus multiple needle aspirations put all 64 patients on a regimen of intravenous Ampicillin, Cefuroxime and Metronidazole. The exclusion criteria was mismatched antibiotics. Initially 83 patients were chosen but 19 of them had been put on a different regimen of antibiotics. This shows the lack of a protocolised antibiotic regimen in this region. However, the study's focus was on the better mode of drainage of PLA rather than determining a better antibiotic regimen[20]. Another study that looked at 60 patients were put on Cefazolin and Gentamicin. However, the study primarily looked at a better form of drainage of the abscess. The patients excluded from the study were

patients that were put on a different antibiotic regimen[21]. Again, this demonstrates the poor application of protocolised antibiotic therapy of PLA.

Summary

Research should endeavour to ascertain the burden of PLA in South Africa as it is evident that there is little research conducted in Sub-Saharan Africa regarding PLA. It is an important condition that requires targeted and prompt treatment. The causative organisms of PLA have not been profiled in this region. Once the common causative organisms are established then an empiric antibiotic regimen can be designed accordingly.

References

1. González-Alcaide G, Peris J, Ramos JM (2017) Areas of research and clinical approaches to the study of liver abscess. World J Gastroenterol 23:357-365
2. Huang CJ, Pitt HA, Lipsett PA, et al (1996) Pyogenic hepatic abscess. Changing trends over 42 years. Ann Surg 223:600-607; discussion 607-609
3. Mohsen AH, Green ST, Read RC, et al (2002) Liver abscess in adults: ten years experience in a UK centre. Qjm 95:797-802
4. Kaplan GG, Gregson DB, Laupland KB (2004) Population-based study of the epidemiology of and the risk factors for pyogenic liver abscess. Clin Gastroenterol Hepatol 2:1032-1038
5. Meddings L, Myers RP, Hubbard J, et al (2010) A population-based study of pyogenic liver abscesses in the United States: incidence, mortality, and temporal trends. Am J Gastroenterol 105:117-124
6. Tsai FC, Huang YT, Chang LY, et al (2008) Pyogenic liver abscess as endemic disease, Taiwan. Emerg Infect Dis 14:1592-1600
7. Mischnik A, Kern WV, Thimme R (2017) [Pyogenic liver abscess: Changes of Organisms and Consequences for Diagnosis and Therapy]. Dtsch Med Wochenschr 142:1067-1074
8. Rahimian J, Wilson T, Oram V, et al (2004) Pyogenic liver abscess: recent trends in etiology and mortality. Clin Infect Dis 39:1654-1659
9. Bächler P, Baladron MJ, Menias C, et al (2016) Multimodality Imaging of Liver Infections: Differential Diagnosis and Potential Pitfalls. Radiographics 36:1001-1023

10. Chemaly RF, Hall GS, Keys TF, et al (2003) Microbiology of liver abscesses and the predictive value of abscess gram stain and associated blood cultures. Diagn Microbiol Infect Dis 46:245-248
11. Lübbert C, Wiegand J, Karlas T (2014) Therapy of Liver Abscesses. Viszeralmedizin 30:334-341
12. Cai YL, Xiong XZ, Lu J, et al (2015) Percutaneous needle aspiration versus catheter drainage in the management of liver abscess: a systematic review and meta-analysis. HPB (Oxford) 17:195-201
13. Fong Y, Wong J (2009) Evolution in surgery: influence of minimally invasive approaches on the hepatobiliary surgeon. Surg Infect (Larchmt) 10:399-406
14. Khim G, Em S, Mo S, et al (2019) Liver abscess: diagnostic and management issues found in the low resource setting. Br Med Bull 132:45-52
15. Johannsen EC, Sifri CD, Madoff LC (2000) Pyogenic liver abscesses. Infect Dis Clin North Am 14:547-563, vii
16. Siu LK, Yeh KM, Lin JC, et al (2012) Klebsiella pneumoniae liver abscess: a new invasive syndrome. Lancet Infect Dis 12:881-887
17. Solomkin JS, Mazuski JE, Bradley JS, et al (2010) Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis 50:133-164
18. Chen YW, Chen YS, Lee SS, et al (2002) A pilot study of oral fleroxacin once daily compared with conventional therapy in patients with pyogenic liver abscess. J Microbiol Immunol Infect 35:179-183
19. Lardière-Deguelte S, Ragot E, Amroun K, et al (2015) Hepatic abscess: Diagnosis and management. J Visc Surg 152:231-243

20. Yu SC, Ho SS, Lau WY, et al (2004) Treatment of pyogenic liver abscess: prospective randomized comparison of catheter drainage and needle aspiration. Hepatology 39:932-938

21. Zerem E, Hadzic A (2007) Sonographically guided percutaneous catheter drainage versus needle aspiration in the management of pyogenic liver abscess. AJR Am J Roentgenol 189:W138-142

22. Neill L, Edwards F, Collin SM, et al (2019) Clinical characteristics and treatment outcomes in a cohort of patients with pyogenic and amoebic liver abscess. BMC Infect Dis 19:490

23. Osman K, Srinivasa S, Koea J (2018) Liver abscess: contemporary presentation and management in a Western population. N Z Med J 131:65-70

24. Hendricks MK, Moore SW, Millar AJ (1997) Epidemiological aspects of liver abscesses in children in the Western Cape Province of South Africa. J Trop Pediatr 43:103-105

25. Gordon DM, Feldman C (2010) CIKPLA: Cryptogenic invasive Klebsiella pneumoniae liver abscess (and meningitis) - an emerging disease in South Africa? Southern African Journal of Epidemiology and Infection 25:28-29

26. Casella F, Finazzi L, Repetti V, et al (2009) Liver abscess caused by Klebsiella pneumoniae: two case reports. Cases J 2:6879

Chapter 2: Publication Ready Manuscript

An 8-year retrospective review of Pyogenic Liver Abscesses at Groote Schuur Hospital, Cape Town, South Africa.

Authors:

N Govender*[1], K Naicker[2], O Chihaka[1], S Dlamini[3], L Raphael[1], KJ Gqada[1], E Jonas[1], JEJ Krige[1], JC Kloppers[1]

Affiliations:

University of Cape Town Health Sciences Faculty and Groote Schuur Hospital, Anzio Road, Observatory, Cape Town, South Africa.

- [1] Surgical Gastroenterology Unit, Division of General Surgery.
- [2] Mayosi Research Group, Department of Medicine.
- [3] Infectious Diseases Unit.

***Corresponding author:**

Nieleshen Govender

Email : nieleshen.govender@gmail.com, Phone : +27 21 404 9111

Keywords: pyogenic liver abscess; causative organisms; empiric antibiotics.

Manuscript word count: 2546 words

The authors declare no conflicts of interest.

No funding was received for this research.

Abstract

Background

Pyogenic liver abscess (PLA) is the most common abdominal solid organ abscess with significant associated morbidity and mortality (2-30%). High variance in the causative organism exists therefore identifying the responsible pathogens and providing targeted therapy is needed for optimal outcomes. This study aims to describe patient variables, outcomes and the local microbiome to guide future empiric antibiotic protocols.

Methods

We performed a retrospective review of 121 patients with PLA from 2012 to 2020 at Groote Schuur Hospital. We analyzed patient demographics, microbiology results from cultures of PLA (bile, percutaneous aspiration or intra-operative sampling) and blood samples, empiric antibiotic regimens used, interventions and outcomes.

Results

The five most common organisms cultured were *Escherichia coli* [26 (21%)], *Klebsiella pneumoniae* [24 (19.8%)], *Pseudomonas aeruginosa* [12 (9.9%)], Anaerobic organisms Isolated [11 (9%)] and *Enterobacter cloacae* Complex [7 (5.1%)]. Twenty different regimens were used to treat PLA. Primary intervention (antibiotics alone, percutaneous drainage, open surgery) was successful in 72 patients (60%). Further intervention was required in 49 patients (40%). Open surgical drainage was required in 16 patients (13%). 30-day mortality was 9.1% (n=11). Biliary sepsis was the most common cause of PLA (31%). Our study showed Gentamicin [52 isolates (65%)], Ciprofloxacin [49 isolates (61%)] and Co-Amoxiclav [37 isolates (46%)] to be the most effective in covering the five most common isolates.

Conclusion

Optimal PLA management remains challenging with multiple combinations of empiric antibiotic regimens initiated. Local data on the topic is sparse and this research is hypotheses generating for future research to improve outcomes.

Abstract word count: 250 words

Introduction

Pyogenic liver abscess (PLA) is the most common abdominal solid organ abscess with annual incidences rising in recent years and estimated at 2.3-17.59 per 100 000 [2-6]. It is a potentially fatal disease with mortality between 2 - 30% [8, 27-29]. PLA remains a significant clinical condition particularly in developing countries where resources are limited and impacts patient outcomes.

The liver is frequently exposed to physiological bacterial loads through various sources, which are normally cleared. Pathogenic organisms may enter the liver through the biliary tree, portal vein or hepatic artery. Entry may also occur due to trauma or direct spread from adjacent pathologies such as advanced cholecystitis, diverticulitis, etc. The microbiology of the causative organism differs according to the presumed route of hepatic assault [30]. Invasion by a bacterial inoculum is followed by an inflammatory response and infiltration of neutrophils and thus the formation of an organised abscess.

Risk factors for PLA include states of immunosuppression such as Human Immunodeficiency Virus (HIV), diabetes mellitus and malignancy. Increased incidence of PLA is also associated with hepato-biliary interventions, including bilio-digestive anastomoses and liver transplantation [2-4, 31]. Patients usually present with fever (90%), and/or abdominal symptoms, for example, right upper quadrant pain associated with guarding and rebound tenderness in 50-75% of patients [8]. Diagnosis is made by clinical assessment, blood investigations and imaging, most commonly, contrast-enhanced computed tomography (CE-CT) or ultrasound (US) [9]. Early diagnosis and appropriate management are prerequisites for optimal outcomes [10].

Antibiotic therapy is the mainstay of treatment with drainage individualized in patients based on the clinical picture, size and multiplicity of abscesses for therapeutic and/or diagnostic purposes [11]. Percutaneous catheter drainage is the preferred method of drainage with open surgical or laparoscopic drainage (OSD) reserved for suboptimal image-guided percutaneous drainage or with synchronous treatment of an underlying cause [2, 12, 13]. A wide variety of causative organisms are implicated in PLA and they are often polymicrobial [32]. The microorganisms most commonly found include enteric gram-negative bacilli such as *Escherichia coli* and *Klebsiella pneumoniae* and gram positives such as *Streptococcus* spp [5, 32]. At present there are no local clinical guidelines in South Africa on empiric antibiotics for the management of PLA. Furthermore there is limited evidence in the region to guide clinicians on the choice of antibiotic. Early empiric antibiotic therapy directed at local causative organisms and targeted treatment if necessary are key to appropriate resource allocation in low to middle income countries [10, 30].

The paucity of data that exists in Sub-Saharan Africa on PLA limits our understanding of how to effectively manage this condition. Our study aims to describe the demographics, aetiological factors, characteristics, interventions, local microbiome, empiric antibiotic regimens used, and discuss some of the clinical outcomes of patients with PLA. This would provide the groundwork to guide future research in developing an empiric antibiotic protocol for PLA in South Africa.

Materials and methods

We conducted an analysis of a prospectively maintained registry of all adult patients that received treatment for PLA at Groote Schuur Hospital (GSH), Cape Town, South Africa between January 2012 and December 2020. Consecutive patients above 18 years of age who

underwent intervention for PLA were included. All patients who had a hepatic abscess that was of amoebic or hydatid origin were excluded. Demographics were reviewed according to age, gender and pre-existing co-morbidities. The aetiologies and characteristics of PLA were quantified and described. Microbiology data from blood cultures and liver cultures (samples from the abscess, bile or free abdominal fluid) were analysed. These cultures were classified into three categories: (1) no-growth (2) monomicrobial (3) polymicrobial. The empiric regimen initiated and the duration of treatment for each patient was reviewed. Treatment success was defined as 30 day mortality, surgical complications and number of interventions.

Data Analysis

A descriptive analysis was employed due to the sample size using RedCap and Excel.

Ethics approval and consent for publication

Ethics clearance was granted by the Human Research Ethics Committee of the University of Cape Town (260/2020).

Results

The study included 121 patients, with a median age of 49 years (range 18-83 years) of whom 67 (55.4%) were male. A total of 73 patients (60.3%) had comorbidities. Hypertension and diabetes mellitus were the most common co-morbidities as seen in Table 1. HIV was prevalent in 12 patients (9.9%), however only 49 patients (41%) were tested. The various aetiologies of PLA are summarized in Table 2. Injuries that were classified as iatrogenic that resulted in PLA included portal vein injury during surgery, microwave ablation, liver resection, retained biliary

stent as patient was lost to follow up, post ERCP cholangitis and angio-embolisation of a hepatic artery.

Table 1. Demographic data and risk factors in patients with PLA.

Variable	***n***	**(%)**
Age, years, median (range)	49 (18-83)	
Gender: male	67	55.4
Gender: female	54	44.6
Co-morbidities:	73	60.3
Hypertension	40	33,1
Diabetes Mellitus	33	27.3
HIV	12	9.9
Cirrhosis	2	1.7
Other	38	31.4
None	48	28

Table 2. Aetiology of PLA.

Cause	***n***	**%**
Biliary sepsis	38	31.4%
Cryptogenic	22	18.2%
Portal pyaemia	21	17.4%
Trauma	13	10.7%
Iatrogenic	11	9.1%
Direct spread	10	8.3%
Arterial hematogenous spread	6	5.0%

A total of 20 different antibiotic regimens were used empirically (Table 3). Co-amoxiclav was the most frequently prescribed antibiotic, used in 54 patients (45%). A change in regimen was not needed in 57 patients (47%). At least one regimen change was needed in 50 patients (41%) while data was unclear in 14 patients (12%). The average number of days to any change in antibiotic was 6.12 (range of 1-30 days).

Table 3. Antibiotic regimens initiated empirically in PLA.

Antibiotic	**Patients (n=118)**
Co-amoxiclav	54
Ertapenem	13
Piperacillin-Tazocin + Amikacin	9
Co-amoxiclav + Metronidazole	8
Ceftriaxone + Metronidazole	8
Ceftriaxone	5
Ampicillin + Gentamycin	2
Clarithromycin + Metronidazole	2
Piperacillin-Tazocin	2
Gentamycin + Metronidazole	2
Ertapenem + Metronidazole	2
Metronidazole	2
Ampicillin + Gentamycin + Metronidazole	2
Albendazole	1
Amoxicillin	1
Doxycycline + Metronidazole	1
Ceftriaxone + Ampicillin	1
Meropenem	1

Imipenem	1
Ceftriaxone + Co-amoxiclav	1

Specimens used to identify the causative organisms were blood (n=5), bile (n=2), PLA aspirate (n=109) and intra-operative tissue (n=5). Solitary blood cultures were used in three patients with no supplementary hepatic specimens. Sterile cultures from a hepatic source were found in two patients but they had positive blood cultures. Blood cultures were done in 94 patients. These blood cultures yielded no growth in 68 patients (72.3%), monomicrobial growth in 21 patients (22.3%) and polymicrobial growth in five patients (5.3%). PLA cultures were reported in 116 (96%) patients. Of these, 27 patients (23.3%) yielded no growth, monomicrobial growth in 61 patients (52.6%) and polymicrobial growth in 28 patients (24.1%). PLA cultures (n=116) and five blood cultures were used to direct antibiotic therapy. We found no growth in 28 patients (23.1%), monomicrobial growth in 62 patients (51.2%), polymicrobial growth (2 organisms) – 19 patients (15.7%), polymicrobial growth (3 organisms) – 11 patients (9.1%) and polymicrobial growth (4 organisms) – 1 patient (0.8%).

The five most common organisms cultured were *Escherichia coli* [26 (21%)], *Klebsiella pneumoniae* [24 (19.8%)], *Pseudomonas aeruginosa* [12 (9.9%)], Anaerobic organisms Isolated (categorized broadly by the National Health Laboratory Services) [11 (9%)] and *Enterobacter cloacae* Complex [7 (5.1%)]. The full cohort of causative micro-organisms from liver and blood cultures are detailed in Figure 1. Our study showed Gentamicin [52 isolates (65%)], Ciprofloxacin [49 isolates (61%)] and Co-Amoxiclav [37 isolates (46%)] to be the most effective in covering the five most common isolates (Figure 2). There was no anaerobic cover with Gentamicin and Ciprofloxacin while Co-Amoxiclav provided anaerobic cover. A greater spectrum of antibiotic cover is depicted in Figure 2.

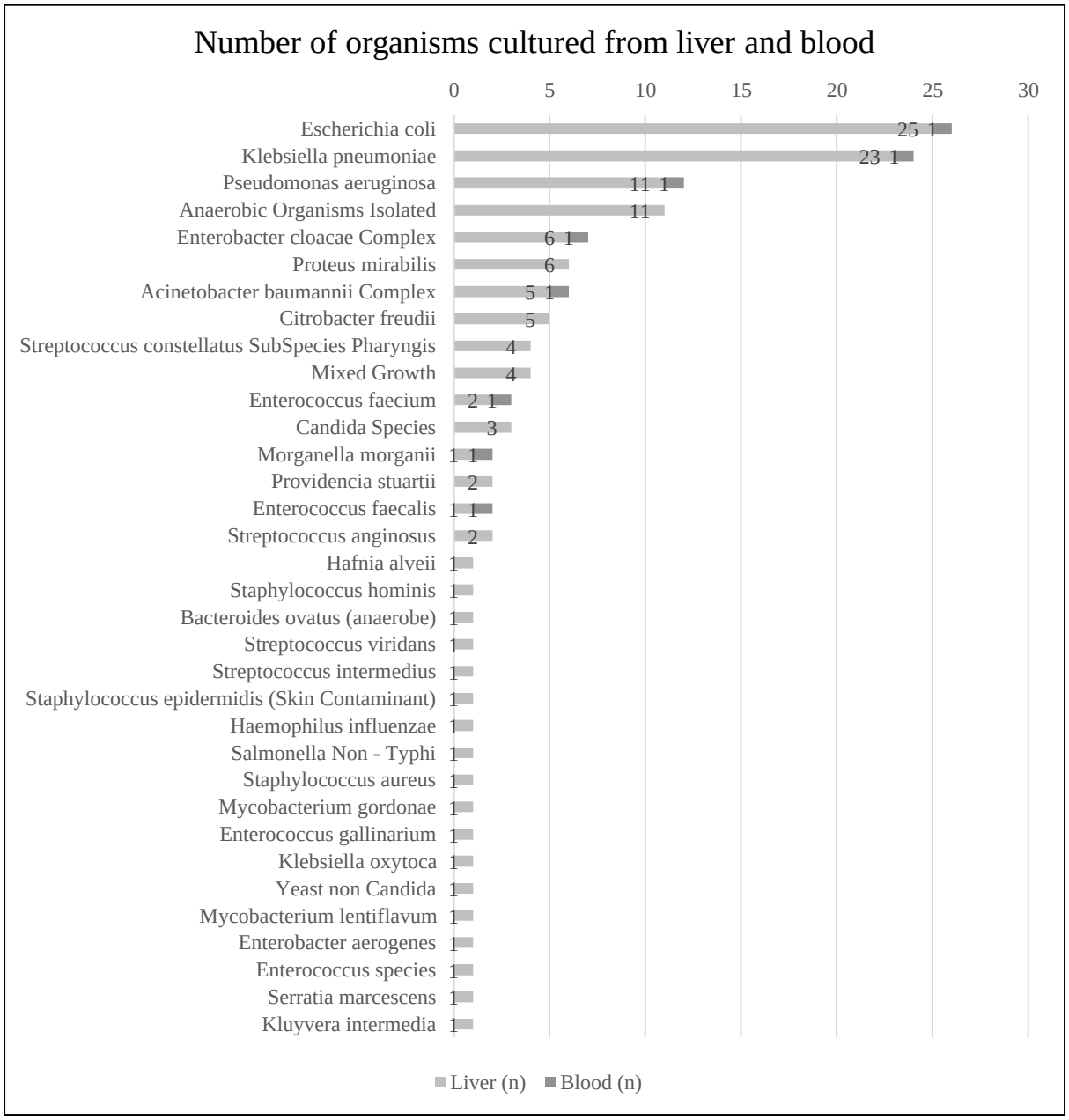


Figure 1. Organisms cultured from the Liver Abscess (96%) and the blood cultures (4%) that directed treatment in the absence of liver cultures.

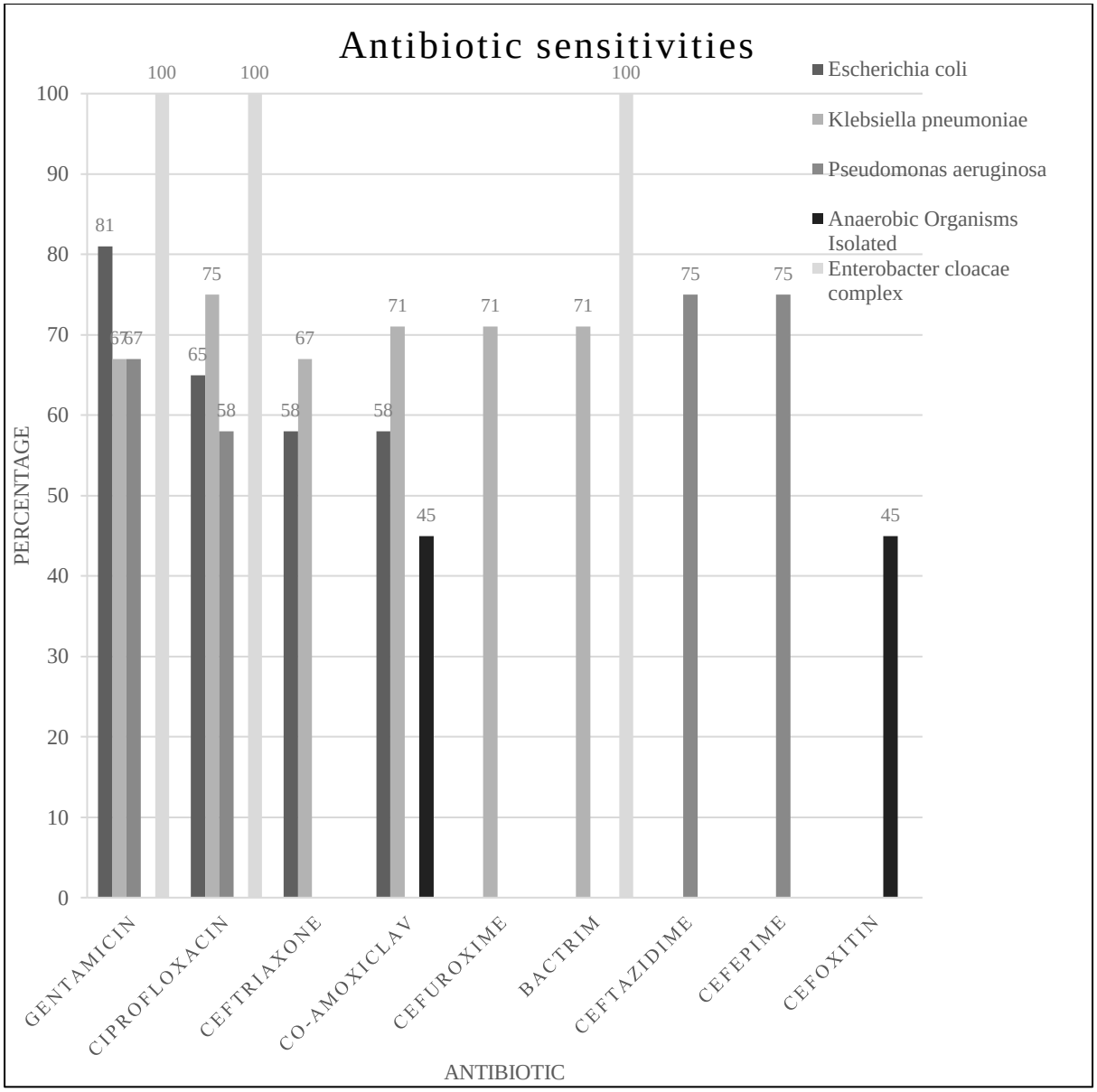


Figure 2. Antibiotic Sensitivities in the five most common isolates of PLA.

Primary intervention (antibiotics alone, percutaneous drainage, OSD) was successful in 72 patients (60%). PLA according to size on CE-CT were four patients (0-2cm), 23 patients (2-5cm), 62 patients (5-10cm) and 31 patients (>10cm). The PLA was 5cm or larger in 78% of patients. The average PLA measured 8.7 cm in its widest diameter. PLA size was more than 5cm in 91% (n=10) of patients that did not survive more than 30 days. Secondary intervention was required in 35 patients with a PLA larger than 5cm. In patients that required OSD (n=16),

the PLA was larger than 5cm in 11 patients (73%) [1 (0-<2cm), 3 (2-<5cm), 6 (5-10cm), 5 (>10cm)]. One patient was operated on before having a CE-CT therefore the size of the PLA was not quantified. Post-operative complications in the OSD intervention group were experienced by 11 patients graded according to the Clavien-Dindo Classification [33] (Table 4). Readmissions (due to persistent symptomatology) occurred in 26 patients (21.5%). The 30-day mortality of the study cohort was 9.1% (n=11) (Figure 3). The details of interventions, complications and outcome data analysed are summarized in Figure 4.

Table 4. Clavien-Dindo Classification of OSD Complications.

Grade	**Number**
Nil	5
I	1
II	1
IIIa	1
IIIb	1
IV	5
V	2

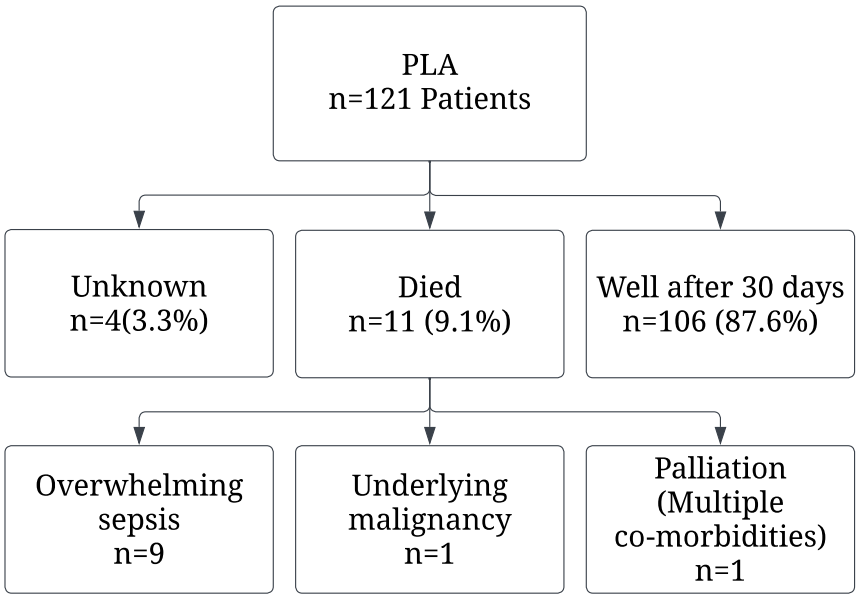


Figure 3. 30 day Mortality in PLA.

Primary Intervention n=121	Successful: n=72 Unknown: 1
Antibiotics alone: 4 Percutaneous Needle Aspiration: 11 Percutaneous Catheter Drainage: 100 Open Surgical Drainage: 6	Excluded from secondary PLA intervention: 6 -Demised: 5 -ERCP, PTC and drain: 1

Secondary Intervention n=42	Successful: n=25 Unknown: 2
Antibiotics alone: 1 Percutaneous Needle Aspiration: 3 Percutaneous Catheter Drainage: 22 Upsizing of Percutaneous Catheter Drain: 9 Open Surgical Drainage: 7	Excluded from tertiary PLA intervention: 4 -Demised:3 -ERCP, PTC and drain: 1

Tertiary Intervention n=11	Successful: n=6 Unknown: 1
Antibiotics alone: 2 Percutaneous Needle Aspiration: 1 Percutaneous Catheter Drainage: 2 Upsizing of Percutaneous Catheter Drain: 3 Open Surgical Drainage: 3	No exclusions

Quaternary Intervention n=4	Successful: n=2
Percutaneous Catheter Drainage: 1 Upsizing of Percutaneous Catheter Drain:3	Not successful: 2 (demised)

Figure 4. PLA Interventions.

Discussion

Our study showed a predominance of PLA amongst males (55.4% vs 44.6%) with an average age of 48 years. These findings are in keeping with other studies [28, 34-36]. In recent years immunosuppression has been identified as a key risk factor for PLA [37]. Zhang et al described atypical presentations of PLA in HIV positive patients, who often have co-existing infections thus directed antibiotic therapy in these patients is critical [38]. Considering the burden of HIV and *Mycobacterium Tuberculosis* (TB) in South Africa, only a tenth of the cohort was HIV positive with only one case of TB in a HIV negative patient. Diabetes mellitus is acknowledged as the most commonly associated risk factor predisposing patients to PLA [39-41]. However, our study showed a high prevalence of both hypertension and diabetes mellitus with rates of 33,1% and 27.3% respectively.

Biliary sepsis was found to be the leading cause of PLA which is consistent with the aetiologies found internationally [8, 15]. Biliary stents were noted in 18 patients prior to presenting with PLA indicating previous biliary disease. South Africa has a high trauma burden with increasing rates of inter-personal violence and penetrating injuries reported particularly in the Western Cape province and the liver being the most commonly injured intra-abdominal organ [42, 43]. Navsaria et al describe PLA as one of the common liver-related complications following gunshot liver injuries as reflected in our study where trauma was responsible for 10% of cases of PLA [44].

Antibiotics and percutaneous drainage are the foundation of treatment for PLA. Antibiotic therapy is initiated empirically as soon as a diagnosis is made before any other strategy. Due

to resource limitations within the South African setting, antibiotics are more readily available than percutaneous drainage. Interventional radiology is a scarce commodity in low to middle income countries, often only being offered at tertiary referral centres [30]. Therefore the choice of early antibiotics is critical for a favourable outcome. However, there is limited data on the profile of regional or institutional microbiomes in PLA within sub-Saharan Africa [1]. In these low resource settings, protocols are not tailored to the local bacterial environment and taken from protocols of other regions where different microbiomes are prevalent [14]. Developing an empiric antibiotic protocol for PLA is encumbered by this paucity of data and several challenges in appropriately defining the causative organisms of PLA exist. Specimens are often collected after the administration of antibiotics which may lead to an underestimation of organisms and create questions on selection bias. Subsequent positive cultures may also have a more resistant profile. [30, 45]. The wide array of empiric antimicrobial regimens started in this study underlines our lack of clear guidelines locally. Our study showed that Co-amoxiclav was the most frequently prescribed antibiotic empirically. Several studies suggest that empiric antibiotics should cover Gram positive and Gram negative organisms as well as anaerobes. Co-amoxiclav, Piperacillin, Tazobactam, and third generation Cephalosporins in conjunction with an Aminoglycoside are suggested. Metronidazole provides cover for some anaerobes and also provides cover if an amoebic abscess is suspected [17-21]. It is evident that compared to suggested empiric treatment protocols, that this cohort was subject to a narrower empiric protocol. In almost half the patients (46%), the antibiotic treatment was altered at least once. This change in therapy may be due to several reasons including culture results and sensitivities becoming available, resistance, or clinical deterioration of the patient. The causative organism that directed therapy was cultured from a liver source in 96% of patients. There were 116 cultures taken directly from a liver source that guided antibiotic therapy, and only five patients

were guided by a blood culture result. When a liver culture was not available, blood culture results serve as an important adjunct to direct antibiotic therapy.

A variety of organisms are implicated in PLA. *Klebsiella pneumoniae* is becoming a frequent cause of PLA in Asia [16, 46]. The United States of America (USA) showed that *Streptococci* was the most common causative organism of PLA [5]. *Escherichia coli* and *Klebsiella pneumoniae* have been found to be the most common causative organisms worldwide [14, 15]. We have found this to be consistent with our research (Figure 1). Identifying the antibiotic sensitivity profile of these prevalent micro-organisms would be central to creating a targeted empiric antibiotic guideline in the future.

Further research needs to be done to develop an empiric antibiotic regimen for PLA. The Clinical and Laboratory Standards Institute from the USA has guidelines for establishing a cumulative antibiogram [47]. They suggest (a) inclusion of organisms for diagnostic purposes (b) the first organism isolated per patient per analysis (c) a minimum of 30 isolates per organism cultured to provide significant data (d) antibiogram review at least annually to ensure accuracy of data. In building a dataset for a cumulative antibiogram it is important to include patient variables and consider community acquired and hospital acquired infection.

The overall 30-day mortality of our study was 9.1% which was low in comparison to internationally reported mortality of up to 30% (Figure 3) [7-10]. Primary intervention, classified as antibiotics and/or percutaneous/surgical drainage, was only successful in 60% of patients (Figure 4). Rismiller et al demonstrated a high success rate of 85% with percutaneous drainage in the USA [48]. Percutaneous drainage is also considered superior to percutaneous needle aspiration and has shown better success rates of PLA resolution. In a meta-analysis of

five randomized control trials, percutaneous drainage had a success rate of 96% with more favourable outcomes than percutaneous needle aspiration [12]. Another study from a single centre in Singapore showed that percutaneous drainage in liver abscesses larger than 10cm had a complication rate of 25% [49]. Our study showed that having a PLA larger than 5cm was associated with more complications and poorer outcomes. OSD was required in 13% of patients in this study. OSD was performed due to persistent sepsis whereby non-operative management failed, overwhelming sepsis (acute abdomen or septic shock), patients not amenable to percutaneous drainage or part of another operation. OSD rates ranged between 3-15% in other studies [3, 28, 38-40].

A clear approach to the management of patients presenting with suspected PLA is needed, Figure 5. outlines a suggested management algorithm based on findings from our study. Several factors influence poor outcomes in these patients, including resource constraints, cost effectiveness and practical difficulties faced in low income settings within sub-Saharan Africa. This provides further fuel to drive the need for more directed empiric antibiotic protocols to improve outcomes in PLA.

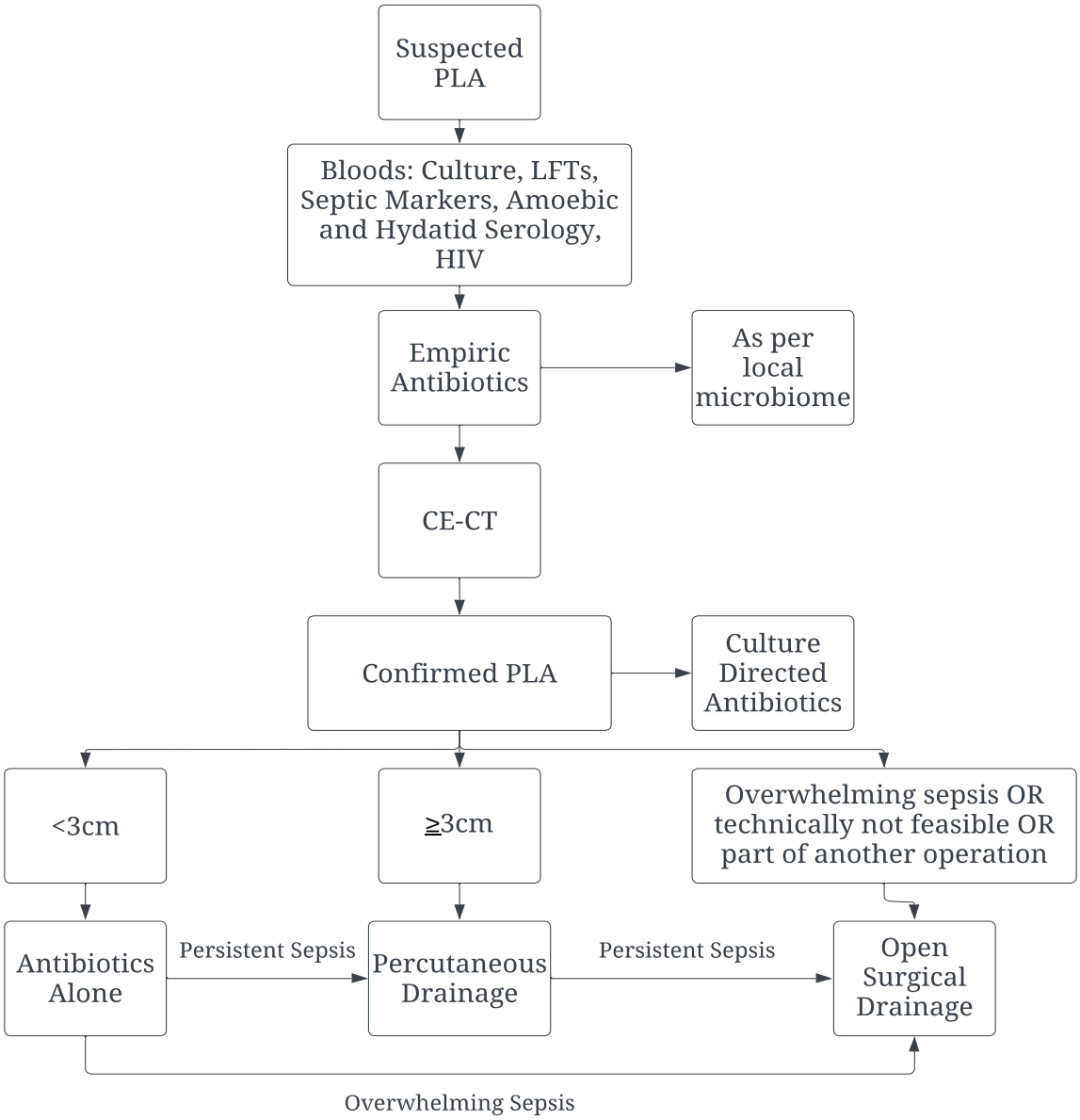


Figure 5. Suggested Management of PLA.

Limitations

A retrospective single-centre registry review has its shortcomings. During this time period not all patients that were treated at GSH with a PLA were captured into the registry. Incomplete data was captured when full medical records were not available. Some patients did not have positive cultures. Some patients may have been partially treated before they had drainage and microbiology assessment. A descriptive analysis approach was used as we had a limited sample

size that did not provide any statistical power. Local trends in antibiotic resistance should also be considered. This dataset extends beyond five years and poses a potential disadvantage with varying epidemiological trends over time.

Conclusion

PLA remains a significant and potentially life-threatening surgical condition. Early targeted antimicrobial intervention is crucial for favourable outcomes particularly in resource limited settings. Locally, varying empiric antibiotic regimens are being initiated due to lack of clear treatment guidelines. There are several gaps in current literature on the optimal management of PLA in Sub-Saharan Africa. Our study identified prevalent microorganisms within a single centre, generating hypotheses for further large scale research in the region.

Funding

No external funding was received for this review.

Conflict of Interest

The authors declare no conflicts of interest.

References

1. González-Alcaide G, Peris J, Ramos JM (2017) Areas of research and clinical approaches to the study of liver abscess. World J Gastroenterol 23:357-365
2. Huang CJ, Pitt HA, Lipsett PA, et al (1996) Pyogenic hepatic abscess. Changing trends over 42 years. Ann Surg 223:600-607; discussion 607-609
3. Mohsen AH, Green ST, Read RC, et al (2002) Liver abscess in adults: ten years experience in a UK centre. Qjm 95:797-802
4. Kaplan GG, Gregson DB, Laupland KB (2004) Population-based study of the epidemiology of and the risk factors for pyogenic liver abscess. Clin Gastroenterol Hepatol 2:1032-1038
5. Meddings L, Myers RP, Hubbard J, et al (2010) A population-based study of pyogenic liver abscesses in the United States: incidence, mortality, and temporal trends. Am J Gastroenterol 105:117-124
6. Tsai FC, Huang YT, Chang LY, et al (2008) Pyogenic liver abscess as endemic disease, Taiwan. Emerg Infect Dis 14:1592-1600
7. Mischnik A, Kern WV, Thimme R (2017) [Pyogenic liver abscess: Changes of Organisms and Consequences for Diagnosis and Therapy]. Dtsch Med Wochenschr 142:1067-1074
8. Rahimian J, Wilson T, Oram V, et al (2004) Pyogenic liver abscess: recent trends in etiology and mortality. Clin Infect Dis 39:1654-1659
9. Bächler P, Baladron MJ, Menias C, et al (2016) Multimodality Imaging of Liver Infections: Differential Diagnosis and Potential Pitfalls. Radiographics 36:1001-1023

10. Chemaly RF, Hall GS, Keys TF, et al (2003) Microbiology of liver abscesses and the predictive value of abscess gram stain and associated blood cultures. Diagn Microbiol Infect Dis 46:245-248
11. Lübbert C, Wiegand J, Karlas T (2014) Therapy of Liver Abscesses. Viszeralmedizin 30:334-341
12. Cai YL, Xiong XZ, Lu J, et al (2015) Percutaneous needle aspiration versus catheter drainage in the management of liver abscess: a systematic review and meta-analysis. HPB (Oxford) 17:195-201
13. Fong Y, Wong J (2009) Evolution in surgery: influence of minimally invasive approaches on the hepatobiliary surgeon. Surg Infect (Larchmt) 10:399-406
14. Khim G, Em S, Mo S, et al (2019) Liver abscess: diagnostic and management issues found in the low resource setting. Br Med Bull 132:45-52
15. Johannsen EC, Sifri CD, Madoff LC (2000) Pyogenic liver abscesses. Infect Dis Clin North Am 14:547-563, vii
16. Siu LK, Yeh KM, Lin JC, et al (2012) Klebsiella pneumoniae liver abscess: a new invasive syndrome. Lancet Infect Dis 12:881-887
17. Solomkin JS, Mazuski JE, Bradley JS, et al (2010) Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis 50:133-164
18. Chen YW, Chen YS, Lee SS, et al (2002) A pilot study of oral fleroxacin once daily compared with conventional therapy in patients with pyogenic liver abscess. J Microbiol Immunol Infect 35:179-183
19. Lardière-Deguelte S, Ragot E, Amroun K, et al (2015) Hepatic abscess: Diagnosis and management. J Visc Surg 152:231-243

20. Yu SC, Ho SS, Lau WY, et al (2004) Treatment of pyogenic liver abscess: prospective randomized comparison of catheter drainage and needle aspiration. Hepatology 39:932-938

21. Zerem E, Hadzic A (2007) Sonographically guided percutaneous catheter drainage versus needle aspiration in the management of pyogenic liver abscess. AJR Am J Roentgenol 189:W138-142

22. Neill L, Edwards F, Collin SM, et al (2019) Clinical characteristics and treatment outcomes in a cohort of patients with pyogenic and amoebic liver abscess. BMC Infect Dis 19:490

23. Osman K, Srinivasa S, Koea J (2018) Liver abscess: contemporary presentation and management in a Western population. N Z Med J 131:65-70

24. Hendricks MK, Moore SW, Millar AJ (1997) Epidemiological aspects of liver abscesses in children in the Western Cape Province of South Africa. J Trop Pediatr 43:103-105

25. Gordon DM, Feldman C (2010) CIKPLA: Cryptogenic invasive Klebsiella pneumoniae liver abscess (and meningitis) - an emerging disease in South Africa? Southern African Journal of Epidemiology and Infection 25:28-29

26. Casella F, Finazzi L, Repetti V, et al (2009) Liver abscess caused by Klebsiella pneumoniae: two case reports. Cases J 2:6879

27. Lee YT, Wang CC, Li CF, et al (2021) Utility of Acute Physiology and Chronic Health Evaluation (APACHE II) in Predicting Mortality in Patients with Pyogenic Liver Abscess: A Retrospective Study. J Clin Med 10

28. Serraino C, Elia C, Bracco C, et al (2018) Characteristics and management of pyogenic liver abscess: A European experience. Medicine (Baltimore) 97:e0628

29. Shelat VG, Chia CL, Yeo CS, et al (2015) Pyogenic Liver Abscess: Does Escherichia Coli Cause more Adverse Outcomes than Klebsiella Pneumoniae? World J Surg 39:2535-2542

30. Khim G, Em S, Mo S, et al (2019) Liver abscess: diagnostic and management issues found in the low resource setting. Br Med Bull 132:45-52

31. Justo I, Jiménez-Romero C, Manrique A, et al (2018) Management and Outcome of Liver Abscesses After Liver Transplantation. World Journal of Surgery 42:3341-3349

32. Trillos-Almanza MC, Restrepo Gutierrez JC (2020) How to manage: liver abscess. Frontline Gastroenterol 12:225-231

33. Clavien PA, Barkun J, de Oliveira ML, et al (2009) The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 250:187-196

34. Ahmed M, Alam J, Hussain S, et al (2021) Prospective randomized comparative study of percutaneous catheter drainage and percutaneous needle aspiration in the treatment of liver abscess. ANZ J Surg 91:E86-e90

35. Kulhari M, Mandia R (2019) Prospective randomized comparative study of pigtail catheter drainage versus percutaneous needle aspiration in treatment of liver abscess. ANZ J Surg 89:E81-e86

36. Santos-Rosa OM, Lunardelli HS, Ribeiro-Junior MA (2016) PYOGENIC LIVER ABSCESS: DIAGNOSTIC AND THERAPEUTIC MANAGEMENT. Arq Bras Cir Dig 29:194-197

37. Mavilia MG, Molina M, Wu GY (2016) The Evolving Nature of Hepatic Abscess: A Review. J Clin Transl Hepatol 4:158-168

38. Zhang W, Yu H, Luo N, et al (2020) Clinical Characteristics and Treatment Outcomes in Human Immunodeficiency Virus (HIV)-Infected Patients with Liver Abscess: A Retrospective Study of 53 Patients. Med Sci Monit 26:e923761

39. Du Z, Zhou X, Zhao J, et al (2020) Effect of diabetes mellitus on short-term prognosis of 227 pyogenic liver abscess patients after hospitalization. BMC Infect Dis 20:145

40. Zhang J, Du Z, Bi J, et al (2019) Comparison of clinical characteristics and outcomes of pyogenic liver abscess patients < 65 years of age versus ≥ 65 years of age. BMC Infect Dis 19:233

41. Neill L, Edwards F, Collin SM, et al (2019) Clinical characteristics and treatment outcomes in a cohort of patients with pyogenic and amoebic liver abscess. BMC Infect Dis 19:490-490

42. Hommes M, Chowdhury S, Visconti D, et al (2018) Contemporary damage control surgery outcomes: 80 patients with severe abdominal injuries in the right upper quadrant analyzed. Eur J Trauma Emerg Surg 44:79-85

43. Clancy TV, Gary Maxwell J, Covington DL, et al (2001) A statewide analysis of level I and II trauma centers for patients with major injuries. J Trauma 51:346-351

44. Navsaria P, Nicol A, Krige J, et al (2019) Selective nonoperative management of liver gunshot injuries. European Journal of Trauma and Emergency Surgery 45:323-328

45. Sifri C, Madoff L Infections of the liver and biliary system (liver abscess, cholangitis, cholecystitis) In: Bennett JE, Dolin R, Blaser MJ.(eds.). Principles and Practice of Infectious Diseases, Philadelphia: Elsevier Saunders, 2015.

46. Tsai F-C, Huang Y-T, Chang L-Y, et al (2008) Pyogenic liver abscess as endemic disease, Taiwan. Emerg Infect Dis 14:1592-1600

47. Klinker KP, Hidayat LK, DeRyke CA, et al (2021) Antimicrobial stewardship and antibiograms: importance of moving beyond traditional antibiograms. Ther Adv Infect Dis 8:20499361211011373

48. Rismiller K, Haaga J, Siegel C, et al (2017) Pyogenic liver abscesses: a contemporary analysis of management strategies at a tertiary institution. HPB (Oxford) 19:889-893

49. Ahmed S, Chia CL, Junnarkar SP, et al (2016) Percutaneous drainage for giant pyogenic liver abscess--is it safe and sufficient? Am J Surg 211:95-101

ADDENDUM A: MANUSCRIPT SUBMISSION GUIDELINES AND REQUIREMENTS FOR THE WORLD JOURNAL OF SURGERY

MANUSCRIPT PREPARATION AND ORGANIZATION

General instructions:

• Use a normal, plain font (e.g., 10-12 point Times Roman or Arial) for text

• Double-space the text

• Use italics for emphasis

• Include page numbers

• Do not use field functions

• Use tab stops or other commands for indents, not the space bar

• Use the table function, not spreadsheets, to make tables

Manuscript style and text formatting:

Styling and text formatting refers to the use of special effects to enhance the appearance of the published article. Please make note of the following "Dos and Don'ts" regarding styling:

• DO enter all lists as single column lists.

• DO use your word processing features to indicate bold, italic, superscript, and subscript text within a paragraph or heading.

• DO NOT centre text for headings. All text should be justified left, with ragged (unjustified) right margins.

• DO NOT use italic, underline, or other type effects for the entire text of a heading.

• DO NOT use all capital letters for a heading; use initial caps instead.

• DO NOT use multiple spaces to set up columns or tables; use tabs instead.

• DO NOT use carriage returns at the end of each line of text (use the word wrap feature).

Manuscript organization:

Manuscripts should be organized and follow the sequence as indicated below:

TITLE PAGE: The title page should include:

- A concise and informative title
- The name(s) of the author(s) including the affiliation(s) and address(es) of each author. The complete name and address of the author to whom correspondence should be sent, as well as his/her phone number, fax number, and email address.
- A short title for use as a running head.
- Keywords: 3-6 keywords relevant to the manuscript
- Trial registration number for randomized clinical trials (see "Types of Manuscripts: Original Scientific Reports" above)
- Grant support for the research reported
- Statements to comply with ethical requirements (see "Compliance with Ethical Requirements" below for more details):
- A statement for each author in the manuscript must be included declaring whether there are any conflicts of interest in the manuscript. Even if there is no conflict of interest, this should also be explicitly stated as none declared on the title page.
- Statement of informed consent should be included if individual participants are included in the study. For example: "Informed consent was obtained from all individual participants included in the study."

- Statement of human and/or animal rights should be included (if applicable) stating that the study was approved by the appropriate institution and/or national research ethics committee
- Manuscript word count of your submission

ABSTRACT (if applicable):

The abstract must appear between the title page and the Introduction section of the manuscript, even if it has been uploaded separately. Manuscripts that require an abstract should contain a structured abstract of not more than 250 words. It should be a factual description of the study performed organized with the headings of: Background (includes aims, hypotheses, or objectives), Methods (includes patient population, procedures, and data analysis), Results, and Conclusions.

The abstract should contain the data to support the key findings or conclusions of the study. The trial registration number for randomized clinical trials must be included at the end of the abstract. The first time an abbreviated term is used, spell it out in full and follow with the abbreviation in parentheses – for example: ultrasound (US).

TEXT:

Original Scientific Reports should be arranged in sections titled Introduction, Material and Methods, Results, and Discussion.

1. Introduction: conveys the background and purpose of the report
2. Material and Methods
3. Results & Discussion

When required by the nature of the report, manuscripts that do not follow this specific format may be accepted.

ACKNOWLEDGEMENTS:

A brief statement should acknowledge individuals, other than authors, who were of direct help in the reported work or if the work was supported by a federal or commercial grant. All acknowledged persons should give their written consent to being named in the manuscript. This consent is to be uploaded upon manuscript submission.

REFERENCES:

Reference citations in the text should be identified by numbers in brackets (e.g. [4]). Number the references in order of their first appearance in the text (not alphabetically). Once a reference is cited, all subsequent citations should be to the original number. References may not appear in your Reference List unless they have been cited in the text or tables. Manuscripts that have been accepted for publication or are in press may be listed as references, but the Journal does not reference unpublished data and personal communications. Use the form for references adopted by the U.S. National Library of Medicine, as in Index Medicus. For each reference, show inclusive page ranges (e.g., 7-19).

In references to journal articles, please include:

1. surname and initials (without periods) of the first three authors and ‘et al’ for all others,
2. the year in parentheses
3. title of article
4. abbreviated Journal name
5. volume number
6. inclusive page numbers, in that order.

TABLES:

• All tables are to be numbered using Arabic numerals

• Tables should always be cited in text in consecutive numerical order

• For each table, please supply a table heading

• The table title should explain clearly and concisely the components of the table

• Identify any previously published material by giving the original source in the form of a reference at the end of the table caption

• Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body

ARTWORK, General:

Figure Submission

• Supply all figures electronically

• Indicate what graphics program was used to create the artwork

• For vector graphics, the preferred format is EPS; for halftones, please use TIFF format. MS Office files are also acceptable.

• Vector graphics containing fonts must have the fonts embedded in the files

• Save and name your figure files with "Fig" and the figure number (e.g., Fig1.eps)

ABBREVIATIONS, DRUG AND PRODUCT NAMES, DIGITS:

Please use the standard abbreviations and units listed in Scientific Style and Format: The CBE Manual for Authors, Editors, and Publishers, Sixth Edition (Reston, Va., Council of Biology Editors, 1994). The first time an abbreviated term is used, spell it out in full and follow with the abbreviation in parentheses – for example: ultrasound (US).

Generic names for drugs and chemicals should be used the first time the drug or chemical is mentioned in the text and, preferably, thereafter. The first reference to a drug or chemical in

the text should be followed by the manufacturer name, city, state or province, and country – and, if you wish, the trade name – in parentheses.

Please express digits as numerals except when they are the first word in a sentence. Decimals should be written in North American format. Express units of measurement in the metric system whenever possible, and abbreviate them when used with numbers.

PERMISSIONS

If you include figures, tables, or text passages that have already been published elsewhere, you must obtain permission from the copyright owner(s) for both the print and online formats. The corresponding author must obtain written permission from the copyright holder (usually the publisher, not the author, of the original work) to reprint it in World Journal of Surgery. Any material received without such evidence will be assumed to originate from the authors. Please be aware that some publishers do not grant electronic rights for free and that Springer will not be able to refund any costs that may have occurred to receive these permissions. In such cases, material from other sources should be used. Any reuse of published material must acknowledge the original source and cited within the manuscript.

COMPLIANCE

Compliance with Ethical Requirements

WJS requests that all authors comply with the journal's ethical policies below.

Compliance with Sex-Inclusive SJEG Guidelines

Uniform, defined reporting of the sex used for all human, animal, tissue, and cell research should be included in your manuscript. If only one sex is studied, authors must include a justification statement as to why a single-sex study was conducted. WJS also will require sex-

based reporting and analysis of data. The full statement was published online in WJS on June 12, 2018 and is available at https://link.springer.com/article/10.1007/s00268-018-4695-6

Conflict of Interest:

Authors must disclose all relationships or interests that could have direct or potential influence or impart bias on the work. In addition, interests which go beyond financial interests and compensation that may be important to readers should be disclosed. EACH author must complete a Conflict of Interest form. The recommended form to use can be downloaded at: http://www.icmje.org/conflicts-of-interest/

The corresponding author should then collect the completed forms from all authors and upload them together at the time of submission. Please also make sure to include a conflict of interest disclosure statement for each author on the title page of the manuscript.

Statement of Informed Consent

All individuals have individual rights that are not to be infringed. Authors are responsible for obtaining informed consent from all individual participants in writing prior to inclusion in the study.

Authors must include a statement of informed consent on the title page of the manuscript.

Duplicate Submission and Publication

In general, if a manuscript has been peer-reviewed and published, any subsequent publication is duplication.

Exceptions to this general rule may be:

a) Prior publication in meeting program abstract booklets or expanded abstracts such as those published by the Surgical Forum of the American College of Surgeons or Transplantation Proceedings. However, these must be referenced in the final manuscript.

b) A manuscript which extends an original database (a good rule might be expansion by 50% or more) or which analyses the original database in a different way in order to prove or disprove a different hypothesis. Previous manuscripts reporting the original database must, however, be referenced.

c) Manuscripts which have been published originally in non-English language journals, provided that the prior publication is clearly indicated on the English language submission and referenced in the manuscript. In some circumstances, permission to publish may need to be obtained from the non- English language journal.

Consensus Statement on Surgery Journal Authorship - 2006

In the majority of clinical and research studies submitted to surgery journals for possible publication, many individuals participate in the conception, execution, and documentation of each of those works. However, recognition of work in the form of authorship has varied widely. This consensus statement is being issued to clarify and define the criteria for surgical journal authorship.

The following guidelines should be used to identify individuals whose work qualifies them as authors as distinct from those who are contributors to the work under consideration. All persons designated as authors should qualify for authorship, and all those who qualify should be so credited.

A. Authorship Criteria

Individuals claiming authorship should meet all of the following 3 conditions:

1. Authors make substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data;

2. Authors participate in drafting the article or revising it critically for important intellectual content; and

3. Authors give final approval of the version to be submitted and any revised version to be published.

Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Allowing one's name to appear as an author without having contributed significantly to the study or adding the name of an individual who has not contributed or who has not agreed to the work in its current form is considered a breach of appropriate authorship.

Acquisition of funding, collection of data, contributing cases, or general supervision of the research group, of itself, or just being the Chair of the department does not justify authorship if the above criteria are not fulfilled.

B. Order of Authors

The order of authorship on the by line should be a joint decision of the co-authors. Authors should be prepared to explain the order in which authors are listed.

C. Multi-Centre Studies

When a large, multi-centre group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above and editors will ask these individuals to complete journal-specific author and conflict of interest disclosure forms. When submitting a group-author manuscript, the corresponding author should clearly indicate the preferred citation and should clearly identify all individual authors as well as the group name.

D. Contributors Listed in Acknowledgments

All contributors who do not meet the criteria for authorship should be listed in an acknowledgments section. Examples of those who might be acknowledged include: individuals who allowed their clinical experience (i.e., cases) to be included, a person who provided purely

technical help, writing assistance, or a department Chair who provided only general support. Financial and material support should also be acknowledged.

Groups of persons who have contributed materially to the paper but whose contributions do not justify authorship may be listed under a heading such as “collaborators” or “clinical investigators” or “participating investigators,” and their function or contribution should be described - for example, “served as scientific advisors,” “critically reviewed the study proposal,” “collected data,” or “provided and cared for study patients.”

Because readers may infer their endorsement of the data and conclusions, all persons listed as contributors must give written permission to be acknowledged.

E. In Conclusion

This consensus statement is intended as a basic guide for authors. In the interest of promoting the highest ethics in surgical publishing and the surgical sciences, we ask that authors take these criteria into careful consideration when submitting a manuscript to a peer-reviewed surgical journal.

Author Proofs

After a submission is accepted and processed through production, a proof of the article is made available to the corresponding author. The purpose of the proof is to check for typesetting or conversion errors and the completeness and accuracy of the text, tables and figures. It is particularly important to check the proofs for accurate spelling of the author’s names and affiliations. It will be impossible to change an incorrectly spelled author’s name after publication. Substantial changes in content, e.g., new results, corrected values, title and authorship, are not allowed without the approval of the Editor-in-Chief. Please note that the corresponding author will only receive one proof for review. Revised proofs are provided only upon request of the corresponding author. The article will be published online after receipt of

the corrected proofs. This is the official first publication citable with the DOI (Digital Object Identifier). After online publication, further changes can only be made in the form of a Correction (i.e., Erratum), which will be hyperlinked to the article. After release of the online and printed issue, the article can also be cited by issue and page numbers.

ADDENDUM B: Ethics Approval

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

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

02 June 2020

HREC REF: 260/2020

Dr J Kloppers
Division of General Surgery
J-Floor, OMB
Email: jckloppers@gmail.com
Student; Nieleshen.govender@gmail.com

Dear Dr Kloppers

PROJECT TITLE: EMPIRIC ANTIBIOTIC TREATMENT FOR LIVER ABSCESSES-MMED CANDIDATE-DR NIELESHEN GOVENDER

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

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

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020.

Approval is granted for one year until the 30 May 2021.

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

The HREC acknowledge that the student: - Ms Nieleshen Govender will also be involved in this study.

Please quote the HREC REF in all your correspondence.

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

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

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

HREC 260/2020sa

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) **This serves as notification of annual approval, including any documentation described below.**			
☑ Approved	Annual progress report	Approved until/next renewal date	30.07.2022
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	15/7/21

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	14/7/2021		
HREC REF Number	260/2020	Current Ethics Approval was granted until	30/5/2021
Protocol title	**Empiric Antibiotic Treatment for Liver Abscesses**		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?		☐ Yes	■No
If yes, could you please provide the HREC Reference number for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.			

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

ADDENDUM C: Hospital Approval

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL
Enquiries: Dr Bernadette Eick
e-mail: Bernadette.Eick@westerncape.gov.za

Dr J. C. Kloppers
GENERAL SURGERY

E-mail: jckloppers@gmail.com / Nieleshen.Govender@gmail.com

Dear Dr Kloppers,

RESEARCH PROJECT: Empiric Antibiotic Treatment or Liver Abscesses (MMed. Dr Nieleshen Govender)

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 May 2021.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) Confidentiality must always be maintained.
d) No additional costs to the hospital should be incurred i.e. Lab, consumables or stationary. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form.**
e) **No patient folders may be removed from the premises or be inaccessible.**
f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
g) Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges
m) Kindly submit a copy of the publication or report to this office on completion of the research.
n) At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.

I would like to wish you every success with the project.

Yours sincerely

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 23 July 2020

C.C. Mr. L. Naidoo
Dr B. Jacobs
Professor E. Panieri
Professor E. Muller

G46 Management Suite, Old Main Building,
Observatory 7925
Tel: +27 21 404 6288 fax: +27 21 404 6125

Private Bag X,
Observatory, 7935
www.westerncape.gov.za/health